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HLA-Matched Sibling versus Unrelated versus Haploidentical Related Donor Allogeneic Hematopoietic Stem Cell Transplantation for Patients Aged Over 60 Years with Acute Myeloid Leukemia: A Single-Center Donor Comparison

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A B S T R A C T

Haploidentical related donor (HRD) allogeneic hematopoietic stem cell transplantation (allo-HSCT) was developed as a valid option for the treatment of acute myeloid leukemia (AML) in the absence of a matched donor. However, many investigators are reluctant to consider the use of this alternative in elderly patients, anticipating high morbidity. Here, we report a single-center comparison of HRD versus matched sibling donor (MSD) and unrelated donor (UD) allo-HSCT for patients with AML aged ≥60 years. Ninety-four patients (MSD: n = 31; UD: n = 30; HRD: n = 33) were analyzed. The median age was 65 (range, 60 to 73) years. We observed a higher cumulative incidence of grade 3 to 4 acute graft-versus-host disease (GVHD) after UD allo-HSCT (MSD versus UD versus HRD: 3% versus 33% versus 6%, respectively; $P = .006$). Two-year cumulative incidence of moderate or severe chronic GVHD was 17%, 27%, and 16% in the MSD, UD, and HRD groups, respectively ($P = .487$). No difference was observed in the 2-year cumulative incidence of relapse or nonrelapse mortality (NRM) (relapse: MSD versus UD versus HRD: 32% versus 25% versus 25%, respectively; $P = .411$; NRM: MSD versus UD versus HRD: 19% versus 27% versus 24%, respectively; $P = .709$). At 2 years, progression-free survival, overall survival, and GVHD- and relapse-free survival were 48%, 50%, and 39%, respectively, in the MSD group; 48%, 51%, and 23%, respectively, in the UD group; and 50%, 52%, and 32%, respectively, in the HRD group, without statistically significant differences between the groups. We conclude that HRD allo-HSCT is highly feasible and no less efficient than MSD or UD allo-HSCT in patients with AML aged ≥60 years. Thus, the absence of a HLA-identical donor should not limit the consideration of allo-HSCT for the treatment of AML.

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a curative option for patients with acute myeloid leukemia (AML). However, most of them are diagnosed after the age of 60 years, thereby limiting the access to intensive treatment. In addition, old age is frequently associated with a lower probability of recruiting a suitable matched sibling donor (MSD), decreasing the access to curative treatment. Unrelated donor (UD) allo-HSCT is an alternative, but this option is associated with higher costs and complex logistics for cell procurement and higher morbidity in recipients, especially in relation to a higher incidence of graft-versus-host disease (GVHD). The recent development of T-replete allo-HSCT from a haploidentical related donor (HRD) represents a potential

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breakthrough to extend the feasibility of allo-HSCT through the identification of several potential donors for virtually all patients [1]. Different modalities of T-replete HRD allo-HSCT for various hematological malignancies were reported in recent studies, which showed similar outcomes while using HRD compared with MSD or UD [2-6]. This was also observed in the specific context of patients with AML [7-11]. As initially described by Luznik *et al.* [12], nonmyeloablative HRD allo-HSCT with post-transplantation cyclophosphamide (PT-Cy) results in low incidence of GVHD, an approach especially appealing for elderly patients [12-14]. We previously reported that this benefit in GVHD incidence may improve outcome when compared with UD allo-HSCT in elderly patients with hematological diseases [15]. Recent single-center studies have shown that HRD allo-HSCT with PT-Cy is feasible for elderly patients with AML or myelodysplastic syndrome (MDS), but no global comparison among MSD, UD, and HRD has been made in elderly patients with AML up to now [16,17]. We, therefore, report our single-center comparative evaluation of MSD versus UD versus HRD allo-HSCT for patients with AML aged ≥60 years.

MATERIALS AND METHODS

Selection Criteria

We included in this retrospective analysis all consecutive patients with the following inclusion criteria: (1) aged ≥60 years; (2) diagnosis of AML; (3) first allo-HSCT at Paoli Calmettes Institute (Marseille, France) between 2011 and 2016; and (4) allo-HSCT from MSD, UD (9 or 10 of 10 using high-level HLA matching based on HLA-A, -B, -C, -DR, and -DQ loci), or HRD.

Conditioning Regimens

Different conditioning regimens were used during the inclusion period. According to the European Society for Blood and Marrow Transplantation classification, the conditioning regimens were categorized as follows: (1) nonmyeloablative conditioning (NMAC) (low-dose total body irradiation [TBI]); (2) reduced-intensity conditioning (RIC) (intravenous busulfan [Bu] total dose ≤260 mg/m^2); and (3) myeloablative conditioning (MAC) (intravenous Bu total dose >260 mg/m^2). For patients in the HRD group, NMAC involved a combination of fludarabine (Flu) (150 mg/m^2), cyclophosphamide (Cy) (29 mg/m^2), and 2 Gy TBI (Cy-Flu-TBI), as previously described [12]. RIC regimens for the HRD group were based on Flu (120 to 160 mg/m^2) and Bu (260 mg/m^2) with the addition of either cyclophosphamide (29 mg/m^2, Cy-Flu-Bu) in an initial phase or thiotepa (TT) (5 mg/kg, TT-Flu-Bu) later on. The NMAC treatment regimen for patients in the MSD and UD groups involved a combination of Flu (90 mg/m^2) and 2 Gy TBI (Flu-TBI), whereas RIC or MAC regimens were based on the combination of Flu (150 mg/m^2) and Bu (260 to 520 mg/m^2) (Flu-Bu). GVHD prophylaxis was based on PT-Cy (50 mg/kg on days +3 and +4) in the HRD group while antithymocyte globulins (ATG) (Thymoglobulin rabbit ATG at the total dose of 5 mg/kg) was used in the MSD and UD groups.

Statistical Analyses

We used Glucksberg and National Institutes of Health classifications to classify acute and chronic GVHD, respectively [18,19]. Cumulative incidences were calculated considering the presence of competing risks. For these calculations, death from any cause was considered a competing event for GVHD, and relapse and nonrelapse mortality (NRM) were considered mutually competing events. Progression-free survival (PFS), overall survival (OS), and GVHD- and relapse-free survival (GRFS) were estimated using the Kaplan-Meier method. We, in addition to others, have previously reported that such a composite endpoint is relevant to evaluate the overall outcome of allo-HSCT, including a quality-of-life assessment [20,21]. In this study, relapse, death from any cause, grade 3 to 4 acute GVHD, and moderate or severe chronic GVHD were considered as relevant events for the calculation of GRFS [21]. The Fine-Gray and log-rank tests were used for univariate comparisons of cumulative incidence and survival, respectively. In addition, the impact of donor type was assessed using the multivariate Cox regression model, including age (continuous variable), cytogenetics (favorable and intermediate versus unfavorable), conditioning regimen (NMAC versus RIC versus MAC), hematopoietic cell transplantation-comorbidity index (<3 versus ≥3), and disease status at the time of allo-HSCT (complete remission [CR] versus no CR). A P value of <.05 was considered to be statistically significant. Statistics were computed with R version 3.3.2 software (R Project for Statistical Computing, Vienna, Austria).

RESULTS

Patient and Transplantation Characteristics

We retrospectively analyzed 94 consecutive patients divided into 3 donor groups (MSD group: n = 31; UD group: n = 30, including 3 patients with 9/10 HLA matching [mismatch A: n = 1, mismatch B: n = 2]; and HRD group: n = 33; Table 1). The median age of the patients was 65 (range, 60 to 73) years. Although most patients underwent allo-HSCT for AML in CR (n = 70, 85%), the HRD group included a significantly higher proportion of patients with more advanced diseases (refractory AML at the time of allo-HSCT: MSD versus UD versus HRD, 13% versus 7% versus 24%, respectively; P = .037). A total of 52 (61%) patients had hematopoietic cell transplantation-comorbidity index ≥3 and 30 (28%) had

Table 1
Patient and Transplantation Characteristic

	All patients		MSD		UD*		HRD		*P*
	n	%	n	%	n	%	n	%	
n	94		31		30		33		
Age									.136
60-64 yr	46	49	19	61	15	50	12	36	
≥65 yr	48	51	12	39	15	50	21	64	
AML status at allo-HSCT									.037
CR1	66	70	21	68	27	90	18	55	
CR2	14	15	6	19	1	3	7	21	
No CR	14	15	4	13	2	7	8	24	
Cytogenetics									.131
Favorable	5	5	2	6	3	10	0	0	
Intermediate	61	65	23	74	15	50	23	70	
Unfavorable	28	30	8	26	13	43	7	21	
HCT-CI									.218
<3	33	39	13	48	12	43	8	27	
≥3	52	61	14	52	16	57	22	73	
Not available	9		4		2		3		
Conditioning intensity									.007
NMAC	13	14	4	13	0	0	9	27	
RIC	71	76	22	71	25	83	24	73	
MAC	10	11	5	16	5	17	0	0	

HCT-CI indicates hematopoietic cell transplantation comorbidity index.
* 3 patients of the UD group received 9/10 HLA-matched allo-HSCT.