Biol Blood Marrow Transplant 23 (2017) 648–653

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

ASBMT American Society for Blood and Marrow Transplantation

Clinical Research: Alternative Donors

T Cell–Replete Peripheral Blood Haploidentical Hematopoietic Cell Transplantation with Post-Transplantation Cyclophosphamide Results in Outcomes Similar to Transplantation from Traditionally Matched Donors in Active Disease Acute Myeloid Leukemia

Joan How, Michael Slade, Khoan Vu, John F. DiPersio, Peter Westervelt, Geoffrey L. Uy, Camille N. Abboud, Ravi Vij, Mark A. Schroeder, Todd A. Fehniger, Rizwan Romee *

BMT and Leukemia Program, Department of Medicine, Washington University School of Medicine, St. Louis, Missouri

Article history:
Received 26 October 2016
Accepted 8 January 2017

Keywords:
Acute myeloid leukemia
Active disease
Haploidentical transplantation

A B S T R A C T

Outcomes for patients with acute myeloid leukemia (AML) who fail to achieve complete remission remain poor. Hematopoietic cell transplantation (HCT) has been shown to induce long-term survival in AML patients with active disease. HCT is largely performed with HLA-matched unrelated or HLA-matched related donors. Recently, HCT with HLA-haploidentical related donors has been identified as a feasible option when HLA-matched donors are not immediately available. However, there are little data comparing outcomes for AML patients with active disease who receive haploidentical versus traditionally matched HCT. We retrospectively analyzed data from 99 AML patients with active disease undergoing allogeneic HCT at a single institution. Forty-three patients received unrelated donor HCT, 32 patients received matched related donor HCT, and 24 patients received peripheral blood haploidentical HCT with post-transplantation cyclophosphamide. We found no significant differences between treatment groups in terms of overall survival (OS), event-free survival, transplantation-related mortality, cumulative incidence of relapse, and cumulative incidence of acute and chronic graft-versus-host disease (GVHD). We performed univariate regression analysis of variables that modified OS in all patients and found only younger age at transplantation and development of chronic GVHD significantly improved outcome. Although limited by our relatively small sample size, these results indicate that haploidentical HCT in active AML patients have comparable outcomes to HCT with traditionally matched donors. Haploidentical HCT can be considered in this population of high-risk patients when matched donors are unavailable or when wait times for transplantation are unacceptably long.

INTRODUCTION

Acute myeloid leukemia (AML) is one of the most common hematologic malignancies in the nonpediatric patient population [1]. Allogeneic hematopoietic cell transplantation (HCT) is the most curative therapeutic option in patients who have been able to achieve complete remission (CR) after induction chemotherapy [2,3]. However, only around 50% of young and 39% of elderly AML patients in poor prognostic groups are able to achieve CR with current intensive induction regimens [4]. The prognosis of patients not achieving CR or who relapse and have minimal residual disease or active disease at the time of allogeneic HCT remains dismal, and it is negligible for all patients who cannot proceed to HCT. In previous reports, overall survival (OS) in active AML patients undergoing HLA-matched related or HLA-matched unrelated HCT has ranged from 20% to 30% [5-8]. Allogeneic HCT remains the best option for patients who otherwise fail to achieve remission because of refractory or relapsed disease [5].

Recently, HCT with HLA-haploidentical related donors has emerged as a viable option for transplantation, with outcomes comparable to those of traditionally matched donors [9-11]. The use of T cell–replete grafts with post-transplantation cyclophosphamide has largely circumvented the unacceptably high rates of graft failure and infection seen after T cell–depleted haploidentical HCT [12,13], and

Financial disclosure: See Acknowledgments on page 652.

* Correspondence and reprint requests: Rizwan Romee, MD, Division of Oncology, Washington University School of Medicine, 660 South Euclid Avenue, Campus Box 8007, St. Louis, MO 63110.
E-mail address: rromee@wustl.edu (R. Romee).

http://dx.doi.org/10.1016/j.bbmt.2017.01.068
1083-8791/

it has been adopted at our institution for all haploidentical HCTs. Haploidentical HCT remains an important source of alternative donors, as a substantial proportion of patients in need of HCT will not have an optimally matched donor [14]. This is especially true in minority populations, in which HLA matching of unrelated donors is particularly difficult [15].

There has been evidence to suggest that increasingly mismatched HCTs may be associated with an increased graft-versus-leukemia (GVL) effect, resulting in improved outcomes in patients with high-risk disease [16]. Previous studies have suggested lower rates of relapse in high-risk AML patients with the use of haploidentical HCT compared with the rates for matched unrelated or related HCT [17]. Comparative outcomes in active disease, however, remain unknown. We retrospectively analyzed outcomes from active disease AML patients who underwent unrelated donor, related donor, or haploidentical HCT. Although haploidentical HCT has been shown to be feasible in active AML patients, there are little data on how outcomes of haploidentical HCT compare with those of traditionally matched donor HCT [18].

MATERIALS AND METHODS

Study Population

All adult patients with active disease AML who underwent allogeneic HCT at Washington University Medical Center in St. Louis from 2012 to 2015 were included for analysis. *Active disease* was defined as ≥5% blasts in pretransplantation bone marrow, presence of extramedullary disease at time of transplantation, or persistent abnormal cytogenetic findings on chromosome analysis or fluorescent in situ hybridization. Patients were excluded if they had undergone prior allogeneic HCT. This study was approved by the institutional review board at Washington University School of Medicine, St. Louis.

Outcomes and Definitions

Study outcomes included OS, event-free survival (EFS), cumulative incidence of relapse, and cumulative incidence of acute and chronic graft-versus-host disease (GVHD). *OS* was defined as time from transplantation to time of death from any cause or last follow-up. *EFS* was defined as survival without relapse or death. *Treatment-related mortality* (TRM) was defined as any death before day +28 or any death while in continuous remission after day +28. *Neutrophil engraftment* was defined as the first day in which the absolute neutrophil count was ≥500 for 3 consecutive days. *Platelet engraftment* was defined as the first day in which the platelet count was ≥20 for 3 consecutive days without need for platelet transfusion. *Graft failure* was defined as failure of neutrophil engraftment after HCT (primary), or loss of donor chimerism after initial engraftment with ≥95% recipient cells at any time, not due to relapsed disease (secondary). *Relapse* in patients achieving CR after HCT was defined as presence of ≥5% blasts in bone marrow. *Cytomegalovirus (CMV) reactivation* was defined as presence of CMV DNA after at least 4 weeks of nondetectable levels during active surveillance [19]. Functional status and comorbidities were evaluated using the Karnofsky performance score and hematopoietic cell transplantation-comorbidity index (HCT-CI) [20]. Acute GVHD was graded according to International Bone Marrow Transplant Registry staging guidelines [21]. Chronic GVHD was graded according to National Institute of Health consensus criteria [22].

Statistical Analyses

Patient, disease, and transplantation characteristics were collected from the electronic medical records for all qualifying patients as discussed above. Death in remission was considered a competing risk event for cumulative incidence of relapse. Graft failure, relapse, or death were considered as competing risk events for cumulative incidence of acute and chronic GVHD. Continuous variables between groups were compared with Mann-Whitney *U*-testing. Dichotomous variables between groups were compared with chi-square testing or Fisher's exact test, when appropriate. Cumulative incidence was measured with the cumulative incidence function. Time-to-event functions were measured using Kaplan-Meier curves and the log-rank test. Univariate Cox proportional hazards regression analysis was used to determine patient and disease variables that modified OS, with chronic GVHD treated as a time-dependent variable.

RESULTS

Patient Characteristics

A total of 99 patients with active AML were included in the analysis. Forty-three patients received an unrelated donor HCT, of which 6 had 1 HLA mismatch at the HLA-A, -B, -C, -DRB1, or -DQB1 locus (partially mismatched), and 2 had 2 HLA mismatches at the HLA-A, -B, -C, -DRB1, or -DQB1 locus (mismatched). Thirty-two patients received a matched related donor HCT. Twenty-four patients received haploidentical HCT. Seventy-five percent of the HLA-haploidentical related donors were mismatched at 5 HLA alleles (HLA-A, -B, -C, -DRB1, -DQB1) in both the graft-versus-host and host-versus-graft directions. Active disease as defined by ≥5% blasts in pretransplantation bone marrow was present in 78% of patients, while active disease as defined by persistent cytogenetics or extramedullary disease was present in 20% and 2% of all patients, respectively. There were no significant differences between groups in distribution of active disease types ($P = .88$). Median follow-up of survivors was 18 months.

Patient and disease characteristics are displayed in Table 1. There were no significant differences in patient and disease characteristics between groups. The median ages of active AML patients receiving unrelated donor, related donor, and

Table 1
Patient and Disease Characteristics

Characteristic	UD	RD	Haplo	*P* Value
n	43	32	24	
Age, yr				.09
Median	55	60	54	
Range	23-73	32-72	21-73	
Karnofsky performance status				.85
100	0 (0)	2 (6)	2 (8)	
90	12 (28)	9 (28)	6 (25)	
80	18 (42)	14 (44)	9 (38)	
<70	13 (30)	7 (22)	7 (29)	
HCT-CI risk				.70
0	5 (12)	4 (13)	1 (4)	
1-2	5 (12)	5 (16)	2 (8)	
≥3	33 (77)	23 (72)	21 (88)	
ELN risk				.83
High	17 (40)	13 (41)	12 (50)	
Intermediate	24 (56)	17 (53)	10 (42)	
Low	2 (4)	2 (6)	2 (8)	
Disease etiology				.27
De novo	22 (51)	20 (63)	17 (71)	
Secondary	21 (49)	12 (38)	7 (29)	
Disease status at transplantation				.99
Primary induction failure	22 (51)	18 (56)	12 (50)	
Relapse refractory	21 (49)	14 (44)	12 (50)	
Active disease subtype				.88
Morphology	37 (86)	24 (75)	20 (83)	
Cytogenetics	6 (15)	6 (18)	4 (17)	
Extramedullary disease	0 (0)	2 (6)	0 (0)	
Median relapse to transplantation, mo	4	2	6	.24
Median duration of CR1, mo	4	3	5	.34
Median pretransplantation blast in BM, %	18 (0-72)	9 (0-87)	19.5 (0-84)	.13
Median pretransplantation blast in blood,%	5 (0-32)	4 (0-72)	7 (0-60)	.87

Data presented are n (%) unless otherwise indicated.
UD indicates unrelated donor; RD, related donor; Haplo, haploidentical; ELN, European LeukemiaNet; BM, bone marrow.