Haploidentical Transplantation with Post-Transplantation Cyclophosphamide for High-Risk Acute Lymphoblastic Leukemia

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Samer A. Srour [1,2], Denái R. Milton [3], Asad Bashey [4], Amado Karduss-Urueta [5],
Monzr M. Al Malki [6], Rizwan Romee [7], Scott Solomon [3], Auayporn Nademanee [6], Stacey Brown [4],
Michael Slade [7], Rosendo Perez [5], Gabriela Rondon [1], Stephan J. Forman [6], Richard E. Champlin [1],
Partow Kebriaei [1], Stefan O. Ciurea [1,*]

[1] Department of Stem Cell Transplantation and Cellular Therapy, The University of Texas MD Anderson Cancer Center, Houston, Texas
[2] Department of Medicine, Baylor College of Medicine, Houston, TX
[3] Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, Texas
[4] BMT and Acute Leukemia Program at Northside Hospital, Blood and Marrow Transplant Group of Georgia, Atlanta, Georgia
[5] Bone Marrow Transplant Program, Instituto de Cancerologia-Clinica Las Americas, Medellin, Colombia
[6] Department of Hematology and HCT, City of Hope National Medical Center, Duarte, California
[7] Division of Oncology, Washington University School of Medicine, St. Louis, Missouri

A B S T R A C T

Haploidentical transplantation performed with post-transplantation cyclophosphamide (PTCy)–based graft-versus-host disease (GVHD) prophylaxis has been associated with favorable outcomes for patients with acute myeloid leukemia and lymphomas. However, it remains unclear if such approach is effective for patients with acute lymphoblastic leukemia (ALL). We analyzed outcomes of 109 consecutively treated ALL patients 18 years of age and older at 5 institutions. The median age was 32 years and the median follow-up for survivors was 13 months. Thirty-two patients were in first complete remission (CR1), while the rest were beyond CR1. Neutrophil engraftment occurred in 95% of the patients. The cumulative incidences of grades II to IV and III and IV acute GVHD at day 100 after transplantation were 32% and 11%, respectively, whereas chronic GVHD, nonrelapse mortality, relapse rate, and disease-free survival (DFS) at 1 year after transplantation were 32%, 21%, 27%, and 51%, respectively. Patients in CR1 had 52% DFS at 3 years. These results suggest that haploidentical transplants performed with PTCy-based GVHD prophylaxis provide a very suitable alternative to HLA-matched transplantations for patients with ALL.

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INTRODUCTION

Acute lymphoblastic leukemia (ALL) has an age-adjusted incidence rate of 1.73 per 100,000 person-years in United States with a median age of 14 years [1]. Approximately 6590 new cases and 1430 deaths are estimated for 2016 [2]. There have been notable improvements in cure rates of childhood ALL over past several decades, with 5-year overall survival (OS) rates exceeding 80% in children; 5-year survival is approximately 40% among adults [1,3,4]. However, over 60% of adults will relapse [5,6]; these patients usually have poor long-term outcomes with median OS of <10 months [7,8].

There has been contradictory evidence about the role of frontline allogeneic hematopoietic stem cell transplantation (ASCT) for patients in first complete remission (CR1) [9]. Two recent meta-analyses showed potential benefit [10,11]. In contrast, for patients with relapsed/refractory ALL, ASCT remains the only potential cure [6,7,12,13]. Gokbuget et al. reported outcomes of 547 ALL patients in first relapse where the 3-year OS was 38% for patients who underwent ASCT, while none of the nontransplantation patients survived beyond 1 year [7].

The preferred donor for transplantation is an HLA-matched sibling (MSD), while a matched unrelated donor (MUD) is considered a suitable alternative [12]. However, MUD availability varies widely with recipient's race [14]. Recently, haploidentical donors have emerged as an important alternative donor source because of the use of post-transplantation cyclophosphamide (PTCy) for prevention of graft-versus-

host disease (GVHD) [15,16]. Several recent disease-specific studies showed favorable outcomes for patients with acute myeloid leukemia and lymphoma using PTCy GVHD prophylaxis [17,18], but it remains unclear if patients with ALL would benefit from this approach as well. In a large cancer registry database study, Ruggeri et al. showed no significant differences in ALL outcomes between cord transplantation and haploidentical donor alternatives [19]. However, in this study, different GVHD prophylaxis regimens were used and not limited to those that were PTCy-based. We seek from this report to present the largest multicenter observational study in adult ALL patients assessing the feasibility and efficacy of haploidentical stem cell transplantation (HSCT) with PTCy GVHD prophylaxis.

METHODS

Between October 2005 and November 2015, 124 consecutive patients with ALL underwent HSCT with PTCy at 5 centers; 4 in the United States (MD Anderson Cancer Center, Houston, TX; City of Hope National Medical Center, Duarte, CA; Washington University School of Medicine, St. Louis, MO; Northside Hospital, Atlanta, GA) and 1 in Colombia (Instituto de Cancerologia, Medellin, Colombia). Patients have been followed through June 2016. Pediatric patients (ages <18 years) were excluded from this study (n = 15 patients) and patients who had a haploidentical transplantation as a second HSCT (n = 13) were analyzed separately. The institutional review board from each institution approved this study.

The primary endpoint was disease-free survival (DFS). Secondary endpoints included OS, cumulative incidence (CI) of nonrelapse mortality (NRM), relapse, acute GVHD (aGVHD), and chronic GVHD (cGVHD). *Minimal residual disease* (MRD) was defined as any evidence of detectable disease by cytogenetics, flow cytometry, and/or PCR for patients in morphologic remission at transplantation; PCR was performed for the clonal immunoglobulin gene and/or T cell receptor gene rearrangements. aGVHD and cGVHD were graded according to standard criteria [20,21].

Statistical Methods

DFS was computed from date of transplantation to date of disease progression or death (if the patient died without disease progression) or the last evaluation date. Patients who were alive and did not experience progression of disease at the last follow-up date were censored. OS was computed from date of transplantation to last known vital sign. Patients alive at the last follow-up date were censored. The Kaplan-Meier method was used to estimate OS and DFS. Differences in DFS between groups were assessed using the log-rank test. The association between DFS and patient subgroups was determined using Cox proportional hazards regression models. The cutoff *P* value used to include univariate risk factors in multivariate analyses was <.10. The CI of NRM, relapse, and GVHD were determined using the competing risks method. The competing risk for NRM included relapse, and for the CI for relapse, it included death; patients who were still alive at the last follow-up date were censored. For GVHD, the competing risks included relapse and death, while those patients who did not experience GVHD, did not relapse, and were still alive at the last follow-up date were censored. All statistical analyses were performed using SAS 9.3 for Windows (SAS Institute Inc., Cary, NC). All statistical tests used a significance level of 5%. No adjustments for multiple testing were made.

RESULTS

Patient, disease, and transplantation characteristics are summarized in Table 1. Among the 109 patients included in the study, 96 patients had their first transplantation, while 13 patients had an HSCT as a second transplantation. The majority of patients (79%) had B cell ALL. Median age at transplantation was 31.9 years (range, 18.2 to 66.4). Median time from diagnosis to transplantation was 16.7 months (range, 2.6 to 161.1), with 32 patients (29%) having their transplantation in CR1, 36 (33%) were in CR2, and 41 (38%) were beyond CR2 or had primary refractory disease. Details about stem cell source and conditioning regimens are listed in Table 1. Myeloablative conditioning was used in 70 patients (64%). All patients received PTCy (50 mg/kg on day +3 and day +4) for GVHD prophylaxis, along with mycophenolate

Table 1
Patient, Transplantation, and Disease Characteristics

Measure	All Patients (N = 109)
Gender, n	
Male	64 (59)
Female	45 (41)
Age category, yr	
18-34	60 (55)
35-49	28 (26)
≥50	21 (19)
Ethnicity	
White	56 (52)
Hispanic	28 (26)
Black	15 (14)
Asian	8 (7)
ALL subtype	
B cell ALL	86 (79)
T cell ALL	23 (21)
Philadelphia chromosome (B cell ALL patients only)	
Negative	46 (71)
Positive	19 (29)
Cytogenetic risk*	
Poor	26 (40)
Not poor	39 (60)
Response before transplantation	
CR 1	32 (29)
CR 2	36 (33)
Other (PIF: n = 9; second transplantation: n = 13)	41 (38)
MRD (CR 1 and CR 2 patients only)	
Yes	14 (26)
No	40 (74)
WBC at presentation for B cell ALL	
≤30	38 (68)
>30	18 (32)
WBC at presentation for T cell ALL	
≤100	9 (60)
>100	6 (40)
Hematopoietic cell transplantation-comorbidity index	
0-1	56 (52)
2-3	32 (30)
>3	19 (18)
Cell source	
PB	59 (54)
BM	50 (46)
Donor relation	
Child	19 (17)
Parent	37 (34)
Sibling	53 (49)
Extramedullary disease	
Yes	17 (16)
No	91 (84)
Nonmyeloablative regimen	
Yes	39 (36)
No	70 (64)
Preparative regimen	
Melphalan-based	40 (37)
Flu/Cy/TBI	32 (29)
Busulfan-based	9 (8)
TBI-based	25 (23)
Other	3 (3)

Data presented are n (%) unless otherwise indicated. Because of missing data for some covariates, numbers don't add up for a total of 109 patients in all subgroups.
PIF indicates primary induction failure; PB, peripheral blood; BM, bone marrow; Flu/Cy/TBI, fludarabine/cyclophosphamide/total body irradiation; TBI, total body irradiation.
  * Alvarnas JC, Brown PA, Aoun P, et al. Acute Lymphoblastic Leukemia, Version 2.2015. *J Natl Compr Canc Netw.* 2015;13:1240-1279.

mofetil (100%) and tacrolimus (79%) or cyclosporine. Thirty-one (28%) of the patients experienced disease progression and 51% of the patients died during the assessment period. The median follow up of the surviving patients was 12.8 months (range, .2 to 55.9).