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Allogeneic Hematopoietic Cell Transplantation Outcomes in Acute Myeloid Leukemia: Similar Outcomes Regardless of Donor Type

Erica D. Warlick [1,*], Regis Peffault de Latour [2,3], Ryan Shanley [4], Marie Robin [2], Nelli Bejanyan [1], Alienor Xhaard [2], Claudio Brunstein [1], Flore Sicre de Fontbrune [2], Celalettin Ustun [1], Daniel J. Weisdorf [1], Gerard Socie [2,5,6]

[1] *Blood and Marrow Transplant Program, Division of Hematology, Oncology, and Transplantation, University of Minnesota, Minneapolis, Minnesota*
[2] *Service d'Hematologie Greffe, Hôpital Saint-Louis, AP-HP, Paris, France*
[3] *Equipe d'accueil 3518, Hôpital Saint-Lou11is, AP-HP, Paris, France*
[4] *Biostatistics Core, Masonic Cancer Center, University of Minnesota, Minneapolis, Minnesota*
[5] *INSERM (Institut national de la santé et de la recherche médicale), UMR1160 (Unité mixte de recherche 1160 - Alloimmunité - Autoimmunité – Transplantation), Hôpital Saint- Louis, AP-HP, Paris, France*
[6] *Université Paris VII Diderot, Paris, France*

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A B S T R A C T

The use of alternative donor transplants is increasing as the transplantation-eligible population ages and sibling donors are less available. We evaluated the impact of donor source on transplantation outcomes for adults with acute myeloid leukemia undergoing myeloablative (MA) or reduced-intensity conditioning (RIC) transplantation. Between January 2000 and December 2010, 414 consecutive adult patients with acute myeloid leukemia in remission received MA or RIC allogeneic transplantation from either a matched related donor (n = 187), unrelated donor (n = 76), or umbilical cord blood donor (n = 151) at the University of Minnesota or Hôpital St. Louis in Paris. We noted similar 6-year overall survival across donor types: matched related donor, 47% (95% confidence interval [CI], 39% to 54%); umbilical cord blood, 36% (95% CI, 28% to 44%); matched unrelated donor, 54% (95% CI, 40% to 66%); and mismatched unrelated donor, 51% (95% CI, 28% to 70%) ($P < .11$). Survival differed based on conditioning intensity and age, with 6-year survival of 57% (95% CI, 47% to 65%), 39% (95% CI, 28% to 49%), 23% (95% CI, 6% to 47%), 47% (95% CI, 36% to 57%), and 28% (95% CI, 17% to 41%) for MA age 18 to 39, MA age 40+, or RIC ages 18 to 39, 40 to 56, and 57 to 74, respectively ($P < .01$). Relapse was increased with RIC and lowest in younger patients receiving MA conditioning (hazard ratio, 1.0 versus 2.5 or above for all RIC age cohorts), $P < .01$. Transplantation-related mortality was similar across donor types. In summary, our data support the use of alternative donors as a graft source with MA or RIC for patients with acute myeloid leukemia when a sibling donor is unavailable.

INTRODUCTION

Allogeneic hematopoietic cell transplantation (HCT) remains the only therapy that can provide extended disease-free survival (DFS) for the majority of patients with acute myeloid leukemia (AML) [1-3] However, post-transplantation disease relapse remains a major therapeutic challenge. Efforts to identify patient, disease, and transplantation features playing a role in post-HCT relapse risk continue, with numerous reports documenting the role of cytogenetic risk, conditioning intensity, age, and disease status in transplantation outcomes for AML [4-11].

We analyzed the outcome of a large population of AML patients who underwent transplantation at 2 large centers, the University of Minnesota and Hôpital Saint Louis in Paris. We report the impact of specific patient, disease, and transplantation variables on clinical outcomes in cohorts receiving similar myeloablative (MA) and reduced-intensity conditioning (RIC) regimens. Our data highlight the interactions of age, conditioning intensity, and donor source on post-transplantation outcomes and support the use of alternative donors when a sibling donor is not available.

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* Correspondence and reprint requests: Erica D. Warlick, MD, Division of Hematology, Oncology and Transplantation, University of Minnesota, 20 Delaware Street SE, Minneapolis, MN 55455.
E-mail address: ewarlick@umn.edu (E.D. Warlick).

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METHODS

Study Population

Between January 2000 and December 2010, 414 consecutive adult patients with AML in remission complete remission [CR 1, CR 2, or C3] received MA or RIC allogeneic HCT from either an HLA-identical matched related donor (MRD) (n = 187), unrelated donor (URD) (n = 76), or umbilical cord blood (UCB) donor (n = 151). Patients receiving more than 1 transplant for AML, those with French American British subtype M3, and those in relapse or with primary induction failure were excluded.

Risk Stratification

Patients were risk stratified based on disease status at transplantation (CR 1, CR 2, or CR 3) and by cytogenetic risk. Cytogenetic classification was limited by the differential availability of specific details between the 2 databases. The Paris data was available in ProMISe (Project Manager Internet Server) and the European Group for Blood and Marrow Transplantation Web shared data base, in the following format: normal or abnormal chromosomes, presence or absence of complex karyotype, presence or absence of molecular markers with partial reporting of which molecular marker (NPM-1 [nucleophosmin 1], FLT-3 [FMS-like tyroisube kinase-3], BCR-ABL [breakpoint cluster region-ABL1 fusion], WT-1 [Wilms Tumor 1], MLL [Mixed lineage leukemia with 11q23 abnormality, AML-ETO]) was present. The availability of this data was confounded by the time period of the study since 2000. Complete cytogenetic data were available for the majority of University of Minnesota cases and FLT-3 or NMP-1 molecular data was available in more recent years. Merging these 2 data sets, we classified risk using cytogenetic and molecular risk data as follows: *standard risk* included normal karyotype, favorable abnormalities including t(8;21) or inversion 16, CEBPA mutation, or NPM-1 mutation in the absence of FLT-3 ITD; *poor risk* included complex karyotype, monosomy 7, monosomy 5, monosomal karyotype, BCR-ABL, FLT-3 ITD, MLL (11q23), or all other known high-risk abnormalities; *abnormal* and *uncertain* significance included cases where an abnormality was documented without specifics or an abnormality of uncertain clinical significance was present (examples include CBF (core binding factor) + c-KIT (protooncogene encoding the tyrosine kinase KIT) +WT-1 or NPM-1 + WT-1).

HLA Typing, Matching, and Donor Selection

HLA-identical MRD were primarily siblings based on family testing. URDs were defined as matched (8/8) if HLA-A, -C,-B, and-DRB1 were identical at the allele level [12]. Stem cells were harvested for sibling or URDs via marrow harvest (n = 74) or filgrastim-mobilized peripheral blood (n = 189). UCB unit nucleated cell dose and matching have been described elsewhere [13]; however, in brief they were required to have a minimum of 4/6 antigen match between each cord and the recipient. In the absence of a sibling donor, UCB was the graft choice of preference for the University of Minnesota based on research priorities, whereas Hôpital Saint-Louis utilized URDs in this situation. Preparative regimens were classified as either MA or RIC by established Center for International Blood and Marrow Transplant Research functional definitions [14-16].

Treatment

Patients received either MA or RIC conditioning. MA conditioning from Paris included 120 mg/kg cyclophosphamide (60 mg/kg, on each of 2 consecutive days) and busulfan (3.2 mg/kg i.v. daily on 4 consecutive days), or 12 Gy total body irradiation (TBI) in a fractionated regimen. For the University of Minnesota, the MA regimen for MRD and URD was cyclophosphomide (60 mg/kg × day −6 and −5) plus TBI (165 cGy twice daily for 8 fractions on days −4 through −1). UCB MA conditioning consisted of fludarabine (25 mg/m^2 daily on days −8 through −6), cyclophosphamide (60 mg/kg i.v. daily on days −7 and −6), and TBI (165 cGy twice daily for 8 fractions on days −4 through −1). RIC at the Hôpital Saint-Louis consisted predominantly of fludarabine (30 mg/m^2 i.v. daily from days −5 through −1), busulfan (3.2 mg/kg i.v. twice daily on days −4 and −3) plus rabbit antithymocyte globulin (ATG; 5 mg/kg for siblings and 10 mg/kg for URDs on days −2 and −1). The University of Minnesota RIC regimen consisted of cyclophosphamide (50 mg/kg on day −6), fludarabine (30 to 40 mg/m^2 i.v. daily on days −6 through −2), and TBI (200 cGy on day −1) for all donor sources. Equine ATG (15 mg/kg twice daily for 6 doses from day −6 through day −4) in the setting of RIC was used for those URDs who had only 1 cycle of multiagent chemotherapy within 3 months or for related donors with only 1 cycle of multiagent chemotherapy within 6 months before HCT. Graft-versus-host disease (GVHD) prophylaxis included cyclosporine (day −3 through +100 to 180) plus mycophenolate mofetil (days −3 to +30) (56%) or cyclosporine plus methotrexate (40%).

Supportive care was similar in both institutions. Patients were hospitalized in single rooms utilizing high efficiency air filtration systems. Patients received prophylactic acyclovir for herpes simplex virus or cytomegalovirus prophylaxis plus antibacterial prophylaxis until day +21 or longer if on prednisone for GVHD; fungal prophylaxis with either fluconazole or voriconazole for 100 days; and pneumocystis juroveci prophylaxis typically with trimethoprim sulfamethoxazole for 1 year.

Data Collection

All patients were treated on protocols approved by the institutional review board of each hospital with prior informed consent for treatment and data analysis.

Data were prospectively collected. Data from Hôpital Saint-Louis in Paris was retrieved through the European Group for Blood and Marrow Transplantation and data from the University of Minnesota were prospectively collected in the institutional blood and marrow transplantation database. Data were merged for the combined analysis.

Statistical Analysis

The primary endpoint was overall survival (OS). Secondary endpoints included hematopoietic recovery, occurrence of acute GVHD and chronic GVHD, transplantation-related mortality (TRM), incidence of relapse, and DFS. *OS* was defined as time to death from any cause and a 6-year time point was used because of the availability of extended follow-up. *Hematopoietic recovery* was defined as time to absolute neutrophil count (ANC) $\geq$ 500 neutrophils/μL for 3 consecutive days. Incidence and grade of acute GVHD (aGVHD) at day +100 and absence or presence of chronic GVHD (cGVHD) at 2 years were recorded based on consensus criteria [17,18]. *TRM* was defined as any death in the first 28 days after HCT or death after day 28 without evidence of relapsed leukemia. TRM results are reported at 1 year to capture later deaths due to transplantation-related toxicity. *Relapse* was defined as hematologic evidence of disease recurrence with those surviving without relapse censored at the date of last contact. Relapse was reported at 2 years as most post-transplantation relapses are evident within that time period. *DFS* was defined as survival without death or relapse censoring at the date of last contact.

Univariate probabilities of DFS and OS were calculated using the Kaplan-Meier estimator with variance estimated by Greenwood's formula [19]. Probabilities of aGVHD, cGVHD, TRM, and relapse were calculated using cumulative incidence curves to accommodate competing risks [20]. Ninety-five percent confidence intervals (CI) for all probabilities and *P* values of pair-wise comparisons were derived from point-wise estimates and calculated. Single variable comparisons were made using log-rank tests with standard weights.

Multivariable regression models were fit for each outcome: Cox regression [21] for OS and DFS, and Fine and Gray [22] competing risks regression for all other outcomes, reported as hazard ratios (HR). TRM was analyzed with a competing risk of relapse, and relapse, GVHD, and hematopoietic recovery were analyzed with a competing risk of mortality. All models were prespecified and included categorical factors for cytogenetic (standard, poor, abnormal but unknown significance), donor type (MRD, UCB, matched URD, mismatched URD), disease status (CR1, CR2, or CR3), and age and conditioning combinations (MA 18 to 39, MA 40 to 56, RIC 18 to 39, RIC 40 to 56, and RIC 57 to 74) because of their association. Subgroup analysis investigation showed no significant association between donor source and conditioning and, thus, was not included in final modeling. Treatment center had minimal influence; thus, was not included in the final models. SAS software (SAS Institute, Cary, NC) was used to perform statistical analyses.

RESULTS

Patient Characteristics

Patient characteristics (Table 1) were similar across donor types (MRD, UCB, URD) with respect to gender, Karnofsky performance status, and age. MRD had fewer cases with poor-risk cytogenetic/molecular profile compared with UCB or to matched and mismatched URD (38% versus 53%, 51%, and 52%, respectively). There were many MRD treated in CR1 (78% versus 58% in UCB, 73% in matched URD, and 48% in mismatched URD). UCB (64%) transplant recipients were more likely to receive RIC compared with MRD (40%) and compared with matched (25%) or mismatched URDs (10%). Those receiving URD stem cell sources were more likely to be exposed to ATG in their conditioning compared with MRD and UCB (45% to 48% matched and mismatched URD versus 11% MRD and 15% UCB). GVHD prophylaxis associated with conditioning intensity, with a higher percentage of cyclosporine/methotrexate in the MRD and URD cohorts.