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Full Length Article
Allogeneic – Adult

Outcomes of Allogeneic Hematopoietic Cell Transplantation in T Cell Prolymphocytic Leukemia: A Contemporary Analysis from the Center for International Blood and Marrow Transplant Research

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A B S T R A C T

T cell prolymphocytic leukemia (T-PLL) is a rare, aggressive malignancy with limited treatment options and poor long-term survival. Previous studies of allogeneic hematopoietic cell transplantation (alloHCT) for T-PLL are limited by small numbers, and descriptions of patient and transplantation characteristics and outcomes after alloHCT are sparse. In this study, we evaluated outcomes of alloHCT in patients with T-PLL and attempted to identify predictors of post-transplantation relapse and survival. We conducted an analysis of data using the Center for International Blood and Marrow Transplant Research database on 266 patients with T-PLL who underwent alloHCT between 2008 and 2018. The 4-year rates of overall survival (OS), disease-free survival (DFS), relapse, and treatment-related mortality (TRM) were 30.0% (95% confidence interval [CI], 23.8% to 36.5%), 25.7% (95% CI, 20% to 32%), 41.9% (95% CI, 35.5% to 48.4%), and 32.4% (95% CI, 26.4% to 38.6%), respectively. In multivariable analyses, 3 variables were associated with inferior OS: receipt of a myeloablative conditioning (MAC) regimen (hazard ratio [HR], 2.18; $P < .0001$), age >60 years (HR, 1.61; $P = .0053$), and suboptimal performance status, defined by Karnofsky Performance Status (KPS) <90 (HR, 1.53; $P = .0073$). Receipt of an MAC regimen also was associated with increased TRM (HR, 3.31; $P < .0001$), an elevated cumulative incidence of grade II-IV acute graft-versus-host disease (HR, 2.94; $P = .0011$), and inferior DFS (HR, 1.86; $P = .0004$). Conditioning intensity was not associated with relapse; however, stable disease/progression was correlated with increased risk of relapse (HR, 2.13; $P = .0072$). Both in vivo T cell depletion (TCD) as part of conditioning and KPS <90 were associated with worse TRM and inferior DFS. Receipt of total body irradiation had no significant effect on OS, DFS, or TRM. Our data show that reduced-intensity conditioning without in vivo TCD (ie, without antithymocyte globulin or alemtuzumab) before alloHCT was associated with long-term DFS in patients with T-PLL who were age ≤60 years or who had a KPS >90 or chemosensitive disease.

INTRODUCTION

T cell prolymphocytic leukemia (T-PLL) is a rare aggressive malignancy, representing approximately 2% of mature lymphocytic leukemias in adults [1,2]. Patients tend to be older, with a median age of 65 years at diagnosis. Typically, T-PLL presents with such signs as marked leukocytosis, hepatosplenomegaly, lymphadenopathy, and cutaneous lesions. Treatment options are generally limited, and outcomes are poor, with a reported median survival of 19 months [3]. Alemtuzumab, an anti-CD52 humanized monoclonal antibody, is often used in the front-line treatment of T-PLL. Although rates of complete remission (CR) with alemtuzumab are high (60% to 80%), most responses are brief, and the relapse rate remains high [4,5]. Survival of patients with relapsed T-PLL is dismal, as responses to second-line therapies are limited and generally short-lived [2,6].

Allogeneic hematopoietic cell transplantation (alloHCT) is a potential curative therapy for T-PLL and has been reported to yield durable remissions, most notably in patients who are in CR before transplantation [7–12]. AlloHCT was found to be beneficial in small subsets of patients with T-PLL in studies reported by the Center for International Blood and Marrow Transplant Research (CIBMTR) [10], European Society for Blood and Marrow Transplantation (EBMT) [7,13], Francophone Society of Bone Marrow Transplantation and Cellular Therapy (SFGM-TC) [9], and Japanese Society for Transplantation and Cellular Therapy (JSTCT) [14]. However, the benefits of alloHCT are limited by a high rate of nonrelapse mortality, ranging from 28% to 40%. In addition, there is high risk of post-transplantation relapse, many occurring within 2 years of alloHCT [10,15]. Because these studies were relatively small, the researchers were unable to identify factors associated with sustained remission and improved overall survival (OS). Thus,

the present study was conducted to evaluate the effectiveness of alloHCT in patients with T-PLL using the CIBMTR database, and to identify predictors of post-transplantation relapse and survival.

METHODS

Data Sources

The CIBMTR is a nonprofit research collaboration of the National Marrow Donor Program/Be the Match and the Medical College of Wisconsin. More than 300 medical centers worldwide submit clinical data to the CIBMTR about HCT and other cellular therapies. Participating centers are required to report all transplantations consecutively. The CIBMTR ensures data quality through computerized checks for discrepancies, physicians' reviews of submitted data, and onsite audits of participating centers. The CIBMTR complies with federal regulations that protect human research participants. The Institutional Review Boards of the Medical College of Wisconsin and the National Marrow Donor Program approved this study.

Patient Selection

Adults (age ≥18 years) who underwent first alloHCT for T-PLL between 2008 and 2018 were included in this analysis. Graft sources included peripheral blood stem cells and bone marrow. Eligible donors included HLA-identical sibling donors and unrelated donors matched at the allele level at HLA-A, -B, -C, and -DRB1, as well as alternative donors (haploidentical and mismatched unrelated). Cord blood and ex vivo T cell- depleted grafts recipients were excluded, as were patients who received syngeneic transplants. AlloHCT recipients who underwent in vivo T cell depletion (TCD) with antithymocyte globulin (ATG) or alemtuzumab were included.

Definitions and Study Endpoints

Disease response was defined based on National Cancer Institute-sponsored working group guidelines for chronic lymphocytic leukemia [16]. The intensity of conditioning regimens was defined using published consensus criteria [17]. The primary endpoint was OS. Death from any cause was considered an event, and surviving patients were censored at the time of their last follow-up. Secondary endpoints included cumulative incidences of acute graft-versus-host disease (aGVHD), chronic graft-versus-host disease (cGVHD), treatment-related mortality (TRM), progression/relapse, and disease-free survival (DFS). TRM was defined as death without preceding disease relapse/progression; relapse and progression were considered competing events. Progressive disease (PD) and recurrence of T-PLL were defined as progression after alloHCT and recurrence following CR, respectively; TRM was considered a competing event. DFS was defined as survival following alloHCT without relapse or progression. Patients who survived without evidence of disease relapse or progression were censored at their last follow-up. The causes of death were reported as described previously [18].

Statistical Analysis

The cumulative incidences of GVHD, relapse/progression, and TRM were calculated using the cumulative incidence estimator to account for competing risks. Probabilities of OS and DFS were calculated using the Kaplan-Meier method for univariable analysis. Multivariable regression analysis was performed using logistic regression for aGVHD; a proportional cause-specific hazards model for chronic GVHD, relapse, and TRM; and a Cox proportional hazards model for DFS and OS. The assumption of proportional hazards for each factor was tested for the proportional hazards and cause-specific hazards models, and forward stepwise selection was used to select significant risk factors. In the final model, we retained factors with a statistical significance of $P < .05$. We examined the interaction between the main effect and the other significant variables and found no center effect based on the score test of homogeneity [19]. The variables considered in the multivariable models included recipient age, Karnofsky Performance Status (KPS), Hematopoietic Cell Transplantation Comorbidity Index, disease status at transplantation, intensity of conditioning regimen, use of total body irradiation (TBI) in conditioning, time from diagnosis to transplantation, recipient cytomegalovirus (CMV) serostatus, GVHD prophylaxis, donor type, graft source, use of ATG/alemtuzumab, and year of transplantation. Adjusted probabilities [20,21] were calculated based on the final regression models for OS, DFS, relapse, and TRM.

RESULTS

Baseline Characteristics

The study included 266 adults who underwent alloHCT for T-PLL. The median duration of follow-up was 49 months (range, 3.32 to 116.84 months). The baseline patient-, disease-, and transplantation-related characteristics are described in Table 1 and Supplementary Table S1. Participants' median age at the time of alloHCT was 59.1 years (range, 25.0 to 76.3 years), 53% were male, and 58% had a KPS ≥90. The majority of alloHCT recipients were white (87%). Disease status at the time of HCT was CR in 56% of the participants, partial remission (PR) in 30%, and chemorefractory disease in 11%. Most patients received peripheral blood stem cells grafts (89%) and calcineurin-based GVHD prophylaxis (80%). Matched related donors (30%) and 8/8 matched unrelated donors (43%) were the most common donor types. Reduced-intensity and nonmyeloablative conditioning (RIC/NMA) was administered to 70% of patients, and myeloablative conditioning (MAC) was given to 30%. Commonly used MAC regimens included cyclophosphamide-TBI (n = 33) and busulfan-fludarabine (n = 20), and commonly used RIC/NMA regimens included fludarabine-melphalan (n = 55), fludarabine-busulfan (n = 33), and fludarabine-TBI (n = 32). Forty-nine patients (18%) underwent in vivo TCD with ATG (n = 47) or alemtuzumab (n = 2).

OS and DFS

The 4-year OS and DFS were 30.0% (95% CI, 23.8% to 36.5%) and 25.7% (95% CI, 20% to 32%), respectively (Supplementary Table S2). The 4-year OS based on donor type was 40.1% (95% CI, 28.9% to 51.8%) for HLA-matched sibling donors (MSDs), 24.6% (95% CI, 16.2% to 34.2%) for 8/8 matched unrelated donors (MUDs), 33.9% (95% CI, 15% to 56%) for haploidentical (haplo) donors, and 26.8% (95% CI, 9.6% to 48.9%) for 7/8 mismatched unrelated donors (MMUDs). The 4-year DFS for these 4 donor types was 34.9% (95% CI, 24.4% to 46.3%), 19.6% (95% CI, 12% to 28.5%), 23.4% (95% CI, 8.2% to 43.3%), and 28.9% (95% CI, 10.4% to 52.1%), respectively (Supplementary Table S3).

On multivariate analyses, receipt of an RIC/NMA conditioning regimen was significantly associated with longer DFS (hazard ratio [HR], 1.86; 95% CI, 1.32 to 2.61; $P = .0004$) and OS (HR, 2.18; 95% CI, 1.53 to 3.09; $P < .0001$) compared with receipt of an MAC regimen (Figures 1 and 2). A KPS <90 was associated with both inferior DFS (HR, 1.51; 95% CI, 1.12 to 2.05; $P = .0075$) and inferior OS (HR, 1.53; 95% CI, 1.12 to 2.08; $P = .0073$), as was recipient age >60 years (HR, 1.41; 95% CI, 1.03 to 1.93 [$P = .0337$] and 1.61; 95% CI, 1.15 to 2.24 [$P = .0053$], respectively). Use of in vivo TCD resulted in inferior DFS (HR, 1.50; 95% CI, 1.05 to 2.15; $P = .0276$) but had no significant effect on OS (Table 2). The time from diagnosis to transplantation did not have any significant effect on DFS or OS.

The effect of TBI on OS and DFS was analyzed as part of the analysis of conditioning intensity (Supplementary Table S7). Comparing MAC without TBI (MAC-chemo) with MAC with TBI showed that TBI had no significant effect on OS (HR, 0.83; 95% CI, 0.49 to 1.41; $P = .0073$) or DFS (HR, 1.01; 95% CI, 0.60 to 1.71; $P = .9628$). The same analysis comparing RIC with TBI and RIC without TBI (RIC-chemo) found that TBI had no significant effect on OS (HR, 1.22; 95% CI, 0.81 to 1.82; $P = .3437$) or DFS (HR, 1.17; 95% CI, 0.79 to 1.72; $P = .4390$).

TRM

The 1-year and 4-year cumulative incidences of TRM were 21.5% (95% CI, 16.7% to 26.7%), and 32.4% (95% CI, 26.4% to 38.6%), respectively. The 4-year TRM based on donor type was 20.4% (95% CI, 11.8% to 30.7%) for MSDs, 36.6% (95% CI, 27.3% to 46.4%) for MUDs, 31.6% (95% CI, 15.5% to 50.3%) for haplo donors, and 42.1% (95% CI, 23.2% to 62.4%) for MMUDs (Supplementary Table S3).

On multivariate analysis, MAC was associated with an increased cumulative incidence of TRM (HR, 3.31; 95% CI, 2.01 to 5.45; $P < .0001$) compared with RIC (Figure 3). In addition, KPS <90 (HR, 1.98; 95% CI, 1.25 to 3.14; $P = .0036$) and in vivo

Table 1
Baseline Characteristics of Patients Who Underwent First AlloHCT for T-PLL in 2000 to 2018

Characteristic	Value
Patients, n	266
Centers, n	87
Sex, n (%)	
Male	140 (53)
Female	126 (47)
Age, yr, median (range)	59.1 (25.01-76.26)
Age group, n (%)	
18-29 yr	1 (0)
30-39 yr	7 (3)
40-49 yr	38 (14)
50-59 yr	98 (37)
60-69 yr	101 (38)
≥70 yr	21 (8)
KPS score, n (%)	
90-100	153 (58)
<90	101 (38)
Not reported	12 (4)
HCT-CI, n (%)	
0	73 (27)
1-2	84 (31)
3-4	77 (25)
≥5	28 (11)
Not reported	4 (6)
Remission status at HCT, n (%)	
CR	149 (56)
PR	80 (30)
No response/stable/progression	31 (11)
Not reported	6 (2)
Graft source, n (%)	
Bone marrow	30 (11)
Peripheral blood	236 (89)
Time from diagnosis to HCT, mo, median (range)	7.85 (2.07-81.74)
Time from diagnosis to HCT, n (%)	
<6 mo	82 (31)
6-11 mo	103 (39)
≥12 mo	81 (30)
Donor type, n (%)	
HLA-identical sibling	80 (30)
Haploidentical	30 (11)
URD 8/8	115 (43)
URD 7/8	33 (12)
Other related	8 (3)
Conditioning regimen intensity, n (%)*	
MAC with TBI	44 (17)
MAC without TBI	34 (13)
RIC with TBI	75 (28)
RIC without TBI	113 (42)
GVHD prophylaxis, n (%)	
CNI + MMF ± others (except PTCy)	68 (26)
CNI + MTX ± others (except MMF and PTCy)	123 (46)
CNI + others (except MMF, MTX, and PTCy)	20 (8)
Other prophylaxis†	55 (21)
In vivo TCD (ATG/alemtuzumab), n (%)‡	
Yes	49 (18)
No	217 (82)
Follow-up, mo, median (range)	(3.32-116.84)

HCT-CI indicates Hematopoietic Cell Transplantation Comorbidity Index; URD, unrelated donor; CNI, calcineurin inhibitor; MMF, mycophenolate mofetil; MTX, methotrexate.

* Refer to Supplementary Table S1 for a full list of conditioning regimens.

† Other: CNI alone, n = 12; CNI + PTCy + MMF, n = 32; PTCy-MMF, n = 1; sirolimus + PTCy, n = 2; MTX alone, n = 3; sirolimus-MMF-PTCy, n = 1; monoclonal antibody + MMF, n = 3; PTCy alone, n = 1.

‡ ATG, n = 47; alemtuzumab, n = 2.

TCD (HR, 1.79; 95% CI, 1.07 to 2.98; P = .0263) were associated with an increased incidence of TRM (Table 2).

The effect of TBI on TRM was analyzed as part of conditioning intensity (Supplementary Table S7). Comparing MAC without TBI (MAC-chemo) with MAC with TBI showed that TBI had no significant effect on TRM (HR, 0.48; 95% CI, 0.22 to 1.05; P = .0662). Comparing RIC with TBI and RIC without TBI (RIC-chemo) again showed that TBI had no significant effect on TRM (HR, 1.39; 95% CI, 0.74 to 2.64; P = .3068).

aGVHD and cGVHD

The cumulative incidence of grade II-IV aGVHD at day 180 post-alloHCT was 22.5% (95% CI, 16.8% to 28.9%), and that of grade III-IV aGVHD at day 180 post-alloHCT was 5.3% (95% CI, 2.8% to 8.6%) (Supplementary Table S4). The cumulative incidence of grade II-IV aGVHD at day 180 based on donor type was 14.3% (95% CI, 6.4% to 24.7%) for MSD, 25.7% (95% CI, 16.6% to 36%) for MUD, 36.4% (95% CI, 17.5% to 57.8%) for haplo, and 20% (95% CI, 5.6% to 40.4%) for MMUD (Supplementary Table S3). On multivariate analysis, MAC was predictive for increased risk of grade II-IV aGVHD (OR, 2.94; 95% CI, 1.54 to 5.62; P = .0011), whereas post-transplantation cyclophosphamide (PTCy) was predictive for reduced grade II-IV aGVHD (OR, 0.26; 95% CI, 0.10 to 0.71; P = .0082) (Table 2). In vivo TCD did not have a significant effect on aGVHD. Comparing MAC with TBI to MAC without TBI as well as RIC with TBI to RIC without TBI showed that TBI had no significant effect on aGVHD (Supplemental Table S7).

The cumulative incidence of cGVHD was 38.8% (95% CI, 32.9% to 44.9%) at 1 year and 45.5% (95% CI, 39.2% to 51.8%) at 2 years post-transplantation. Among the patients with cGVHD at 1 year, 71% had extensive cGVHD and 29% had limited cGVHD, whereas at 2 years, cGVHD was extensive in 72% and limited in 28%. The cumulative incidence of cGVHD at 2 years post-transplantation based on donor type was 47.5% (95% CI, 35.8% to 59.3%) for MSD, 47.6% (95% CI, 37.9% to 57.4%) for MUD, 33.9% (95% CI, 16.6% to 53.9%) for haplo, and 49.1% (95% CI, 31.5% to 66.8%) for MMUD (Supplementary Table S3).

Age, conditioning intensity, and in vivo TCD had no significant effect on cGVHD. PTCy-based GVHD prophylaxis was associated with less cGVHD compared with calcineurin-based GVHD prophylaxis (Table 2). We also found that alloHCT performed before 2011 was associated with an increased incidence of cGVHD compared with than those performed after 2011 (Supplementary Table S6).

Relapse

The cumulative incidence of relapse/progression was 27.6% (95% CI, 22.3% to 33.2%) at 1 year and 41.9% (95% CI, 35.5% to 48.4%) at 4 years. Based on the multivariate analyses (Table 2),

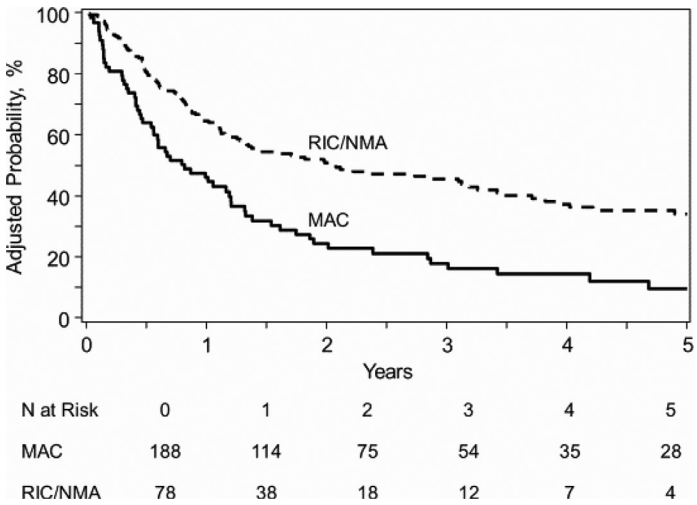

Figure 1. Adjusted OS by conditioning intensity ($P < .0001$).

age and conditioning intensity were not associated with the rate of relapse. Stable disease or PD at the time of alloHCT was associated with an increased incidence of relapse (HR, 2.13; 95% CI, 1.23 to 3.71; $P = .0072$) compared with CR. However, the depth of response at HCT (PR versus CR), in vivo TCD, and TBI-based conditioning were not associated with the incidence of relapse.

Causes of Death

The most common cause of death was relapse of the primary disease (52%), followed by infection (15%) and GVHD (13%) (Supplementary Table S5).

DISCUSSION

Using the CIBMTR database, we have shown that long-term DFS can be achieved in patients with T-PLL. We observed that RIC/NMA conditioning regimens are associated with reduced TRM and improved DFS and OS. Our analysis also found that the use of in vivo TCD strategies (with ATG and/or alemtuzumab) resulted in an increased TRM and inferior DFS. Disease relapse continues to pose a challenge, with a 4-year relapse incidence of 41%. Patients with chemosensitive disease before transplantation had a reduced incidence of relapse.

Data from this analysis are consistent with previous registry studies from the SFGM-TC and the JSHCT (Table 3). The SFGM-TC study retrospectively reported 3-year OS and DFS estimates of 36% and 26%, respectively, in 27 patients with a median follow-up of 33 months, and the JSHCT reported 3-year OS and PFS of 39.8% and 33.5%, respectively, in 20 patients with a median follow-up of 51 months [9,14]. The EBMT study, a prospective observational study of recipients age ≤65 years with a median follow-up of 50 months, reported a 4-year OS and PFS of 42% and 30%, respectively [13]. However, in the EBMT series, the oldest patient was 59 years, whereas in this current CIBMTR study, 42% of the patients were older than 60 years, which more closely reflects the median age at T-PLL diagnosis in the US.

The intensity of conditioning regimens was comparable across the studies. RIC/NMA regimens were used in 70% of the patients in the current study, compared with 60% in the SFGM-TC study, 50% in the JSHCT study, and 65% in the EBMT study. In younger patients, RIC/NMA conditioning was associated with reduced TRM and improved DFS and OS compared with MAC conditioning. The survival benefit offered by RIC/NMA conditioning may be explained by the graft-versus-leukemia (GVL) effect. Sellner et al [22]. evaluated longitudinal

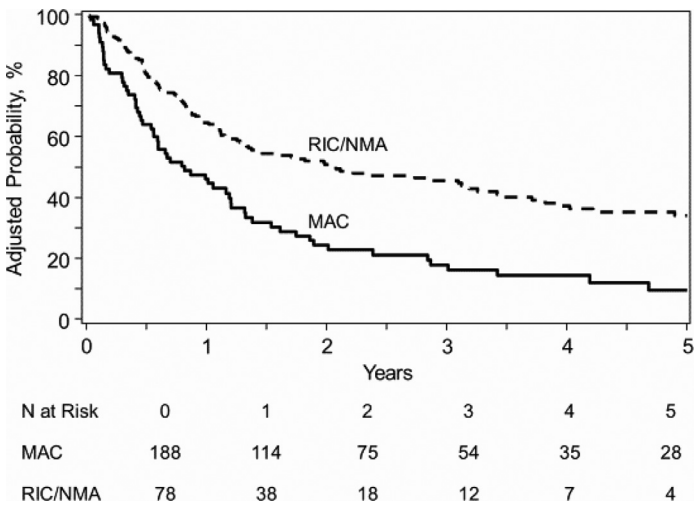

Figure 2. Adjusted DFS by conditioning intensity ($P = .0004$).

Table 2
Multivariable Regression Analysis

Variable	n	OR/HR (95% CI)	*P* Value	Overall *P* Value
OS				
Conditioning regimen				
RIC/NMA	188	1.00 (reference)		<.0001
MAC	78	2.18 (1.53-3.09)	<.0001	
Age				
≤60 yr	142	1.00 (reference)		.0053
>60 yr	122	1.61 (1.15-2.24)	.0053	
KPS				
≥90	153	1.00 (reference)		.0272
<90%	101	1.53 (1.12- 2.08)	.0073	
Not reported	12	1.23 (0.60- 2.54)	.573	
DFS				
Conditioning regimen				
RIC/NMA	77	1.00 (reference)		.0004
MAC	187	1.86 (1.32-2.61)	.0004	
Age				
≤60 yr	142	1.00 (reference)		.0337
>60 yr	122	1.41 (1.03- 1.93)	.0337	
KPS				
≥90	152	1.00 (reference)		.0075
<90	101	1.51 (1.12- 2.05)	.0075	
Not reported	11	1.13 (0.53-2.44)	.7507	
In vivo TCD				
No	215	1.00 (reference)		.0253
Yes	49	1.50 (1.05-2.13)	.0253	
TRM				
Conditioning regimen				
RIC/NMA	187	1.00 (reference)		<.0001
MAC	77	3.31 (2.01-5.45)	<.0001	
Age				
≤60 yr	142	1.0 (reference)		.0108
>60 yr	122	1.87 (1.16- 3.04)	.0108	
KPS				
≥90	152	1.00 (reference)		.0142
<90	101	1.98 (1.25- 3.14)	.0036	
Not reported	11	1.18 (0.36-3.83)	.7811	
In vivo TCD				
No	215	1.00 (reference)		.0263
Yes	49	1.79 (1.07-2.98)	.0263	
aGVHD				
Conditioning regimen				
RIC/NMA	172	1.00 (reference)		.0011
MAC	75	2.94 (1.54- 5.62)	.0011	
GVHD prophylaxis				
CNI + MMF	65	1.00 (reference)		.0093
CNI + MTX	114	0.56 (0.28-1.14)	.1077	
CNI + others (except MMF, MTX, and PTCy)	18	0.36 (0.11-1.17)	.0902	
PTCy ± others	33	0.26 (0.10-0.71)	.0082	
Other prophylaxis	17	2.17 (0.71-6.60)	.174	
cGVHD				
GVHD prophylaxis				
CNI + MMF ± others (except PTCy)	67	1.00 (reference)		.0015
CNI + MTX ± others (except MMF and PTCy)	121	1.06 (0.68-1.65)	.8045	
CNI + others (except MMF, MTX, and PTCy)	20	2.35 (1.31-4.20)	.0041	
PTCy ± others	37	0.44 (0.19-1.05)	.0645	
Other prophylaxis	17	0.65 (0.25-1.66)	.3677	
Year of transplantation				

(*continued*)

Table 2 (*Continued*)

Variable	n	OR/HR (95% CI)	*P* Value	Overall *P* Value
2008-2011	50	1.00 (reference)		.0216
2012-2015	110	0.62 (0.39-0.97)	.0382	
2016-2018	102	0.48 (0.28-0.82)	.0069	
Relapse				
Disease status at HCT				
CR	149	1.00 (Reference)		.0486
PR	80	1.40 (0.91-2.17)	.1257	
No response/SD/PD	31	2.13 (1.23-3.71)	.0072	
Not reported	6	0.94 (0.23- 3.87)	.932	

SD indicates stable disease.

quantitative minimal residual disease using clone-specific T cell receptor-based real-time quantitative PCR and found that minimal residual disease responses post-alloHCT were associated with a shift from a clonal, T-PLL-driven profile to a polyclonal signature, effectively validating the GVL effect in T-PLL [22]. In our analysis, a surrogate marker of GVL, the impact

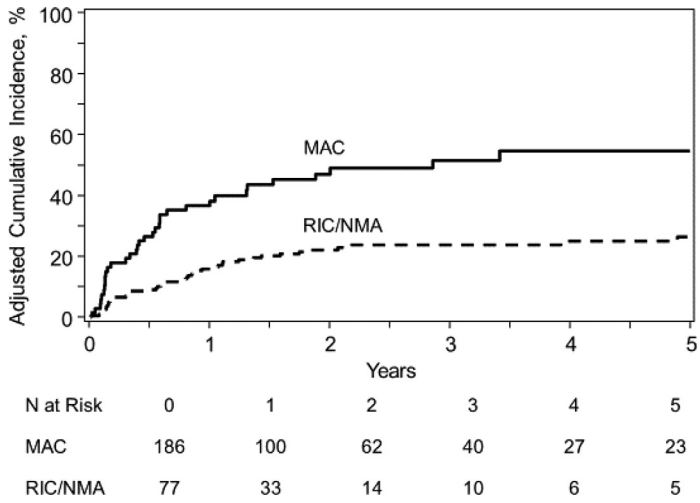

Figure 3. Adjusted TRM by conditioning intensity ($P < .0001$).

Table 3
Selected Studies of AlloHCT for T-PLL

Study	Sponsor	No. of Patients	Remission Status at AlloHCT, n	Donor Type, n	Regimen Intensity, n	Outcomes
Wiktor-Jedrzejczak et al [13].	EBMT	37*	CR: 22 PR: 10 Other: 5	MRD: 15 MUD: 22	MAC: 13 RIC: 24	4-year OS: 42% 4-year NRM: 32% 4-year relapse: 38%
Kalaycio et al [10].	CIBMTR	47 (21 T-PLL)†	CR: 16 PR: 8 Other: 21	MRD: 11 MUD: 19 Other: 13	MAC: 19 NMA: 14	1-year OS: 48% 1-year NRM: 28% 1-year relapse: 28%
Guillaume et al [9].	SFGM-TC	27	CR: 14 PR: 10 Other: 3	MRD: 10 MUD: 17	MAC: 10 NMA: 17	3-year OS: 36% 3-year NRM: 31% 3-year relapse: 47%
Dholaria et al [8].	Moffitt Cancer Center	11	CR: 9 PR: 1 Other: 1	MRD : 5 MUD: 3 Other: 3	MAC: 8 RIC: 3	4-year OS: 56% 4-year NRM: 34% 4-year relapse: 21%
Yamasaki et al [14].	JSHCT	20	CR: 6 PR: 1 Other: 13	MRD : 5 MUD: 6 Haplo: 2 MMUD: 7 UCB: 2	MAC: 10 RIC: 10	3-year OS: 39.8% 1-year NRM: 20.9% 3-year relapse: 69.6%
Present study	CIBMTR	266	CR: 149 PR: 80 Other: 37	MRD : 80 MUD: 115 Haplo: 30 MMUD: 33 Other: 8	MAC: 78 RIC: 188	4-year OS: 30% 4-year TRM: 32.4% 4-year relapse: 41.9%

MRD indicates matched related donor; NRM, nonrelapse mortality; UCB, umbilical cord blood.
* Data available for 36 patients.
† T-PLL and B cell prolymphocytic leukemia.

of in vivo TCD on relapse, was not evident. The use of in vivo TCD was associated with inferior DFS owing to an increased risk of TRM.

A high incidence of TRM has been reported in previous studies of alloHCT for T-PLL. The 4-year TRM of 32.4% is similar to values reported by the EBMT (4-year nonrelapse mortality of 32%) and the SFGM-TC (3-year TRM of 31%). Predictably, we observed reduced TRM and reduced incidence of aGVHD with the use of RIC/NMA regimens. We observed that in vivo TCD was linked to increased TRM. In the current study, 18% of the patients received in vivo TCD, mostly with ATG, whereas 51% received TCD in the EBMT study. AlloHCT with TCD has been associated with delayed immune reconstitution and increased risk of infection [23–25]. Infection was reported as the second most common cause of death. Ongoing TCD caused by pretransplantation alemtuzumab therapy might influence TRM. In addition, it could be hypothesized that ongoing T cell depletion from pretransplantation alemtuzumab therapy, in addition to the use of RIC/NMA regimens and PTCy GVHD prophylaxis, may explain the low incidence of aGVHD and severe aGVHD observed. However, we could not answer this question conclusively in this analysis, because data on the time from the last alemtuzumab dose to transplantation or on T cell reconstitution were not available.

Outcomes by donor type were also reviewed (Supplementary Table S3). Although small in numbers, it is worth mentioning that we observed both haplo donor and MMUD transplants as feasible and effective in patients with T-PLL. Haploidentical transplantation in particular was associated with less cGVHD and TRM compared with MUD and MMUD transplantations and comparable 4-year relapse, DFS, and OS. It is important to note that donor type was not significant on multivariate analyses and that these findings are from univariate analysis only, making it difficult to draw significant conclusions regarding the ideal donor choice. However, with the increased use of haploidentical transplantation [26] and the feasibility and effectiveness of PTCy in alloHCT with MMUD [27], alloHCT should be considered for patients with T-PLL even in the absence of an HLA-matched donor.

Controlling disease and preventing relapse remain difficult in patients after alloHCT. Achieving CR prior to alloHCT was associated with less relapse, but only when compared with stable disease or PD and not when compared with PR, suggesting that chemoresponsive disease before alloHCT is more significant than the depth of remission.

In this analysis, we also investigated the role of TBI. A prospective study by the EBMT identified a TBI dose of $\geq$6 Gy as predictive of reduced relapse risk in a univariable analysis [13]. We looked specifically at whether adding TBI to both MAC and RIC regimens would affect OS, DFS, or TRM. When comparing MAC with TBI to MAC without TBI as well as RIC with TBI to RIC without TBI, we found no significant effect on OS, DFS, and TRM. Our analysis showed that differences in survival outcomes with respect to pretransplantation conditioning were more attributed more to conditioning intensity (MAC versus RIC) rather than the use of TBI.

We found that relapse rates increased over time, from 27.6% at 1 year to 41.9% at 4 years. Unfortunately, there is no standard test of minimal residual disease for T-PLL, and such a test potentially could help forecast early relapse. Late relapse may reflect a waning GVL effect over time. Post-transplantation immune modulation strategies may help prevent late relapse. Venetoclax [28], histone deacetylase inhibitors [29], *p53* reactivators [30,31], and Janus kinase/signal transducers and activators of transcription inhibitors [32–35] have previously demonstrated some preclinical and/or clinical activity in T-PLL and warrant further evaluation for post-transplantation maintenance.

This study has the limitations inherent to a retrospective registry study. Because the data were obtained from a transplant registry, we could not compare outcomes with those of patients who did not undergo alloHCT. Another limitation is the lack of pertinent pretransplantation information, such as cytogenetics, mutation data, and details of therapies prior to alloHCT. Details of pre-HCT induction therapy were not available for most of our study participants, so we did not include this information in our analyses. The lack of consensus disease response criteria is a notable limitation. The CIBMTR registry defines T-PLL response criteria based on international consensus response criteria for chronic lymphocytic leukemia [16]. consensus T-PLL response guidelines were published only recently, in 2019 [12]. Given that the patients included in this analysis date back to 2008, using the updated criteria was not feasible. Finally, detailed data were not available on the timing and severity of infections or on immune reconstitution.

CONCLUSION

In summary, alloHCT results in durable remissions and disease control in some patients with T-PLL. Relapse remains a barrier to long-term survival. The use of RIC and avoidance of in vivo TCD are associated with improved outcomes. Molecular monitoring of patients for recurrence after transplantation could be undertaken to identify early relapses for treatment, possibly with donor lymphocyte therapy. Other novel approaches combined with alloHCT warrant investigation to further improve outcomes of alloHCT in T-PLL.

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SUPPLEMENTARY MATERIALS

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