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ORIGINAL ARTICLE

Effect of allogeneic hematopoietic cell transplantation for patients with T-prolymphocytic leukemia: a retrospective study from the Adult Lymphoma Working Group of the Japan Society for hematopoietic cell transplantation

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Abstract

Alemtuzumab is the treatment choice for patients with T-prolymphocytic leukemia (T-PLL). However, patients with T-PLL have a poor prognosis, and the option of allogeneic hematopoietic cell transplantation (HCT) remains controversial in these patients. This study aimed to analyze the outcomes of allogeneic HCT among patients with T-PLL to identify the potential clinical efficacy of allogeneic HCT. We retrospectively analyzed data from 20 patients with T-PLL, including five patients with complex chromosomal abnormalities at diagnosis who received an allogeneic HCT between 2000 and 2016. The median follow-up of survivors was 51 months in allogeneic HCT from human leukemia antigen (HLA)-matched donors. All five patients with complex chromosomal abnormalities died after allogeneic HCT. Our data suggest that allogeneic HCT from an HLA-matched donor can be considered for patients with T-PLL without complex chromosomal abnormalities. New treatment strategies of allogeneic HCT are required to improve the safety and efficacy of allografting in patients with T-PLL and complex chromosomal abnormalities. Potential approaches that identify patients with T-PLL and complex chromosomal abnormalities for allogeneic HCT with better disease control may allow identification of individuals who are suitable for allogeneic HCT.

Keywords T-prolymphocytic leukemia · Allogeneic hematopoietic cell transplantation · HLA-matched donor · Complex chromosomal abnormalities

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Introduction

Prolymphocytic leukemias (PLLs) are rare mature lymphoid disorders of B and T cell subtypes. PLLs are characterized by a predominance of activated prolymphocytes in the bone marrow and peripheral blood, based on the World Health Organization classification [1]. B-PLL and T-PLL are rare, accounting for approximately 1% and 2% of mature lymphocytic leukemia in adults, respectively. The most common chromosomal abnormality associated with T-PLL is inv(14)(q11.2q32), which involves the T cell leukemia 1 (TCL1) gene [2]. A complex chromosomal abnormality is defined as three or more chromosomal abnormalities and includes secondary events, such as genetic mutations of TP53 and extra copy numbers of MYC, JAK3, and STAT5B. Complex chromosomal abnormalities result in disease progression after the primary leukemic driver aberration and cause TCL1 rearrangement, and these abnormalities are a poor prognostic factor. This is because patients with complex chromosomal abnormalities may be identified at a later stage of disease [3]. Currently, treatment with the monoclonal anti-CD52 antibody alemtuzumab results in approximately 80% of patients having a complete response, followed by consolidation with allogeneic hematopoietic cell transplantation (HCT) [4]. In a recent prospective observation by the European Group for Blood and Marrow Transplantation, total body irradiation with 6 Gy was the only significant predictor of a low risk of relapse [5]. Factors associated with allogeneic HCT outcomes, including chromosomal abnormality at diagnosis, remain unknown. Therefore, this study aimed to analyze the outcomes of allogeneic HCT among patients with T-PLL with and without chromosomal abnormality to identify the potential clinical efficacy of allogeneic HCT.

Patients and methods

Data source

More than 200 Japanese transplant centers participated in the Transplant Registry Unified Management Program database, including physician-reviewed data with informed consent and yearly follow-ups [6, 7]. This study was approved by the data management committee of the Japanese Society for Hematopoietic Cell Transplantation and the Institutional Review Board of Kyushu Medical Center. All procedures were conducted in accordance with the ethical standards of the institutional and/or national research committee and the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Selection of patients

We identified patients with T-PLL who were aged 18 years or older and received one allogeneic HCT between January 2000 and December 2016. Exclusion criteria for this study were as follows: (1) any history of solid cancers or hematological malignancies before HCT; or (2) two or more HCTs were performed. The inclusion criterion was having cause-of-death data.

We included 20 patients with T-PLL in this analysis. We studied the following variables: (1) patient-related variables, including age at HCT, sex, Karnofsky performance status (KPS) at HCT, number of regimens before HCT, time from diagnosis to HCT, and the HCT-specific comorbidity index at HCT [8]; (2) disease-related variables, including disease status at HCT (complete remission [CR], partial remission, primary induction failure] or relapse), the international prognostic index, B symptom, increased lactate dehydrogenase (LDH) activity, and chromosomal abnormality at diagnosis; and (3) transplantation-related variables, including the conditioning regimen, stem-cell source, donor, year of HCT, time of granulocyte colony-stimulating factor to promote engraftment, time to neutrophil engraftment, graft-versus-host disease (GVHD) prophylaxis, and relapse or refractory disease after HCT. Preparative regimens that were classified as myeloablative conditioning ($n = 10$), including total body irradiation (TBI) > 8 Gy + cyclophosphamide (CY, $n = 8$) or + fludarabine (FLU) + busulfan (BU, $n = 1$) and BU + CY + melphalan (MEL, $n = 1$), and reduced-intensity conditioning ($n = 10$), including FLU + TBI 2–4 Gy + MEL ($n = 6$) or TBI 2–4 Gy + BU ($n = 4$), were defined using the Center for International Blood and Marrow Transplant Research functional criteria [9].

Neutrophil engraftment was defined as occurring on the third of 3 consecutive days after the transplant day on which an absolute neutrophil count > 500 neutrophils/μL was reached. The incidence of grade II–IV acute GVHD and the presence or absence of chronic GVHD were defined as reported previously [10, 11]. Patients were considered evaluable for GVHD if they had engraftment. The percentages of patients who relapsed or were refractory to allogeneic HCT were determined (relapse). The survival rate and overall survival (OS) were calculated. Data for patients who received HCT were censored at the date of the last reported follow-up. Analyzed outcomes included non-relapse mortality (NRM, defined as any death while in continuous remission), progression-free survival (PFS), and OS.

Statistical methods

We determined the frequencies and descriptive statistics for patient-, disease-, and transplantation-related variables in patients who underwent allogeneic HCT. Categorical variables

were compared between the two groups using Pearson's χ^2 or Fisher's exact test, as appropriate, and continuous variables were compared using the Mann–Whitney *U* test. All tests were two-sided and the 95% confidence intervals were calculated. *P* values < 0.05 were considered to be statistically significant. Probabilities of neutrophil engraftment, acute and chronic GVHD, NRM, and relapse were calculated using cumulative incidence curves to accommodate competing risks. NRM was defined as death without evidence of progression/relapse of T-PLL. To accommodate competing risks, the cumulative incidence curves for NRM and relapse between the two groups were estimated and the difference between them was compared using Gray's test. The competing risk events for NRM and relapse were relapse and death, respectively. The effects of patient-, disease-, and transplantation-related variables on NRM or relapse were evaluated by the Fine and Gray model. PFS and OS were calculated using the Kaplan–Meier method, and two-group comparisons were performed using the log-rank test. Multivariate Cox regression analysis was used to determine independent risk factors, including patient-, disease-, and transplantation-related variables. All statistical analyses were performed using the Stata Version 14 statistical package (Stata Corporation, College Station, TX, USA) or EZR (Saitama Medical Center, Saitama, Japan, http://www.jichi.ac.jp/saitama-sct/SaitamaHP.files/statmedEN.html), which is a graphical user interface for R (The R Foundation for Statistical Computing, version 2.13.0). More precisely, EZR is a modified version of R commander (version 1.6-3) that was designed to add statistical functions that are frequently used in biostatistics [12].

Results

Patients' characteristics

Patient- and disease-related variables in patients with T-PLL are shown in Table 1. The 20 patients with T-PLL were divided into two groups as follows: patients received their allogeneic HCT from a human leukemia antigen (HLA)-matched ($n = 11$) donor; and patients received their allogeneic HCT from an HLA-mismatched donor ($n = 9$: HLA-A mismatched unrelated, $n = 1$; HLA-DR mismatched related or unrelated, $n = 6$; HLA-A, DR, and B or C mismatched unrelated cord blood, $n = 2$). Most patients showed a normal chromosomal profile at diagnosis ($n = 11$, 55%), including five of six patients at the first relapse. With regard to complex chromosomal abnormalities, four of five patients received allogeneic HCT at primary induction failure and one of five patients received allogeneic HCT at the first relapse. Chromosomal abnormalities included inv(2)(p23q21), which was detected in patients who received their allogeneic HCT from an HLA-matched donor (HLA-matched group). Another chromosomal abnormality was t(1:11)(p36;p15), which was detected in patients who received their allogeneic HCT from an HLA-DR-mismatched donor (HLA-mismatched group).

HCT outcomes

Transplant-related characteristics and HCT outcomes are shown in Table 2. Patients in the HLA-matched group showed a shorter time for granulocyte-colony stimulating factor to promote neutrophil engraftment ($P = 0.0036$) and a higher percentage of patients used methotrexate for GVHD prophylaxis compared with those in the HLA-mismatched group ($P = 0.026$). The onset of sepsis in the HLA-matched group was significantly sooner than that in the HLA-mismatched group ($P = 0.0004$). The reason for this finding could be because of the higher percentage of patients in the HLA-matched group who used methotrexate for GVHD prophylaxis (methotrexate GVHD prophylaxis may contribute to mucositis and delays in engraftment). *Staphylococcus epidermidis* ($n = 4$) and *Staphylococcus mitis/oralis* ($n = 1$) were detected in the HLA-matched group, and coagulase-negative *Staphylococcus* ($n = 3$), *Stenotrophomonas maltophilia* ($n = 2$), and *Staphylococcus epidermidis* ($n = 1$) were detected in the HLA-mismatched group in patients with sepsis.

The Fine and Gray model (Table 3) did not shown any variables as independent risk factors for NRM. A KPS < 90 at HCT ($P < 0.001$) and receiving an HLA-mismatched donor ($P < 0.001$) were independent risk factors for relapse. Multivariate Cox regression analysis showed that a KPS < 90 at HCT ($P = 0.029$) and receiving an HLA-mismatched donor ($P = 0.0050$) were independent risk factors for PFS (Table 3). Receiving an HLA-mismatched donor ($P = 0.0025$) and undergoing HCT in 2000–2010 ($P = 0.049$) were independent risk factors for OS.

The cumulative incidence of relapse was significantly higher in patients who received allogeneic HCT from an HLA-mismatched donor compared with those who received allogeneic HCT from an HLA-matched donor ($P = 0.0017$, Fig. 1 b). A patient with complex chromosomal abnormalities who underwent allogeneic HCT from an HLA-A-mismatched unrelated donor died because of Candida sepsis during treatment of acute and chronic GVHD without disease progression. All eight patients who underwent their allogeneic HCT from an HLA-DR-mismatched donor relapsed. PFS was significantly longer in patients who received allogeneic HCT from an HLA-matched donor compared with those who received allogeneic HCT from an HLA-mismatched donor ($P = 0.0042$; Fig. 1 c). OS was significantly longer in patients who received allogeneic HCT from an HLA-matched donor compared with those who received allogeneic HCT from an HLA-mismatched donor ($P = 0.0023$; Fig. 1 d).

Table 1 Characteristics of patients with T-prolymphocytic leukemia who received allogeneic hematopoietic cell transplantation

Characteristics	Total ($n = 20$)	HLA matched ($n = 11$)	HLA mismatched ($n = 9$)	P
Median age (range) at HCT, years	54 (20–72)	40 (20–61)	58 (43–72)	0.103
Sex, *n* (%)				
Male	9 (45)	6 (55)	3 (33)	0.406
Female	11 (55)	5 (45)	6 (67)	
KPS at HCT, *n* (%) 100	7 (35)	4 (36)	3 (33)	0.497
90	10 (50)	6 (55)	4 (44)	
≥ 80	3 (15)	1 (9)	2 (22)	
IPI at diagnosis, *n* (%) low	3 (15)	2 (18)	1 (11)	0.687
Low-intermediate	12 (60)	7 (64)	5 (56)	
High-intermediate	4 (20)	2 (18)	2 (22)	
High	1 (5)	0	1 (11)	
B symptoms at diagnosis, *n* (%)	2 (10)	0	2 (22)	0.189
Increased LDH activity at diagnosis, *n* (%)	13 (65)	5 (45)	8 (89)	0.070
Chromosomal abnormality at diagnosis, *n* (%)				
Normal	11 (55)	7 (64)	4 (44)	0.600
Complex + inv(14)(q11.2q32.1)	1 (5)	0	1 (11)	
Complex	4 (20)	2 (18)	2 (22)	
7q-	1 (5)	1 (9)	0	
5q-17p-	1 (5)	0	1 (11)	
Others	2 (10)	1 (9)	1 (11)	
No. of regimens before HCT, median (range)	3 (1–6)	2 (1–4)	3 (2–6)	0.538
Median time (range) from diagnosis to HCT, M	8 (3–30)	8 (3–30)	7 (3–27)	0.857
Disease status at HCT, *n* (%) CR1	6 (30)	3 (27)	3 (33)	0.654
PR1	1 (5)	1 (9)	0	
PIF	7 (35)	3 (27)	4 (44)	
Relapse1	6 (30)	4 (36)	2 (22)	
HCI-CI at HCT, *n* (%) 0	15 (75)	8 (73)	7 (78)	0.831
1	2 (10)	1 (9)	1 (11)	
≥ 2	3 (15)	2 (18)	1 (11)	

HCT, hematopoietic cell transplantation; *KPS*, Karnofsky performance status; *IPI*, international prognostic index; *LDH*, lactate dehydrogenase; *M*, month; *CR1*, first complete remission; *PR1*, first partial remission; *PIF*, primary induction failure; *Relapse1*, first relapse; *HCI-CI*, HCT-specific comorbidity index

Variables in the two groups were compared using Pearson's χ^2 test, Fisher's exact test, or the Mann–Whitney *U* test

Discussion

There are currently several treatment options for patients with T-PLL, including HCT [5, 13]. Our study indicated that HLA-DR-mismatched donors were not an alternative for HLA-matched donors in patients with T-PLL who were receiving allogeneic HCT because of the relative risk of relapse. Disease status at HCT was not an independent risk factor for relapse, but all of the five patients with complex chromosomal abnormalities at diagnosis and non-CR at HCT died after allogeneic HCT. Rescuing patients with T-PLL and complex chromosomal abnormalities at diagnosis only by allogeneic HCT might be difficult.

All of our patients with T-PLL relapsed after allogeneic HCT from HLA-DR-mismatched donors. HLA-DR is a major histocompatibility complex (MHC) class II alloantigen-mismatched donor. Our finding of relapse with HLA-DR-mismatched donors indicates that although allogeneic HCT is used to treat patients with T-PLL [14–17], it may not be an alternative for an HLA-matched donor in allogeneic HCT for T-PLL. Ali et al. reported that direct-pathway CD4 T cell alloresponses and indirect pathway responses against an MHC class II alloantigen were curtailed by rapid elimination of donor hematopoietic antigen-presenting cells [18]. However, persistent epitope presentation resulted in continual division and less profound contraction of the class I allopeptide-specific CD4 T cell population, with approximately 10,000 fold more cells persisting than cells following acute allograft rejection [18]. This finding might be explained by the CD4 T cells that are derived from HLA-DR-mismatched donors, which did not control disease progression. To induce long-term disease control, MHC class I-mismatched donors may be a potential candidate for

Table 2 Transplant-related characteristics and outcomes of patients with T-prolymphocytic leukemia who received allogeneic hematopoietic cell transplantation

Characteristics	Total ($n = 20$)	HLA matched ($n = 11$)	HLA mismatched ($n = 9$)	*P*
Conditioning regimen, *n* (%)				
MAC	10 (50)	6 (55)	4 (44)	0.999
RIC	10 (50)	5 (45)	5 (56)	
Stem-cell source, *n* (%)				
BM	11 (55)	6 (55)	5 (56)	0.201
PBSC	7 (35)	5 (45)	2 (22)	
CBSC	2 (10)	0	2 (22)	
Donor, *n* (%)				
HLA-identical sibling	5 (25)	5 (45)	0	–
HLA-matched unrelated	6 (30)	6 (55)	0	
HLA-mismatched related	2 (10)	0	2 (22)	
HLA-mismatched unrelated	7 (35)	0	7 (78)	
Year at HCT, *n* (%)				
2000–2010	10 (50)	5 (45)	5 (56)	0.999
2011–2016	10 (50)	6 (55)	4 (44)	
Time of G-CSF to promote engraftment, days	15 (6–46)	12 (6–46)	16 (10–24)	0.0036
Neutrophil engraftment, median (range) days	16 (11–37)	16 (11–37)	16 (11–21)	0.749
GVHD prophylaxis, *n* (%)				
CyA	8 (40)	6 (55)	2 (22)	0.197
TAC	12 (60)	5 (45)	7 (78)	0.197
MTX	16 (80)	11 (100)	5 (56)	0.026
MMF	3 (15)	0	3 (33)	0.073
Cumulative incidences (95% CI) of grades II–IV acute GVHD at 100 days, %	40.0 (14.1–58.0)	39.3 (0.2–63.2)	33.3 (0–58.0)	0.897
Cumulative incidences (95% CI) of chronic GVHD at 1 years, %	60.0 (25.6–78.5)	60.0 (14.5–81.3)	40.0 (0–66.9)	0.445
Sepsis, *n* (%)	11 (55)	5 (45)	6 (67)	0.406
Onset of sepsis, median (range), day	8 (1–122)	4 (1–13)	12 (5–122)	0.0004
CMV status, *n* (%)				
R+, D+	11 (55)	8 (73)	3 (33)	0.617
R+, D−	4 (20)	1 (9)	3 (33)	
R−, D+	5 (25)	2 (18)	3 (33)	
CMV antigenemia, *n* (%)	14 (70)	8 (73)	6 (67)	0.999
Onset of CMV treatment, median (range), day	40 (25–54)	48 (28–54)	32 (25–40)	0.332
CMV pneumonia, *n* (%)	1 (5)	0	1 (11)	–
Cumulative incidences (95% CI) of NRM at 1 years, %	20.9 (0–40.6)	10.0 (0–26.8)	14.3 (0–36.7)	0.898
Relapse/refractory after HCT, *n* (%)	12 (60)	4 (36)	8 (89)	0.028
Cumulative incidences (95% CI) of relapse, %				
At 1 year	39.3 (11.4–58.3)	11.1 (0–29.4)	70.4 (12.4–90.0)	0.0017
At 3 years	69.6 (33.1–86.2)	40.7 (0–67.8)	–	
PFS, % (95% CI)				
At 1 years	52.8 (28.8–72.0)	80.0 (40.8–94.6)	22.2 (3.3–51.3)	0.0042
At 3 years	33.5 (7.4–44.5)	45.7 (14.3–73.0)	–	
OS, % (95% CI)				
At 1 years	58.1 (33.3–76.4)	90.9 (50.8–98.7)	22.2 (3.3–51.3)	0.0023
At 3 years	39.8 (17.8–61.1)	68.2 (29.7–88.6)	11.1 (0.1–38.8)	
Median (range) follow-up of survivors, M	51 (12–68)	51 (12–68)	–	–
Cause of death, *n* (%)				
Disease	7 (35)	1 (9)	6 (67)	0.211
Candida sepsis	1 (5)	0	1 (11)	
SOS	1 (5)	1 (9)	0	
Acute GVHD	1 (5)	0	1 (11)	
Chronic GVHD	3 (15)	2 (18)	1 (11)	

HCT, hematopoietic cell transplantation; *HLA*, human leukocyte antigen; *MAC*, myeloablative conditioning; *RIC*, reduced intensity conditioning; *BM*, bone marrow; *PBSC*, peripheral blood stem cell, *CBSC*, cord blood stem cell; *G-CSF*, granulocyte colony-stimulating factor; *GVHD*, graft-versus-host disease; *CyA*, cyclosporine A; *TAC*, tacrolimus; *MTX*, methotrexate; *MMF*, mycophenolate mofetil; *CMV*, cytomegalovirus; *R*, recipient; *D*, donor; *M*, month; *CI*, confidence interval; *NRM*, non-relapse mortality; *PFS*, progression-free survival; *OS*, overall survival; *SOS*, sinusoidal obstruction syndrome

Variables in the two groups were compared using Pearson's χ^2 test, Fisher's exact test, or the Mann–Whitney *U* test

chemotherapy-resistant patients with T-PLL, including those with complex chromosomal abnormalities at diagnosis. With regard to graft versus leukemia activity in T-PLL, Sellner et al. detected the non-permanent and relied on a poly-oligoclonal or oligoclonal, rather than a monoclonal, T cell response from samples in patients with T-PLL who received

Table 3 Multivariate analysis for relapse and PFS/OS in patients with T-prolymphocytic leukemia

Variable	Relapse†			PFS‡			OS‡		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
KPS < 90 vs ≥ 90 at HCT	12.63	2.87–55.56	< 0.001	5.12	1.17–22.38	0.029			
HLA mismatched vs matched	14.65	3.38–63.42	< 0.001	6.15	1.72–21.92	0.0050	9.26	2.17–39.38	0.0025
Year at HCT 2000–2010 vs 2011–2016							3.85	1.01–14.77	0.049

PFS, progression-free survival; *OS*, overall survival; *HR*, hazard ratio; *CI*, confidence interval; *KPS*, Karnofsky performance status; *HCT*, hematopoietic cell transplantation; *HLA*, human leukocyte antigen

† Multivariate competing event statistics by Fine and Gray for relapse or ‡ multivariate Cox proportional-hazards regression analysis for PFS and OS were performed

allogeneic HCT [19]. Further research is required on preventing and treating relapse after allogeneic HCT.

This analysis of the Transplant Registry Unified Management Program database is one of the largest to assess patients with T-PLL who underwent allogeneic HCT. However, current strategies for allogeneic HCT might not improve outcomes of patients with T-PLL and complex chromosomal abnormalities at diagnosis and non-CR at HCT [3]. Analysis of the various conditioning regimens used for transplantation was beyond the scope of this study. The best

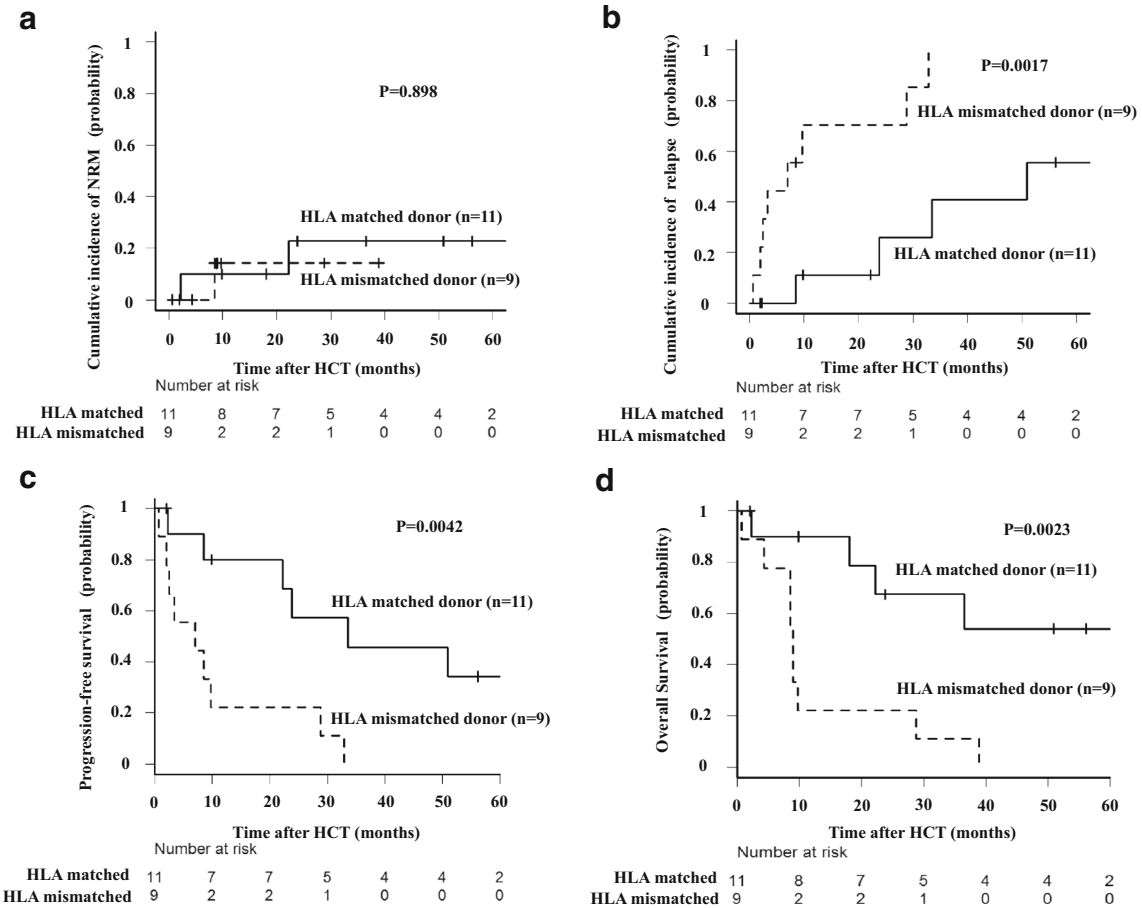

Fig. 1 Cumulative incidence of NRM (**a**) and relapse (**b**) in patients with T-PLL who received allogeneic HCT from an HLA-matched or -mismatched donor. Kaplan–Meier estimates of PFS (**c**) and OS (**d**) in patients with T-PLL who received allogeneic HCT from an HLA-matched or HLA-mismatched donor. The cumulative incidence of relapse was significantly higher in patients who received allogeneic HCT from an HLA-mismatched donor compared with those who received allogeneic HCT from an HLA-matched donor ($P = 0.0017$). PFS and OS were significantly longer in patients who received allogeneic HCT from an HLA-matched donor compared with those who received allogeneic HCT from an HLA-mismatched donor ($P = 0.0042$ and $P = 0.0023$, respectively)

preparative conditioning regimen for allogeneic HCT in patents with T-PLL remains uncertain. Therefore, carefully designed prospective trials are essential to determine the contribution of specific conditioning regimens for successful disease control.

There are some limitations to this retrospective cohort study. The small number of patients may have confounded recognition of small differences in the outcomes. However, our encouraging results confirm the overall safety and tolerability of allogeneic HCT from HLA-matched donors in patients who are deemed eligible for allogeneic HCT in transplantation centers. Additionally, the lack of mutation data, including IL2RG-JAK1-JAK3-STATB [20, 21], is a major limitation in this study, and a more prolonged follow-up may be required to better evaluate eligibility criteria for HCT. We evaluated patients with T-PLL, and the onset of disease progression depended on the time of examination. Therefore, we analyzed transplant-related death and death caused by T-PLL. Additionally, the effects of different chemotherapies before HCT were unclear because details of treatments before HCT were unavailable. Finally, the reasons for choosing allogeneic HCT were unclear in a retrospective cohort study. This may have resulted in bias that was potentially exemplified by donor availability and the degree of HLA matches in the HLA-mismatched donor group or by a younger age and poor-risk disease characteristics.

In conclusion, T-PLL is a rare condition that is associated with a poor prognosis. Our data suggest that the allogeneic HCT from an HLA-matched donor can be considered for patients with T-PLL who lack complex chromosomal abnormalities. Prospective trials of allogeneic HCT and new therapies with targeted agents, such as BCL-2 inhibitors [22–24] and histone deacetylase inhibitors [25], are required to promote better disease control before allogeneic HCT. These trials and therapies could also lead to improvement in safety and efficacy of allografting in patients with T-PLL and complex chromosomal abnormalities. Potential new approaches for preventing and treating GVHD for allogeneic HCT from HLA-mismatched donors might improve outcomes among patients with T-PLL and in those who undergo planned treatment using alemtuzumab before or after allogeneic HCT.

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Compliance with ethical standard

This study was approved by the data management committee of the Japanese Society for Hematopoietic Cell Transplantation and the Institutional Review Board of Kyushu Medical Center.

Informed consent The Transplant Registry Unified Management Program database included physician-reviewed data. Observational studies based on the Transplant Registry Unified Management Program databases are performed with an informed consent.

Conflict of interest The authors declare that they have no conflict of interest.

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