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Allocation to Matched Related or Unrelated Donor Results in Similar Clinical Outcomes without Increased Risk of Failure to Proceed to Transplant among Patients with Acute Myeloid Leukemia: A Retrospective Analysis from the Time of Transplant Approval

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Clinical outcomes after allogeneic hematopoietic stem cell transplantation (allo-SCT) from unrelated donors (URDs) approach those of matched related donor (MRD) transplants in patients with acute myeloid leukemia (AML). Yet, available data fail to account for differences in pretransplantation outcomes between these donor selection strategies. In this regard, URD allo-HSCT is associated with longer waiting times to transplantation, potentially resulting in higher probabilities of failure to reach transplant. We retrospectively analyzed 108 AML patients accepted for first allo-HSCT from the time of approval to proceed to transplant. Fifty-eight (54%) patients were initially allocated to MRD, while URD search was initiated in 50 (46%) patients. Time to transplant was longer in patients allocated to a URD when compared with patients assigned to an MRD (median 142 days versus 100 days; $p < .001$). Forty-three of 58 (74%) patients in the MRD group and 35 of 50 (70%) patients in the URD group underwent transplantation (odds ratio [OR], 1.22; $p = .63$). Advanced disease status at the time of allo-HSCT approval was the only predictor of failure to reach transplantation in the multivariate analysis (OR, 4.78; $p = .001$). Disease progression was the most common cause of failure to reach allo-HSCT (66.7%) in both the MRD and URD groups. With a median follow-up from transplantation of 14.5 (interquartile range, 5 to 29) months, the 2-year estimate of overall survival (OS) from allo-HSCT was 46% in the MRD group and 57% in the URD group ($p = .54$). There were no differences in OS according to donor type allocation in the multivariate analysis (hazard ratio, 1.01; $p = .83$). When including patients from the time of transplant approval, 2-year OS was 39% in the MRD group versus 42% in the URD group. Our study suggests that allocation of AML patients to URDs may result in comparable clinical outcomes to MRD assignment without a significant increase in the risk of failure to reach transplant.

INTRODUCTION

Acute myeloid leukemia (AML) represents the most common indication for allogeneic hematopoietic stem cell transplantation (allo-HSCT) worldwide [1]. Despite major progresses in our understanding of AML biology and the recent arrival of emerging targeted therapies to the field, allo-HSCT remains the first-choice consolidation strategy for fit patients in first remission who are at a high risk of relapse [2,3,4]. Moreover, allo-HSCT is the only therapeutic option resulting in significant long-term survival rates in patients with refractory or relapsed disease [5]. Matched related donors (MRDs) offer the best clinical outcomes and are thus the preferred graft source in this setting, but about two thirds of the patients who require a transplant will not have such a donor. Together with advances in conditioning regimens, graft-versus-host disease (GVHD) prophylaxis, and supportive care, the growing use of alternative donors has extended allo-HSCT eligibility in this population of AML patients without an available MRD. While

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this expansion of the donor pool has allowed that nearly all patients will currently find a potential donor, optimal alternative donor selection is still controversial.

A number of mainly retrospective studies have reported outcomes after unrelated donor (URD) [6,7,8,9,10,11], haploidentical [12,13], or umbilical cord blood (UCB) [14,15] transplantation approaching those of MRD in adult patients with AML, although with conflicting results with regard to the relative virtues and disadvantages of each alternative donor source. Recent data from the European Society for Blood and Marrow Transplantation showed a survival benefit for MRD, fully matched URD or haploidentical allo-HSCT over UCB or partially mismatched URD allo-HSCT [16]. Prior large observational studies have, on the other hand, reported comparable overall survival (OS) after MRD, 8/8 HLA-matched URD (MURD), and 7/8 mismatched URD (MMURD) allo-HSCT, albeit at the expense of higher GVHD incidences in the latter 2 groups [9,11]. Single-center and registry data also suggest that haploidentical transplantation with post-transplant cyclophosphamide prophylaxis may achieve similar OS and lower GVHD incidence as compared with MURD transplants [12,13]. Likewise, UCB transplantation appears to provide similar outcomes as those reported after MURD transplants in some studies [14,15], as well as possibly lower relapse rates among patients with positive pretransplant minimal residual disease [15]. Overall, significant between-study heterogeneity and the inherent difficulties in isolating donor effects from the impact of associated transplantation schemes have so far precluded the definition of a definite hierarchy of alternative donor sources in patients with AML.

Notably, available data are restricted to those subsets of patients who have successfully undergone transplantation and therefore fail to account for differences in pretransplantation outcomes between donor selection strategies. In this regard, URD allo-HSCT is associated with limited donor availability for patients who belong to ethnic minority groups and longer waiting times to transplantation, potentially resulting in higher probabilities of failure to reach transplantation and poorer transplant outcomes [17,18,19]. Conversely, the near universal and expedited access to haploidentical donors or UCB units may favor these graft sources when short-lived remission duration is expected or patient ethnicity predicts a low a priori likelihood of finding a suitable URD. However, the precise role of alternative donor selection on transplant rates and pretransplant clinical outcomes remains speculative. In this context, current practice is hence largely based on institutional experience rather than on evidence-based approaches to alternative donor selection.

In the present study we have evaluated the impact of donor selection on both pretransplant and post-transplant clinical outcomes based on a donor selection strategy consisting in the preferential allocation of AML patients without MRD to MURD or MMURD.

METHODS

Data Source and Patient Population

The study population included patients with AML who received approval for first-time allo-HSCT at our institution between January 2011 and February 2017. Transplantation board meetings were held on a weekly basis. Transplant approval refers to the specific date when the board issued a positive decision regarding the indication of transplantation for any patient and, accordingly, the acceptance of such a patient to proceed to allo-HSCT in our HSCT unit. Patients with a frontline allo-HSCT indication were referred to the transplantation board for allo-HSCT approval concomitantly with the administration of frontline chemotherapy. All these patients were administered at least 1 cycle of consolidation chemotherapy before proceeding to transplant, and a proportion of them received allo-HSCT approval before the assessment of postinduction response (subsequently referred in the text as "transplantation approval at diagnosis"). Patients with advanced disease were evaluated at the discretion of the referring physician, irrespective of disease status and planned treatment before allo-HSCT at the time of referral. Those patients who did not fulfill standard criteria to undergo allo-HSCT based on risk stratification according to international [2] and PETHEMA Group recommendations, as well as those considered unfit for allo-HSCT after evaluation by the transplantation board, were excluded from the analysis. There were no patients denied to proceed to allo-HSCT approval due to medical insurance restrictions. Patients with acute promyelocytic leukemia were excluded from the study. All patients consented to the use of their clinical data and the study was approved by the Hospital Universitario Virgen del Rocío Institutional Review Board. Data were retrospectively collected from electronic records.

Donor Selection Algorithm

HLA typing of first-degree relatives was generally performed early after the diagnosis of AML. Patients were assigned to receive an allo-HSCT from an MRD if available. Nonsibling matched family donors were considered on an individual basis. Search for URD was initiated in the remaining cases. When not done before, high-resolution HLA-A, HLA-B, HLA-C, and DRB1 typing was performed immediately after the confirmation of MRD unavailability. The primary donor choice was 8/8 allele matched URD for patients without an MRD, with 7/8 matched URD being selected as a secondary choice. URD search was not started until transplant approval, once confirmed that an MRD was not available. Patients were assigned to search for a haploidentical donor if a suitable URD was not identified after a maximum of 4 months from the date of search initiation.

Study Endpoints and Definitions

OS was measured separately from the date of approval to undergo allo-HSCT and from the date of allo-HSCT. Relapse was defined as morphological evidence of leukemia recurrence (bone marrow blasts $\geq$5%, reappearance of blasts in the blood, or development of extramedullary disease). Relapse incidence (RI) and leukemia-free survival (LFS) were calculated from the date of transplant approval and from the date of allo-HSCT for patients in complete remission (CR), with death without evidence of relapse or treatment failure (relapse or death from any cause) as competing events, respectively. Patients with active disease were included in the RI and LFS analyses from the date of achievement of CR. Nonrelapse mortality (NRM) was calculated considering relapse as a competing event. Acute GVHD (aGVHD) was graded using the Glucksberg criteria [20]. Chronic GVHD (cGVHD) was evaluated according to the National Institutes of Health consensus criteria [21]. Patients alive at day 100 were evaluable for cGVHD/late-onset aGVHD. aGVHD and cGVHD/late-onset aGVHD incidences were estimated with death without aGVHD within 100 days or death without cGVHD/late-onset aGVHD as competing risks, respectively. Genetic risk was assigned based on cytogenetic data and according to the 2017 European LeukemiaNet risk stratification, with molecular data (*FLT3*-ITD allelic ratio and/or *NPM1* status) considered when available.

Statistical Analysis

The primary purpose of our analysis was the comparison of 2 donor allocation strategies from the time of transplant approval. All comparisons between patient groups were thus made based on the initial assignment to donor type (MRD versus URD) at the time of inclusion into the allo-HSCT program, irrespective of the final donor source in the patients that reached allo-HSCT. Those patients that underwent haploidentical transplantation after URD search failure were therefore included in the URD group. Standardized mean differences (SMDs) were used as an effect size measure of differences in baseline characteristics. Nonparametric cumulative incidences of allo-HSCT from time of transplant approval were estimated for all patients accepted into the program. A multivariate logistic regression model was fitted to assess the impact of donor type assignment on the probabilities of transplantation and to identify independent predictors of failure to reach allo-HSCT after transplant approval. All variables with a p value $<.2$ on univariate logistic regression analysis were evaluated in the multivariate analysis. An interaction term was added to assess the potential effect modification of donor assignment on the association between disease status and failure to reach allo-HSCT. Probabilities of OS and LFS were estimated using the Kaplan-Meier method. Nonparametric cumulative incidences were estimated to assess RI, NRM, aGVHD, and cGVHD. Kaplan-Meier and cumulative incidence curves were compared using the log-rank and the Gray tests, respectively. Cox proportional hazards or Fine-Gray multivariate regression models were constructed to estimate the effect of donor type assignment on clinical outcomes. Reduced submodels were compared with reference models including all the theoretically relevant covariates with a p value $<.2$ on univariate analysis. The final models were selected based on the parsimonious principle (ie, those with the minimum number of covariates and the lowest estimate standard error, allowing for a $\leq$10% estimate change from the reference model). Data management and statistical analyses were conducted in Stata 13 (StataCorp, College Station, TX) and R version 3.3.1 (www.r-project.org).

RESULTS

Patient Baseline Characteristics

Baseline characteristics of the study population are summarized in Table 1. Between January 2011 and February 2017, 108 eligible AML patients were accepted for first allo-HSCT at our center. Fifty-eight (53.7%) patients were initially allocated to MRDs, while URD search was initiated in 50 (46.3%) patients. Median age at inclusion into the program was 47 (range, 17 to 68) years. Patients assigned to URDs were more likely to harbor adverse risk genetics (30.0% versus 19.0%; SMD = .31) and to have advanced disease status at the time of transplant approval (48.0% versus 32.6%; SMD = .52). Conversely, therapy-related AML was more frequent among patients allocated to MRD (13.8% versus 6.0%; SMD = .28).

Predictors of Failure to Reach Transplantation and Pretransplantation Clinical Outcomes

Probabilities to reach transplantation were similar irrespective of initial donor assignment status (Figure 1A). Forty-three of 58 (74.1%) patients in the MRD group and 35 of 50 (70.0%) patients in the URD group underwent transplantation (odds ratio [OR] 1.22; 95% confidence interval [CI], .53 to 2.86; $p = .63$). Patients with advanced disease at the time of allo-HSCT approval were more likely to fail to reach transplantation than those with early disease status (OR, 4.78; 95% CI, 1.94 to 11.78; $p = .001$) (Figure 1B), regardless of donor assignment (for those with MRD: OR, 4.95 [95% CI, 1.42 to 17.31]; for those allocated to URD search: OR, 4.65 [95% CI, 1.23 to 17.67]; p for the interaction = .95). Twenty of 43 (46.5%) patients with advanced disease (12 patients in partial remission [PR] or with refractory/relapsed disease and 8 patients in CR1 after second or further line treatment or ≥CR2) failed to reach transplantation, as compared with only 10 of 65 (15.4%) among newly diagnosed patients or those in CR1 after frontline chemotherapy at the time of acceptance into the program. Age, sex, diagnosis (secondary versus de novo AML), and genetic risk category were associated with the probability of transplantation. In multivariate analysis, advanced disease status at the time of transplant approval remained as the only predictor of failure to reach transplantation (OR, 4.52; 95% CI, 1.79 to 11.42; $p = .001$) (Table 2).

No interaction was detected between donor selection and disease status in the final model ($p = .89$).

Time to transplant was significantly longer in patients allocated to URDs when compared with patients assigned to MRD (median 142 [IQR, 115 to 164] days versus 100 [IQR, 73 to 127] days; $p < .001$). Reflecting the additional time required to complete frontline chemotherapy, median time to transplant from the date of transplant approval was 149 (IQR, 100 to 189) days for patients included at diagnosis, as compared with 115 (IQR, 83 to 141) days for the rest of the patients ($p = .03$). The probability to reach allo-HSCT among subjects included at diagnosis (81.8%) was similar to that of patients with early disease who were included after achievement of CR1 (86.0%) (OR, .73; 95% CI, .18 to 2.91; $p = .66$). Median times to exclusion from transplant were 63 (IQR, 23 to 124) days and 113 (IQR, 63 to 163) days for patients failing to reach allo-HSCT in the MRD and URD cohorts, respectively ($p = .47$) (Figure 2).

Disease progression was the most common cause of failure to reach allo-HSCT: 10 of 15 (66.7%) in both the MRD and URD groups, while intercurrent complications from transplant approval accounted for the remaining cases. By the time of failure to reach allo-HSCT, a suitable URD was available for 9 patients and donor search was still ongoing in 4 cases assigned to URDs, whereas URD search had been unsuccessful for 2 patients (both of whom had available haploidentical donors). Additionally, 4 AML relapses that did not ultimately preclude transplantation were reported among newly diagnosed patients or those in CR at the time of allo-HSCT approval (2 of 43 [4.7%] in the MRD group and 2 of 35 [5.7%] in the URD group; $p = .54$).

Table 1
Baseline Characteristics of Patients Accepted into the HSCT Program

Variable	Donor Type		SMD	*p*
	MRD (n = 58)	URD (n = 50)		
Age category			.08	.91
17-39 yr	18 (31.0)	17 (34.0)		
40-59 yr	33 (56.9)	28 (56.0)		
≥60 yr	7 (12.1)	5 (10.0)		
Sex			.20	.30
Male	29 (50.0)	20 (40.0)		
Female	29 (50.0)	30 (60.0)		
Diagnosis			.28	.56
De novo	35 (60.3)	33 (66.0)		
Therapy-related	8 (13.8)	3 (6.0)		
Pre-existing MDS/MPN or AML with MRC	13 (22.4)	13 (26.0)		
Not reported	2 (3.4)	1 (2.0)		
Genetic risk category			.31	.46
Favorable	6 (10.3)	7 (14.0)		
Intermediate	33 (56.9)	23 (46.0)		
Adverse	11 (19.0)	15 (30.0)		
Not reported	8 (13.8)	5 (10.0)		
Disease status at transplantation approval			.52	.33
Transplantation approval at diagnosis	11 (19.0)	11 (22.0)		
CR1 (first-line treatment)	28 (48.3)	15 (30.0)		
CR1 (second or later-line treatment)	5 (8.6)	7 (14.0)		
≥CR2	1 (1.7)	3 (6.0)		
Partial response	2 (3.4)	2 (4.0)		
Refractory disease	6 (10.3)	3 (6.0)		
Relapsed disease	5 (8.6)	9 (18.0)		

Values are n (%).
MDS indicates myelodysplastic syndrome; MPN, myeloproliferative neoplasm; MRC, myelodysplasia-related changes.

Transplantation Characteristics

Seventy-eight eligible patients underwent a first allo-HSCT during the study period. All 43 patients in the MRD group received an HLA-identical sibling transplant. In the URD group, 19 (54.3%) patients received an 8/8 matched transplant, 14 (40.0%) were assigned to a 7/8 URD, and 2 (5.7%) patients underwent a haploidentical transplant after URD search failure. The graft source was peripheral blood stem cells in all MRD recipients, while 7 (20%) patients in the URD group received a bone marrow transplant. Tacrolimus/methotrexate was the first-choice immunoprophylactic regimen among those patients receiving myeloablative conditioning, with antithymocyte globulin if receiving 7/8 matched URD. Tacrolimus/sirolimus was the GVHD prophylaxis most frequently used for those patients receiving reduced-intensity conditioning. Other patient characteristics are shown in Table 3.

Transplantation Outcomes

OS and LFS

With a median follow-up from transplantation of 14.5 (IQR, 5.4 to 28.5) months, the 2-year unadjusted estimate of OS was 45.9% (95% CI, 29.8% to 60.6%) in the MRD group and 57.1% (95% CI, 38.3% to 72.1%) in the URD group

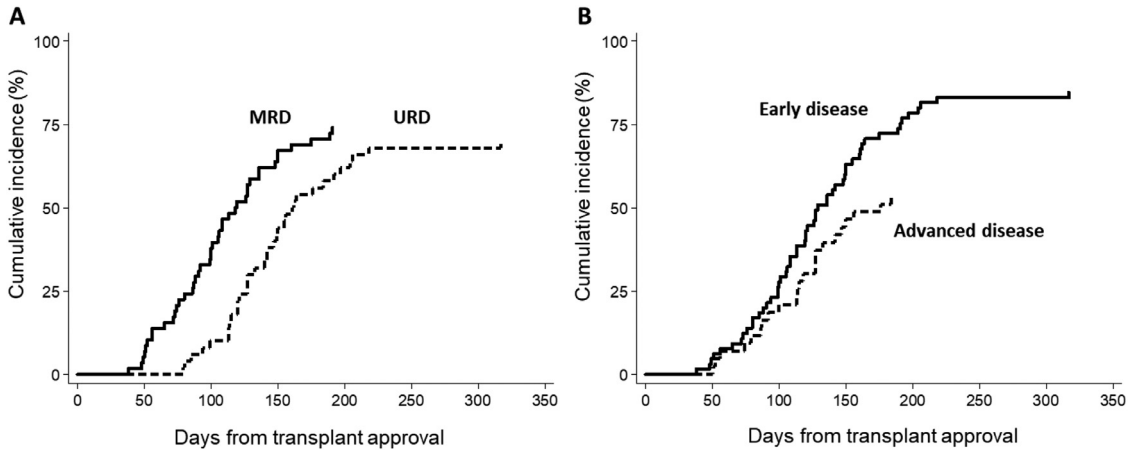

Figure 1. Cumulative incidences of transplantation from the time of approval to proceed to transplant by (A) donor group allocation and (B) disease status at the time of transplantation approval. Early disease refers to CR1 after frontline chemotherapy or transplantation approval at diagnosis, while advanced disease includes CR1 after second or further line treatment, >CR1, PR, or refractory/relapsed (R/R) disease.

Table 2
Predictors of Failure to Reach Transplantation

		Univariate			Multivariate		
Variable		OR	*p*	95% CI	OR	*p*	95% CI,
Age	Per 10-yr increase	1.27	.18	.90-1.80	1.01	.46	.98-1.05
Sex	Male versus female	.61	.26	.26-1.45	-	-	-
Diagnosis	Secondary* versus de novo	1.11	.82	.45-2.76	-	-	-
Genetic risk category	Adverse versus favorable/intermediate	.80	.54	.39-1.63	-	-	-
Disease status at HSCT approval	Advanced versus early disease†	4.78	.001	1.94-11.78	4.52	.001	1.79-11.42
Donor type assignment	URD versus MRD	1.22	.63	.53-2.86	.97	.95	.39-2.41

R/R indicates refractory/relapsed.
* Therapy-related AML, AML with MRC, or MPN-AML.
† Early disease: CR1 after frontline chemotherapy or HSCT approval at diagnosis; advanced disease: CR1 after second or further line treatment, >CR1, PR, or R/R disease.

(Figure 3A). Similarly, the 2-year unadjusted estimate of LFS was 46.8% (95% CI, 30.9% to 61.3%) in the MRD group and 55.0% (95% CI, 35.8% to 70.7%) in the URD group (Figure 3B). There were no differences in OS (hazard ratio [HR], 1.01; 95% CI, .54 to 2.16; p = .83) or LFS (HR, .92; 95% CI, .46 to 1.86; p = .83) in the multivariate analysis (Table 4). When including patients from the time of transplant approval, 2-year OS was 38.9% (95% CI, 26.3% to 51.3%) in the MRD group versus 42.3% (95% CI, 28.2% to 55.7%) in the URD group, while 2-year LFS was 46.1% (95% CI, 30.5% to 60.4%) in the MRD group and 49.0% (95% CI, 32.5% to 63.6%) in the URD group) (Figures 4A and 4B).

RI and NRM

The 2-year unadjusted estimate of RI was 34.9% (95% CI, 20.2% to 50.0%) in the MRD group and 16.3% (95% CI, 5.7% to 31.8%) in the URD group (Figure 3C), while the 2-year unadjusted estimate of NRM was 21.5% (95% CI, 10.5% to 35.2%) in the MRD group and 30.8% (95% CI, 15.7% to 47.3%) in the URD group (Figure 3D). In the multivariate analysis there was a lower risk of relapse in the URD group (subdistribution HR [sHR], .26; 95% CI, .07 to .91; p = .04), accompanied by a significant increase in the risk of NRM (sHR, 2.85; 95% CI, 1.04 to 7.80; p = .04) (Table 4). Differences in 2-year RI were abrogated when the analysis was performed from the time of transplant approval (36.0% [95% CI, 21.4% to 50.8%] in the MRD group and 28.0 [95% CI, 14.8% to 42.8%] in the URD group) (Figure 4C).

Graft-versus-Host Disease

The unadjusted cumulative incidence of grade II to IV aGVHD was 35.7% (95% CI, 20.9% to 50.7%) in the MRD group and 50.1% (95% CI, 32.1% to 65.8%) in the URD group (Figure 3E). The risk of grade III or IV aGVHD was similar in both groups (18.6% [95% CI, 8.6% to 31.6%] in the MRD group and 20.0% [95% CI, 8.7% to 34.7%] in the URD group). Regarding cGVHD, the 2-year unadjusted cumulative incidence (including 3 late-onset aGVHD events) did not differ significantly between the MRD group (47.0% [95% CI, 28.9% to 63.2%] and the URD group (39.7% [95% CI, 21.9% to 56.9%]) (Figure 3F). The risks of grade II to IV aGVHD (sHR, 1.56; 95% CI, .78 to 3.13; p = .21) and cGVHD (sHR, .84; 95% CI, .37 to 1.87; p = .66) were similar in both groups in the multivariate analysis.

Outcomes in the subgroup analysis of recipients of 8/8 or 7/8 matched URD transplantation are shown in the supplementary material (Supplementary Table S1 and Supplementary Figure S1).

DISCUSSION

A number of studies have analyzed the advantages and disadvantages of the different alternative donor sources for adult AML patients without an MRD. While URD, haploidentical and UCB transplantation may lead to similar clinical outcomes, waiting times to transplantation vary significantly between graft sources. In fact, delays associated to URD search have been cited among the reasons that may justify the preferential use of other alternative donors

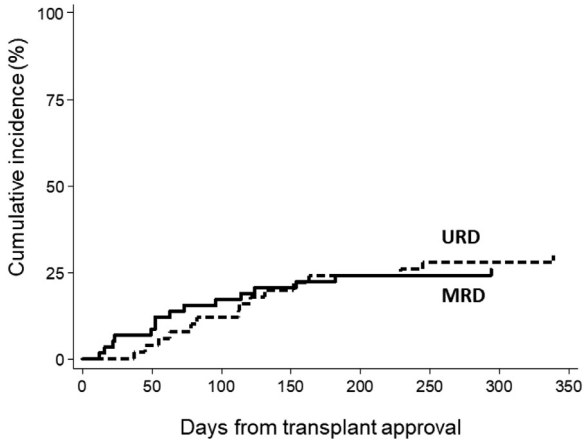

Figure 2. Cumulative incidences of failure to reach transplantation from the time of approval to proceed to transplant by donor group allocation.

[22]. Yet, potential differences in failure rates to reach transplantation by donor type assignment have not been taken into consideration in previous analyses. To our best knowledge, this study represents the first attempt to compare outcomes from the time of allo-HSCT approval between 2 different donor allocation strategies, MRD and URD, in patients with AML.

In our series, 27% of patients receiving approval to undergo allo-HSCT could not reach transplant due to either disease progression or onset of other disease-related complications. This finding is in line with the pretransplantation attrition rate reported among high-risk patients selected for allo-HSCT in the German-Austrian AMLHD98A trial [10]. As expected, URD allocation was associated with a 42-day increase in median time to transplant with respect to MRD assignment. Despite this substantial delay, a similar proportion of patients were able to proceed to allo-HSCT after assignment to either group in our cohort. Advanced disease at the time of the approval of transplant indication emerged as a major predictor of failure to reach transplant in our analysis, while no association was found for other baseline characteristics, including type of donor.

Disease relapse or refractoriness to treatment was the primary driver of failure to reach allo-HSCT among the patients included in the study, accounting for 70% of cases. URD search failure was a rare event on the other hand, being reported in just 2 patients. Disease progression and other complications impeding allo-HSCT often occurred early after the approval of the transplant indication. Median time to proceed to allo-HSCT was 120 days, while median time to exit from the transplantation program was just 89 days. This pattern of early failures may partly explain the lack of impact of donor type allocation on transplantation rates despite the significant delays associated with URD search.

There were no detectable differences with regards to transplantation outcomes in 2-year OS or LFS estimates between donor type groups. In contrast, a significantly lower 2-year RI was counterbalanced by an increased 2-year NRM in the URD group. These results were upheld in subsequent multivariate analyses. Taken together, these data are largely consistent with previous reports showing comparable outcomes after MRD or URD transplantation [6–11]. Moreover, no significant differences in terms of survival or relapse rates were observed upon analyzing outcomes from the time of transplant approval.

Our analysis has several limitations. First, the sample size of the study compromised our ability to perform in-depth

Table 3
Characteristics of Patients who Underwent Transplantation

Variable	Donor Type		SMD	*p*
	MRD (n = 43)	URD (n = 35)		
Age category			.22	.74
17-39 yr	14 (32.6)	13 (37.1)		
40-59 yr	24 (55.8)	20 (57.1)		
≥60 yr	5 (11.6)	2 (5.7)		
Sex			.11	.63
Male	22 (51.2)	16 (45.7)		
Female	21 (48.8)	19 (54.3)		
Diagnosis			.31	.42
De novo	28 (65.1)	23 (65.7)		
Therapy-related	6 (14.0)	2 (5.7)		
Pre-existing MDS/MPN or AML with MRC	9 (20.9)	10 (28.6)		
Genetic risk category			.50	.20
Favorable	4 (9.3)	4 (11.4)		
Intermediate	27 (62.8)	14 (40.0)		
Adverse	7 (16.3)	12 (34.3)		
Not reported	5 (11.6)	5 (14.3)		
Disease status at transplantation approval			.64	.06
CR1 with negative MiRD	28 (65.1)	20 (57.1)		
CR1 with positive MiRD	7 (16.3)	3 (8.6)		
≥CR2	2 (4.7)	9 (25.7)		
Refractory or relapsed disease	6 (14.0)	3 (8.6)		
HCT comorbidity index			.12	.97
Low	9 (20.9)	6 (17.1)		
Intermediate	14 (32.6)	12 (34.3)		
High	17 (39.5)	15 (42.9)		
Not reported	3 (7.0)	2 (5.7)		
Conditioning regimen			.14	.55
Myeloablative	25 (58.1)	18 (51.4)		
Reduced intensity	18 (41.9)	17 (48.6)		
Donor type			-	-
HLA-matched sibling	43 (100)	0		
Unrelated donor (8/8)	0	19 (54.3)		
Unrelated donor (7/8)	0	14 (40.0)		
Haploidentical	0	2 (5.7)		
Stem cell source			.71	.003
Peripheral blood	43 (100)	28 (80.0)		
Bone marrow	0	7 (20.0)		
GVHD prophylaxis*			-	-
CNI/methotrexate	32 (74.4)	8 (22.9)		
CNI/methotrexate/antithymocyte globulin	0	8 (22.9)		
Tacrolimus/sirolimus	11 (25.6)	16 (45.7)		
Other	0	3 (8.6)		
Recipient/donor CMV match			.93	.002
Pos/pos	33 (76.2)	14 (43.6)		
Pos/neg	6 (14.3)	14 (38.5)		
Neg/pos	0	2 (5.1)		
Neg/neg	0	2 (5.1)		
Not reported	4 (9.5)	3 (7.7)		
Recipient/donor sex match			.76	.02
Male/male	11 (25.6)	14 (40.0)		
Male/female	11 (25.6)	2 (5.7)		
Female/male	12 (27.9)	16 (45.7)		
Female/female	9 (20.9)	3 (8.6)		

Values are n (%).
MiRD indicates minimal residual disease; HCT, hematopoietic cell transplantation; CNI, calcineurin inhibitor; CMV, cytomegalovirus; pos, positive; neg, negative.
*Group comparison is not shown as GVHD prophylaxis schemes differ by protocol according to donor source.

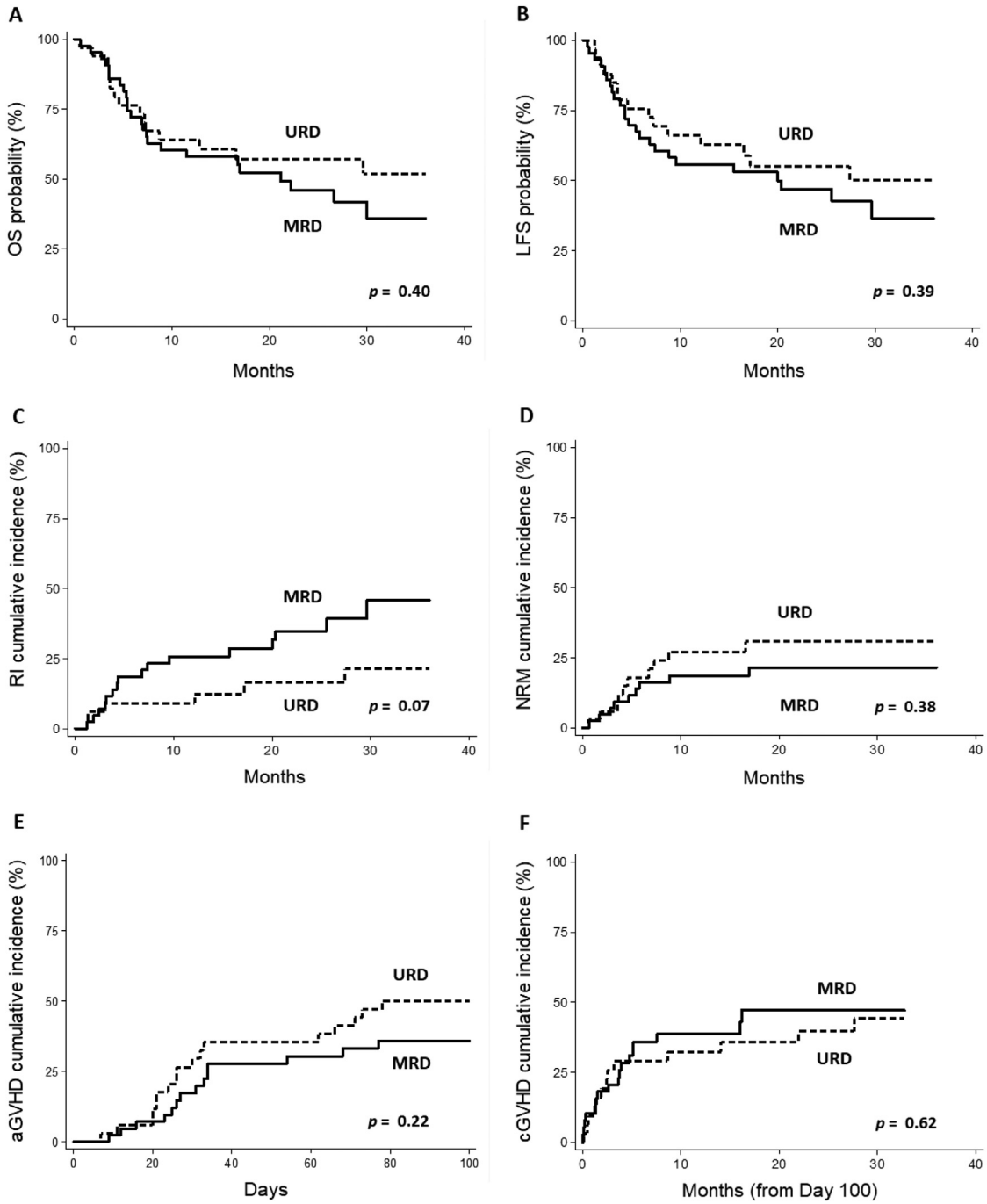

Figure 3. Clinical outcomes from the time of transplant by donor type assignment: (A) OS, (B) LFS, (C) RI, (D) NRM, (E) grade II to IV aGVHD, and (F) cGVHD. Log-rank or Gray's *p* values are shown.

subgroup analyses. We were therefore unable to thoroughly explore whether allocation to URDs may lead to lower transplantation rates in specific patient subpopulations. Although we did not find an interaction between disease status at the time of allo-HSCT approval and donor type assignment, these results require replication in larger studies. For similar reasons, we could not formally compare outcomes between MURD and MMURD recipients. A rough comparison between groups indicates, however, that MMURD allo-HSCT did not result in inferior clinical outcomes in our cohort. Second, the homogenous ethnic composition of our patient population of primarily Caucasian descent limits the generalizability of our conclusions. Analyses based on the U.S. National Marrow Donor Program data estimate that the likelihoods of finding an 8/8 or a ≥7/8 URD may be as low as 18% and 71% among sub-Saharan Africans, as compared with probabilities of 75% and 97%, respectively, for Caucasians [17]. The potential impact of ethnicity on transplantation rates and whether

Table 4
Multivariate Regression Analysis of Transplantation Clinical Outcomes by Donor Type

Outcome	(s)HR (95% CI)	*p*
OS		.83
MRD	1	
URD	1.01 (.54-2.16)	
LFS		.83
MRD	1	
URD	.92 (.46-1.86)	
RI		.04
MRD	1	
URD	.26 (.07-.91)	
NRM		.04
MRD	1	
URD	2.85 (1.04-7.80)	
Grade II-IV aGVHD		.21
MRD	1	
URD	1.56 (.78-3.13)	
cGVHD		.66
MRD	1	
URD	.84 (.37-1.87)	

OS and LFS were adjusted for disease status at transplantation; RI was adjusted for diagnosis (de novo versus secondary AML) and genetic risk category; NRM was adjusted for disease status at transplantation and CMV mismatch; cGVHD was adjusted for the HCT comorbidity index; no additional covariates were selected to be included in the final model for grade II to IV aGVHD.

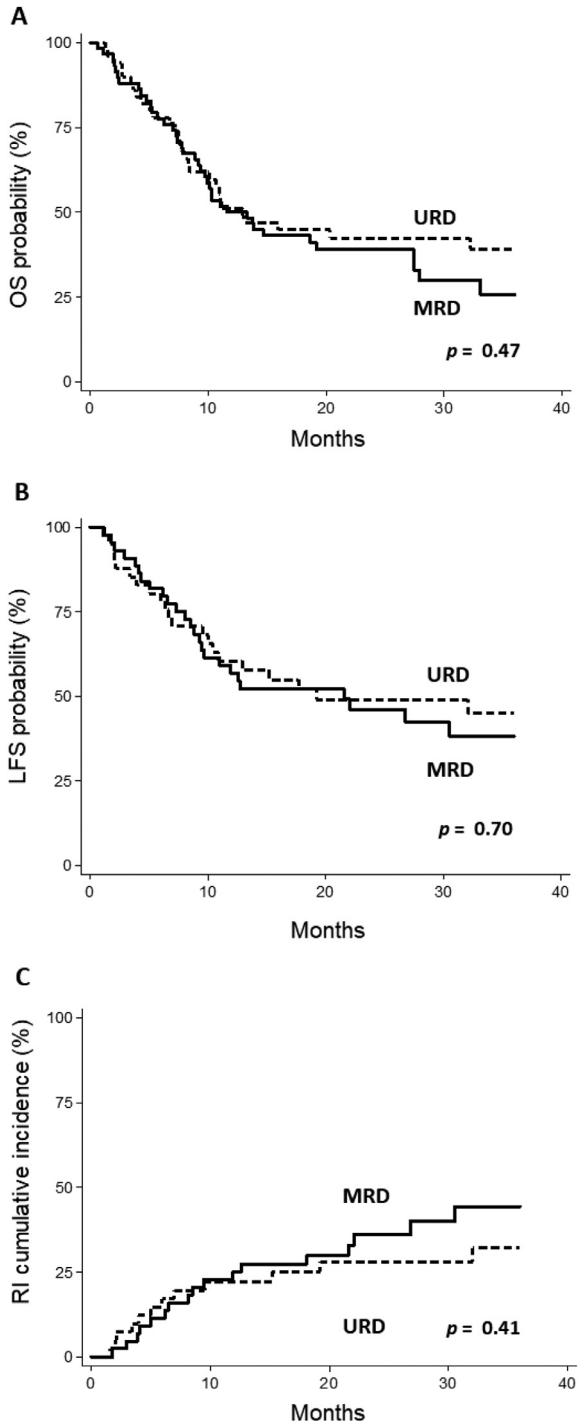

Figure 4. Clinical outcomes from the time of transplant approval by donor type assignment. (A) OS, (B) LFS, and (C) RI. Log-rank or Gray's *p* values are shown.

patients belonging to certain ethnic groups may benefit from early allocation to haploidentical or UCB transplants rather than to URDs search remain key questions that could not be addressed in the present study. Third, waiting times from the time of approval to proceed to transplant are dependent on the efficiency of transplantation programs and differ across health systems and institutions. Thus, the degree to which our data can be extrapolated to other settings needs to be further examined. In this regard, the median time to identify an available URD in the experience of the REDMO (Registro Español de Donantes de Médula Ósea) was 37 (range, 32 to 51) days during the study period, with a reported 80% probability of finding a suitable donor in the first 3 months since the start of the search. Finally, these results may not apply to diagnoses other than AML. In this respect, considering that most patients with AML who are candidates to receive an allo-HSCT can be identified as early as at the time of diagnosis or at the time of disease response evaluation after first induction therapy, the 42-day median delay to proceed to transplant between patients assigned to URDs as compared with MRD allocation had no impact on the probability to reach allo-HSCT. This might not be the case in other clinical scenarios where the transplant indication cannot be anticipated. For instance, even within AML, patients may not be considered candidates to proceed to transplantation a priori but later in the disease course due to poor response to treatment.

Notwithstanding these limitations, our study indicates that allocation of AML patients to URDs may result in comparable clinical outcomes to MRD assignment without an associated increased risk of failure to proceed to transplant. Overall, these data highlight the need for integration of both pretransplantation and post-transplantation data in future studies evaluating donor selection strategies in patients undergoing allo-HSCT. Further validation of these results and comparison with outcomes obtained with other alternative graft sources are warranted.

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SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.bbmt.2018.08.019.

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