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Similar Overall Survival Using Sibling, Unrelated Donor, and Cord Blood Grafts after Reduced-Intensity Conditioning for Older Patients with Acute Myelogenous Leukemia

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A B S T R A C T

For older patients with acute myeloid leukemia (AML), allogeneic hematopoietic cell transplantation (HCT) provides the best chance of long-term survival. A formal comparison between matched sibling (SIB), unrelated donor (URD), or umbilical cord blood (UCB) transplantation has not yet been reported in this setting. We compared reduced-intensity conditioning HCT in 197 consecutive patients 50 years and older with AML in complete remission from SIB (n = 82), URD (n = 35), or UCB (n = 80) transplantation. The 3-year cumulative incidences of transplantation-related mortality were 18%, 14%, and 24% with SIB, URD, and UCB transplantation, respectively ($P = .22$). The 3-year leukemia-free survival rates were 48%, 57%, and 33% with SIB, URD, and UCB transplantation, respectively ($P = .009$). In multivariate analysis, poor-risk cytogenetics was associated with relapse (hazard ratio, 1.7 [95% confidence interval, 1.0 to 3.0]; $P = .04$) and worse leukemia-free survival (hazard ratio, 1.6 [95% confidence interval, 1.0 to 2.5]; $P = .03$), whereas donor choice had no significant impact on overall survival ($P = .73$). Adjusted 3-year overall survival rates were 55% with SIB, 45% with URD, and 43% with UCB transplantation ($P = .26$). Until prospective studies are completed, this study supports the recommendation to consider SIB donor, URD, or UCB for HCT for older patients with AML in complete remission.

INTRODUCTION

Acute myeloid leukemia (AML) occurs frequently in older patients, with an overall poor prognosis [1]. Despite the potential benefit of intensified postremission treatments developed in younger adult AML protocols, this does not benefit the older population [2]. For the older AML patient, allogeneic hematopoietic cell transplantation (HCT) likely provides the best chance of long-term survival [3,4]. HCT is uncommonly used in this population, however, because of the perceived higher risks of transplantation complications, especially using unrelated donors (URDs) or umbilical cord blood (UCB) donors [5]. A large analysis reported comparable outcomes of HCT using reduced-intensity conditioning (RIC) regimens using related donors or URDs among older patients with AML and myelodysplastic syndrome, indicating that age per se is not a contraindication to HCT [6].

Because older patients less often have available healthy HLA identical matched sibling (SIB) donors, alternative donors may broaden access to HCT. Unrelated umbilical cord blood (UCB) has been increasingly accepted as an alternative donor source for patients without an available SIB or URD [7-10]. The feasibility of UCB HCT for older patients with AML or myelodysplastic syndrome has been suggested [11-13], yet a formal comparison of these 3 graft options for older patients with AML has not been reported. We present comparative outcomes of reduced-intensity conditioning (RIC) HCT for AML patients over age 50 years in complete remission (CR) using SIB donors, URDs, or UCB donors.

METHODS

Study Population

From January 2000 to December 2010, 197 consecutive patients with AML in complete remission age 50 years or more (median age, 59; range, 50 to 74) received RIC and allogeneic HCT in 3 institutions (University of Minnesota, Hospital Saint Louis Paris, and University Hospital of Nantes) either from SIB donors (n = 82), URDs (n = 35), or UCB (n = 80). Disease risks were defined as favorable, intermediate, or poor for AML [14]. Karnofsky performance status was recorded before HCT. All patients were treated on protocols approved by the institutional review board of each hospital. Informed consent was obtained in accordance with the Declaration of Helsinki.

Data were collected prospectively, as Hospital Saint Louis Paris and University Hospital of Nantes belong to the European Group for Blood and Marrow Transplantation (EBMT) and sharing ProMISe (Project Manager Internet Server), which is the central data management system used by the EBMT. Both centers prospectively enter patient information and retrieve data directly over a secure Internet connection. At the University of Minnesota, data on all patients undergoing transplantation are prospectively collected in the institutional bone marrow transplantation research

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Table 1
Patient Characteristics According to Type of Donor

Variable	SIB	URD	UCB	*P Value*
No. of patients	82	35	80	
Age at transplantation, median (range), yr	58 (50-74)	59 (50-74)	59 (50-71)	.89
50-59 median (%)	52 (63)	18 (51)	44 (55)	
60-75 median (%)	30 (37)	17 (49)	36 (45)	
Male gender, no. (%)	47 (57)	19 (54)	44 (55)	.95
Karnofsky score before transplant, no. (%)				.043
<90%	8 (10)	1 (3)	15 (19)	
90%-100%	68 (83)	31 (89)	59 (74)	
Not reported	6 (7)	3 (9)	6 (8)	
Cytogenetic risk group, no. (%)				.099
Good	4 (5)	4 (11)	3 (4)	
Intermediate	52 (63)	23 (66)	39 (49)	
Poor	18 (22)	6 (17)	27 (34)	
Unknown	8 (10)	2 (6)	11 (14)	
Disease status at transplant, no. (%)				.26
CR1	59 (72)	26 (74)	49 (61)	
CR ≥ 2	23 (28)	9 (26)	31 (39)	
Interval from diagnosis to HCT, median (range), mo	6 (3-72)	7 (4-58)	6 (2-70)	.22
Less than 6 mo N (%)	40 (49)	10 (29)	42 (52)	
6-12 mo N (%)	24 (29)	17 (49)	11 (14)	
More than 12 mo N (%)	18 (22)	8 (23)	27 (34)	
Median (range) for CR1 patients, mo	5 (3-9)	6 (4-9)	4 (2-24)	<.0001
Median (range) for CR ≥2 patients, mo	25 (6-72)	21 (7-58)	21 (4-70)	.78
Donor/recipient gender matching, no. (%)				.0001
Female/female	20 (24)	7 (20)	14 (18)	
Female/male	16 (20)	6 (17)	35 (44)	
Male/female	15 (18)	8 (23)	22 (28)	
Male/male	31 (38)	13 (37)	9 (11)	
Unknown	0 (0)	1 (3)	0 (0)	
Donor/recipient cytomegalovirus serostatus, no. (%)				<.0001
Negative/negative	15 (18)	11 (31)	31 (39)	
Negative/positive	15 (18)	4 (11)	46 (57)	
Positive/negative	10 (12)	5 (14)	0 (0)	
Positive/positive	31 (38)	7 (20)	0 (0)	
Unknown	11 (13)	8 (23)	3 (4)	
Conditioning regimen, no. (%)				<.0001
FLU/TBI ± other	20 (24)	4 (11)	80 (100)	
BU/FLU	35 (43)	25 (71)	0 (0)	
CY/TBI	23 (28)	1 (3)	0 (0)	
Other	3 (4)	4 (11)	0 (0)	
Unknown	1 (1)	1 (3)	0 (0)	
ATG, no. (%)	25 (30)	30 (86)	23 (29)	<.0001
GVHD prophylaxis, no. (%)				<.0001
CsA ± CS or MTX	23 (28)	15 (43)	1 (1)	
CsA + MMF ± other	59 (72)	19 (54)	77 (96)	
Other	0 (0)	0 (0)	1 (1)	
Unknown	0 (0)	1 (3)	1 (1)	
Graft composition				
Total nucleated cells, median (IQR) × 10^8/kg	10 (8-14)	11 (7-12)	.4 (.3-.4)	<.0001
$CD34^+$ cells, median (IQR) × 10^6/kg	6 (5-8)	8 (6-10)	.5 (.4-.7)	<.0001
Yr of transplantation, no. (%)				.002
2000-2005	26 (32)	1 (3)	25 (31)	
2006-2010	56 (68)	34 (97)	55 (69)	
Center, no. (%)				<.0001
University of Minnesota	31 (38)	3 (9)	74 (92)	
University Hospital of Nantes	21 (26)	18 (51)	5 (6)	
Hospital Saint Louis Paris	30 (37)	14 (40)	1 (1)	

FLU indicates fludarabine; BU, busulfan; CY, cyclophosphamide; CsA, cyclosporine; CS, corticosteroids; MTX, methotrexate; MMF, mycophenolate mofetil; IQR, interquartile range.

database. Data on consecutive eligible patients from all 3 sites were retrieved and merged for this combined analysis.

HLA Typing, Matching, and Donor Selection Policy

All related donors were HLA-matched SIBs based on family studies. Histocompatibility testing and selection of URDs are described in detail elsewhere [15]. Recipients and URDs were defined as matched ("8/8") if HLA-A, -C, -B, and -DRB1 were identical at the molecular level. All URDs but 1 (7/8) were 8/8 allele matched. SIBs and URDs all received filgrastim-mobilized peripheral blood grafts. UCB units were required to be matched at greater than 4 of 6 HLA antigens based on antigen-level HLA-A and -B typing and allele-level HLA-DRB1 typing. Matching at HLA-C, -DQ, and -DP was not considered.

Over the duration of the study, UCB units were required to have a minimum cryopreserved total nucleated cell dose of 2.0×10^7/kg. The target cell dose was greater than or equal to 3.0×10^7 total nucleated cells/kg, however, resulting in the selection of a second partially HLA-matched UCB unit if available. In those for whom a second UCB unit could be identified, the second unit also had a minimum of 4 of 6 antigens matched with the first unit [10,16]. Seventy UCB HCT recipients (88%) received 2 UCB units, and 75 (94%) received at least 1 to 2 HLA-mismatched units. In the absence of a matched SIB donor, UCB grafts were the first-choice option for the Minnesota group based on experience and research priorities. In the same