Identification of an Optimal Population for Allogeneic Hematopoietic Stem Cell Transplantation in Patients With Mature T and NK Cell Neoplasms

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Abstract. *Background/Aim:* The prognosis of mature T and natural killer (NK) cell neoplasms still remains dismal, despite the advancements in the understanding of the heterogeneous features of these diseases. As allogeneic stem cell transplantation (alloSCT) is an attractive salvage option for relapsed/refractory patients, we conducted this study to identify those who might benefit the most from alloSCT. *Patients and Methods:* This was a retrospective, single-center, longitudinal cohort study of patients who received alloSCT between December 2019 and January 2000. *Results:* The median relapse-free survival and overall survival were 4.4 and 10.0 months, respectively. Disease control status at alloSCT and number of previous treatments were associated with survival outcomes. The conditioning intensity did not significantly alter survival. *Conclusion:* AlloSCT offers a cure chance for selected relapsed or refractory T and NK cell neoplasms, especially when used early and the disease is well controlled prior to transplantation.

Mature T and natural killer (NK) cell neoplasms consist of a wide spectrum of lymphoproliferative disorders with varying geographic distributions and clinical courses. With increasing knowledge about their immunophenotypic and

molecular characteristics, these lymphomas have repeatedly been classified (1). Unfortunately, better understanding of this disease has not been accompanied by therapeutic improvements. Cyclophosphamide (Cy)- and anthracycline-based treatment remains the first line therapy in most cases, and even with the introduction of etoposide and l-asparaginase and the incorporation of consolidation autologous stem cell transplantation (autoSCT), the progression-free survival rate at 2 years lingers at 42% (2, 3). Thus, effective treatment strategies to prevent relapse and allow salvage are needed.

Several studies have suggested allogeneic stem cell transplantation (alloSCT) as an option for long-term disease control based on its graft-versus-lymphoma (GVL) effects (4-6). Unfortunately, it is still difficult to define when and who should undergo alloSCT because the outcomes are still unsatisfactory, including high rates of treatment related mortality (TRM). The success of alloSCT with reduced intensity conditioning (RIC) has mitigated some of the concern (6, 7), but questions remain including identification of the optimal population and transplant timing. In this regard, we performed a detailed analysis of Korean patients with mature T and NK cell neoplasms undergoing alloSCT. In particular, we focused on the feasibility of and prognostic factors associated with alloSCT in real-life clinical practice.

Patients and Methods

Study design and subjects. This was a retrospective, longitudinal cohort study of patients with mature T and NK cell neoplasms aged older than 18 years who received alloSCT at Seoul National University Hospital between January 2000 and December 2019. The diagnosis and classification of mature T and NK cell neoplasms were performed according to the World Health Organization criteria at the time of diagnosis (1, 8, 9). Initially, 45 patients with mature

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Figure 1. Subtype of lymphoma. PTCL: Peripheral T-cell lymphoma; TLBL: T lymphoblastic lymphoma; AITL: angioimmunoblastic T-cell lymphoma; ALCL: anaplastic large cell lymphoma.

T and NK neoplasms undergoing alloSCT at any point during their clinical course, whether it was frontline or salvage consolidation, were screened. After eliminating 1 patient who was HIV-positive, 1 with an uncertain diagnosis, and 1 with acute lymphoblastic leukemia, a total of 42 patients were deemed eligible. Among these final 42 patients, 15 (35.7%) had peripheral T-cell lymphoma (PTCL), 14 (33.3%) had T lymphoblastic lymphoma (T-LBL), 8 (19.0%) had NK/T cell lymphoma, 3 (7.1%) had cutaneous T cell lymphoma, and 2 (4.8%) had T-cell prolymphocytic leukemia (T-PLL) (Figure 1). Their medical records were reviewed and analyzed for demographics, baseline disease characteristics, chemotherapy, factors related to alloSCT, response to alloSCT, adverse events, and survival outcomes.

Definitions. Responses to therapy and disease status were defined according to current conventional standard criteria (10, 11). Conditioning regimen intensity was classified according to consensus criteria (12). Acute graft-versus-host disease (GVHD) grading was performed according to the standard criteria (13). Chronic GVHD was classified as mild, moderate, or severe according to the 2014 National Institutes of Health consensus criteria (14). TRM was defined as death without progression of underlying lymphoma. Relapse free survival (RFS) was defined as the time from stem cell infusion to relapse or death from any cause. Overall survival (OS) was defined as the time from stem cell infusion to death of any cause. Neutrophil engraftment was defined as an absolute neutrophil count (ANC) $>0.5 \times 10^9/l$ on 3 consecutive measurements. Platelet recovery was defined as 7 consecutive measurements of $20.0 \times 10^9/l$ without transfusion.

Statistical analysis. Differences between groups were assessed using Student's *t*-test or one-way analysis of variance for continuous variables, and Pearson's chi-square test for categorical variables, as indicated. The RFS and OS curves were estimated using the Kaplan-Meier method. If patients survived without death or progression, survival was censored at the latest date of follow-

up when no death or progression was confirmed. Cumulative incidence curves were used in a competing-risk setting to calculate the probability of acute and chronic GVHD and TRM. For GVHD, death without an event was considered the competing event. For TRM, relapse was considered the competing event. Associations between potential prognostic factors and survival outcomes were evaluated using Cox's proportional hazard regression models. A stepwise backward procedure was used, and all predictors achieving a *p*-value below 0.05 were considered and sequentially removed if the *p*-value in the multivariate model was above 0.05. All data were analyzed using the Statistical Package for the Social Sciences software (SPSS®Statistics, version 22.0, IBM®, New York, NY, USA). Statistical significance was considered at *p*-values <0.05 .

Results

Patient characteristics. Baseline patient characteristics are summarized in Table I. The median age at diagnosis of all patients was 35.0 years (range=17-62 years). The majority of the patients (90.5%) had Ann Arbor stage III-IV disease with bone marrow involvement. The median number of previous lines of therapy before alloSCT was 4 (range=1-8), counting prior autoSCT as one regimen. There were 18 patients (42.9%) who underwent autoSCT. The median time from diagnosis to alloSCT was 16.0 months (range=2-71 months). At the time of transplantation, 17 patients (40.5%) were in the first or subsequent complete response (CR); 9 were in CR1 and 8 were in CR2. There were 12 (28.6%) patients with uncontrolled disease [*i.e.* progressive disease (PD)] at the time of alloSCT. With respect to the donor source, most patients (38/42, 90.5%) had matched donors. Regarding the conditioning regimen, a similar number of

Table I. Baseline characteristics of all patients.

Characteristics	N
Age at alloSCT, years* (median, range)	35.0 (17-62)
Gender, male	33 (71.7%)
Lymphoma subtypes	
Peripheral T-cell lymphoma	15 (35.7%)
T lymphoblastic lymphoma	14 (33.3%)
NK/T cell lymphoma	8 (19.0%)
Cutaneous T cell lymphoma	3 (7.1%)
T-cell prolymphocytic leukemia	2 (4.8%)
PIT score	
0	6 (14.3%)
1	15 (35.7%)
2	19 (45.2%)
Extranodal involvement (>1)	38(90.5%)
Previous lines of treatment before alloSCT	4 (1-8)*
1	3 (7.1%)
2	9 (21.4%)
3	9 (21.4%)
≥4	21 (50.0%)
Previous autoSCT	18 (42.9%)
Time from diagnosis to alloSCT, months*	16.0 (2-71)
Time from last chemo to alloSCT, months*	1.9 (0.5-13.4)
Year of alloSCT	
2000-2004	3 (7.1%)
2005-2009	11 (26.2%)
2010-2014	6 (14.3%)
2015-2019	22 (52.4%)
Disease status at transplantation	
CR	17 (40.5%)
PR	13 (31.0%)
Others	12 (28.5%)
Conditioning regimen	
MAC	23 (54.8%)
BuCy/BuFlu/TBI-based/others	14 (33.3%)/5 (11.9%)/ 3 (7.1%)/1 (2.4%)
RIC	19 (45.2%)
BuFlu/others	16 (38.1%)/ 3 (7.1%)
Donor source	
Matched related donor	27 (64.3%)
Matched unrelated donor	11 (26.2%)
Haplo-identical	4 (9.5%)
Sex matching	
Female donor to male recipient	7 (16.7%)
Modified EBMT risk score	
1-3	21 (50.0%)
4-6	21 (50.0%)
Infused CD34, ×106/kg*	4.93 (1.26-14.34)
GVHD prophylaxis	
Cyclosporine based	34 (70.9%)
Tacrolimus based	8 (19.1%)
ATG use	21 (50%)

AlloSCT: Allogeneic stem cell transplantation; PIT: prognostic index for T-cell lymphoma; CR: complete remission; PR: partial remission; MAC: myeloablative conditioning; RIC: reduced intensity conditioning; Bu: busulfan; Cy: cyclophosphamide; Flu: fludarabine; TBI: total body irradiation; EBMT: European Blood and Marrow Transplantation; CD34: cluster of differentiation; GVHD: graft-versus-host disease; ATG: anti-thymoglobulin. *Represents median (range).

Table II. Transplantation outcomes.

Parameters	N
Follow-up from diagnosis, months (median, range)	33 (4-175)
Neutrophil engraftment	37 (88.1%)
Time to neutrophil engraftment, days (median, range)	14 (8-24)
Platelet recovery	34 (81.0%)
Time to platelet recovery, days (median, range)	13 (7-47)
Cumulative incidence of any acute GVHD at Day 100	
Grade II-IV acute GVHD	31.6%
Cumulative incidence of any chronic GVHD at 1 year	
Moderate-severe chronic GVHD	28.7%
Relapse after alloSCT	27 (64.3%)
Further treatment after alloSCT	14 (33.3%)
CTx only	11 (26.2%)
CTx followed by 2nd alloSCT	2 (4.8%)
RTx only	1 (2.4%)
Treatment related mortality at 1 year	9 (21.4%)
GVHD	2 (4.8%)
Infection	6 (14.3%)
VOD	1 (2.4%)

AlloSCT: Allogeneic stem cell transplantation; GVHD: graft-versus-host disease; CTx: chemotherapy; RTx: radiotherapy; VOD: veno-occlusive disease.

patients underwent myeloablative conditioning (MAC) (23/42, 54.8%) and RIC (19/42, 45.2%).

Engraftment and chimerism. As shown in Table II, neutrophil engraftment was observed in 37 (88.1%) patients and platelet engraftment was observed in 34 (81.0%) patients. The median time to neutrophil and platelet engraftment was 14 days (range=8-24 days) and 13 days (range=7-47 days) respectively. Chimerism at 1 month was available for 31 patients: 21 (67.7%) showed complete chimerism, while 10 patients showed mixed chimerism. Among 23 patients undergoing RIC, 11 patients (47.8%) achieved complete chimerism at 1 month.

Complications of alloSCT. The cumulative incidence of grade II-IV acute GVHD at day 100 was 31.6%, and the cumulative incidence of moderate to severe chronic GVHD at 1 year was 28.7% (Table II). There was no difference in the occurrence of acute GVHD according to the conditioning regimen, including 7 patients who underwent RIC (30.4%) and 6 patients who underwent MAC (31.5%). The occurrence of chronic GVHD between the two groups (RIC, 17.4% vs. MAC, 21.1%) was also similar.

The TRM at 1 year was 21.4%. The main causes of death were as follows: infection in 6 patients (14.3%), GVHD in 2 patients (4.8%) and venous-occlusive disease in 1 patient (2.4%). According to the conditioning intensity, the TRM at 1 year was 26.1% for patients undergoing MAC compared to 10.5% for patients undergoing RIC.

Figure 2. Kaplan-Meier curves of relapse-free survival. (A) All patients; (B) Disease status at allogeneic stem cell transplantation; (C) No. of previous treatment regimens, <4 vs. ≥ 4 ; (D) Conditioning regimen, reduced intensity conditioning (RIC) vs. myeloablative conditioning (MAC); (E) Subtype of lymphoma. CR: Complete response; PR: partial response; PTCL: peripheral T-cell lymphoma; TLBL: T lymphoblastic lymphoma.

Figure 3. Kaplan-Meier curves of overall survival. (A) All patients; (B) Disease status at allogeneic stem cell transplantation (alloSCT); (C) No. of previous treatment regimens, <4 vs. ≥ 4 ; (D) Conditioning regimen, RIC vs. MAC; (E) Subtype of lymphoma. PTCL: Peripheral T-cell lymphoma; CR: complete response; PR: partial response; TLBL: T lymphoblastic lymphoma; MAC: myeloablative conditioning; RIC: reduced intensity conditioning.

Table III. Risk factors for transplantation outcomes on multivariate analyses.

	HR (95%CI)	p-Value
Relapse Free Survival		
No. previous treatment regimen, <4 vs. ≥4	3.340 (0.963-11.592)	0.057
Disease status at alloSCT		0.057
SD+PD	1.000	
PR	0.400 (0.106-1.515)	0.177
CR	0.116 (0.019-0.695)	0.018
Modified EBMT score, 1-3 vs. 4-6	2.042 (0.526-7.921)	0.302
Subtype of lymphoma		0.306
T-lymphoblastic lymphoma	1.000	
Peripheral T-cell lymphoma, NOS	1.121 (0.294-4.275)	0.868
NK/T cell lymphoma	5.186 (0.877-30.669)	0.070
Cutaneous T cell lymphoma	3.877 (0.538-27.938)	0.179
T-cell prolymphocytic leukemia	1.502 (0.128-17.564)	0.746
Conditioning regimen, RIC vs. MAC		
RIC	1.000	
MAC	1.340 (0.442-4.058)	0.605
Overall Survival		
No. previous treatment regimen, <4 vs. ≥4	5.779 (1.547-21.591)	0.009
Disease status at alloSCT		0.033
SD+PD	1.000	
PR	0.490 (0.128-1.873)	0.297
CR	0.090 (0.015-0.546)	0.009
Modified EBMT score, 1-3 vs. 4-6	1.633 (0.479-5.564)	0.433
Subtype of lymphoma		0.038
T-lymphoblastic lymphoma	1.000	
Peripheral T-cell lymphoma, NOS	1.553 (0.399-6.047)	0.526
NK/T cell lymphoma	17.444 (2.577-118.094)	0.003
Cutaneous T cell lymphoma	5.193 (0.699-38.601)	0.107
T-cell prolymphocytic leukemia	3.747 (0.291-48.310)	0.311
Conditioning regimen, RIC vs. MAC		
RIC	1.000	
MAC	2.512 (0.767-8.227)	0.128

AlloSCT: Allogeneic stem cell transplantation; EBMT: European Blood and Marrow Transplantation; RIC: reduced intensity conditioning; MAC: myeloablative conditioning; CR: complete remission; PR: partial remission; SD: stable disease; PD: progressive disease; NOS: not otherwise specified.

Twenty-seven patients (64.3%) relapsed after alloSCT and 14 (33.3%) were able to receive intensive treatment after relapse. All but 1 patients received cisplatin based chemotherapy, either gemcitabine-dexamethasone-cisplatin or dexamethasone-cytarabine-cisplatin, and 2 were able to undergo second alloSCT.

Survival outcomes. The median follow-up duration from diagnosis was 33.0 months (range=4-175 months). The median RFS was 4.4 months (range=0.39-156.04 months) and the median OS was 10.0 months (range=0.39-156.04 months) for all patients. RFS curves for all patients are shown in Figure 2. The followings were associated with RFS: disease status at the time of alloSCT (Figure 2B; CR, 11.18 months; PR, 3.61 months; others 3.80 months; CR vs. others, $p=0.004$; CR vs. PR, $p=0.099$; PR vs. others, $p=0.525$) and number of previous treatment (Figure 2C; <4

lines, 15.21 months vs. ≥4 lines, 3.21 months, $p=0.007$). Multivariate analysis identified CR state at alloSCT as the sole prognostic factor (Table III). There were no differences in RFS with regards to conditioning intensity (RIC, 4.25 months vs. MAC, 4.46 months, $p=0.661$).

The OS curves are shown in Figure 3. The disease status at alloSCT (Figure 3B; CR, 19.68 months; PR, 3.64 months; others 7.20 months; CR vs. others, $p=0.006$; CR vs. PR, $p=0.071$, PR vs. others, $p=0.542$) and number of previous treatment (Figure 3C; <4 lines, 38.29 months vs. ≥4 lines, 4.29 months, $p=0.004$) were associated with OS. In addition, longer OS was observed in patients who underwent RIC compared to those who underwent MAC (Figure 3D; RIC, 11.29 months vs. MAC, 8.89 months, $p=0.434$). Analyzing the differences between lymphoma subtypes, the longest median OS of 16.34 months was noted in the PTCL group (Figure 3E). In multivariate analysis (Table III), more than

Table IV. Long term survivors.

	Age at diagnosis	Age at alloSCT	Dx	No. of previous treatment before alloSCT	mEBMT Score	Disease status before alloSCT	Previous Auto SCT	Month from Diagnosis to alloSCT	HLA matching	Conditioning	GVHD prophylaxis	ATG use	Chimerism at 1 month	Relapse	TRM	Onset of acute GVHD	Onset of chronic GVHD	RFS	Treatment after Relapse	OS
1	30	32	PTCL	3	4	Persistent	Yes	18.03	8/8	BuCy	CSA based	No	Complete	Yes	No	No	No	118	Chemo -therapy resume	156
2	20	20	T-LBL	2	5	CR	No	5.77	8/8	BuCy	CSA based	No	Complete	No	No	SOL0G1	Severe	59	60	
3	28	29	PTCL	3	2	CR	No	16.40	10/10	BuCy	CSA based	No	Complete	No	No	No	No	152	152	
4	45	46	PTCL	3	3	CR	No	1.93	8/8	BuCy	CSA based	No	Complete	No	No	No	Mild	75	75	
5	35	35	PTCL	2	3	CR	Yes	6.27	8/8	BuCy	CSA based	No	Complete	No	No	No	Mild	97	97	
6	34	37	T-LBL	4	1	PR	Yes	28.53	10/10	BuFluATG (MAC)	CSA based	Yes	Mixed	Yes	No	No	No	5	Radio -therapy	107
7	47	49	PTCL	5	3	PR	Yes	25.97	8/8	BuFluATG (MAC)	CSA based	Yes	Mixed	No	No	No	No	101	101	
8	52	52	Extranodal NK/T-cell	1	4	CR	No	5.03	7/8	BuFluATG (RIC)	CSA based	Yes	Mixed	Yes	No	No	No	1	Chemo -therapy +DLI	60
9	31	32	T-PLL	3	2	CR	No	17.53	10/10	BuCy	CSA based	No	Complete	No	No	SOL1G1	Severe	156	156	

AlloSCT: Allogeneic stem cell transplantation; Dx: diagnosis; mEBMT: modified European Blood and Marrow Transplantation; AutoSCT: autologous stem cell transplantation; HLA: human leukocyte antigen; GVHD: graft-versus-host disease; ATG: anti-thymoglobulin; TRM: treatment related mortality; RFS: relapse-free survival; OS: overall survival; PTCL: peripheral T-cell lymphoma; T-LBL: T lymphoblastic lymphoma; T-PLL: T-cell prolymphocytic leukemia; CR: complete remission; PR: partial remission; Bu: busulfan; Cy: cyclophosphamide; Flu: fludarabine; CSA: cyclosporine; DLI: donor lymphocyte infusion.

4 previous lines of treatment (HR=5.779, 95%CI=1.547-21.591, $p<0.009$) and NK/T cell lymphoma subtype (HR=17.444, 95%CI=2.577-118.094, $p=0.003$) were associated with shorter survival, whereas CR status at the time of alloSCT (HR=0.090, 95%CI=0.015-0.546, $p=0.009$) was associated with longer survival.

Long-term survivors. Long-term survivors were defined as patients surviving longer than 60 months post-alloSCT, either with or without relapse. As shown in Table IV, there were 9 long-term survivors: 5 patients with PTCL, 2 with T-LBL, 1 with T-PLL and 1 with extranodal NK-T cell lymphoma. The median RFS and OS for these patients were 97 months and 101 months, respectively. Eight patients (88.9%) had full-matched donors and underwent alloSCT when their disease was under control (*i.e.*, CR or PR state). The median number of treatments prior to alloSCT was 3. All but 1 patients underwent MAC. Three patients (33.3%) relapsed, and all received further treatment: 1 was treated with chemotherapy alone, 1 was treated with chemotherapy and donor lymphocyte infusion (DLI) while 1 was treated with radiotherapy alone. Further details of these patients are presented in Table V.

Discussion

We conducted this study to determine the feasibility of alloSCT in patients with mature T and NK cell neoplasms and found that 1) earlier implementation and good disease control at the time of alloSCT leads to better outcomes; 2) some subtypes of mature T and NK cell neoplasms may not benefit from alloSCT; and 3) alloSCT with RIC is an attractive salvage option, with similar efficacy to and less toxicity than MAC.

According to our study, alloSCT seems to be a viable treatment option for patients with mature T and NK cell neoplasms. In our cohort of 42 patients, the 1- and 3-year RFS rates were 55.6% and 51.3%, respectively, and 1- and 3-years OS rates were 57.9% and 54.4%, respectively. These results are comparable to previous studies reporting the clinical advantages of alloSCT in T-cell lymphoma treatment (7, 15-17). Specifically, the reported 1-year RFS for angioimmunoblastic T-cell lymphoma (AITL) is 62% and 1-year OS 53% (15). For PTCL and advanced mycosis fungoides/Sezary syndrome, the reported 3-year progression-free survival was 30%; 45% with predominantly nodal histologies [peripheral T-cell lymphoma (PTCL), not otherwise specified (NOS), AITL, and anaplastic large cell lymphoma (ALCL)], 6% with predominantly extranodal histologies (7). We identified disease status and number of previous treatments as prognostic factors for both RFS and OS.

Interestingly, we found that particular lymphoma subtypes were more likely to profit from alloSCT. PTCL patients were

Table V. Details of long-term survivors.

Characteristics	N
Age at alloSCT, years* (median, range)	35.1 (20-52)
Gender, male	7 (77.8%)
Lymphoma subtypes	
Peripheral T-cell lymphoma	2 (22.2%)
T lymphoblastic lymphoma	5 (55.6%)
NK/T cell lymphoma	1 (11.1%)
T-cell prolymphocytic leukemia	1 (11.1%)
Modified EBMT risk score	
1/2/3/4/5	1 (11.1%)/2 (22.2%)/3 (33.3%)/2 (22.2%)/1 (11.1%)
Previous lines of treatment before alloSCT	
<4/≥4	7 (77.8%)/2 (22.2%)
Previous autoSCT	4 (44.4%)
Time from diagnosis to alloSCT, months*	16.4 (1.93-28.53)
Disease status at transplantation	
CR/PR/Others	6 (66.7%)/2 (22.2%)/1 (11.1%)
Conditioning regimen	
MAC/RIC	6 (66.7%)/3 (33.3%)
Donor source	
Matched related donor	27 (64.3%)
Matched unrelated donor	11 (26.2%)
Haplo-identical	4 (9.5%)
Sex matching	
Female donor to male recipient	2 (22.2%)
Infused CD34, $\times 10^6/\text{kg}^*$	4.58 (1.26-8.06)
GVHD prophylaxis	
Cyclosporine/Tacrolimus/ATG	9 (100%)/0 (0%)/3 (33.3%)
Chimerism at 1 month	
Complete/Mixed	6 (66.7%)/3 (33.3%)
Onset of acute GVHD/chronic GVHD	2 (22.2%)/4 (44.4%)
Relapse	4 (44.4%)

AlloSCT: Allogeneic stem cell transplantation; EBMT: European Blood and Marrow Transplantation; autoSCT: autologous stem cell transplantation; CR: complete remission; PR: partial remission; MAC: myeloablative conditioning; RIC: reduced intensity conditioning; CD34: cluster of differentiation 34; GVHD: graft-versus-host disease; ATG: anti-thymoglobulin. *Represents median (range).

associated with longest survival, thus these patients were subjected to further investigations (Table VI). In the PTCL group, 10 patients (66.6%) were previously treated with autoSCT and 11 patients (73.3%) were treated with CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisone) as the 1st line of treatment. The OS and PFS rates were superior in patients who received previous autoSCT but the difference did not reach statistical significance (Figure 4A, $p=0.785$ and Figure 5A, $p=0.765$). Additionally, the followings are also related to longer RFS and OS in the subgroup analysis of patients with PTCL, but not statistically significant: disease status at the time of alloSCT (Figure 4C and Figure 5C), 1st line chemotherapy, CHOP *vs.* Non-CHOP (Figure 4D and Figure 5D) and CR1 duration (Figure 4E and

Table VI. Details of PTCL patients.

	Total (N=15)		PTCL, NOS (N=8)		AITL (N=5)		ALCL (N=2)	
	AutoSCT before alloSCT	Non-autoSCT before alloSCT	AutoSCT before alloSCT	Non-autoSCT before alloSCT	AutoSCT before alloSCT	Non-autoSCT before alloSCT	AutoSCT before alloSCT	Non-autoSCT before alloSCT
No. of patients (%)	10 (66.6%)	5 (33.3%)	4 (26.7%)	4 (26.7%)	4 (26.7%)	1 (6.7%)	2 (13.3%)	0 (0%)
Age at alloSCT, years (median, range)	48.2 (20-61)	45.7 (28-53)	40.5 (29-55)	45.5 (35-54)	55.5 (52-62)	47	23.5 (21-26)	
Gender, male	7 (46.7%)	5 (33.3%)	3 (20.0%)	4 (26.7%)	2 (13.3%)	1 (6.7%)	2 (13.3%)	
Modified EBMT risk score, ≥ 4	6 (40.0%)	5 (33.3%)	2 (13.3%)	4 (26.7%)	4 (26.7%)	1 (6.7%)	0 (0%)	
Previous lines of treatment before alloSCT, ≥ 4	6 (40.0%)	2 (13.3%)	2 (13.3%)	1 (6.7%)	2 (13.3%)	1 (6.7%)	2 (13.3%)	
Time from diagnosis to alloSCT, months (median, range)	19.0 (6.3-55.0)	6.3 (1.9-16.4)	20.4 (17.6-27.8)	5.6 (2.1-6.8)	32.5 (17.2-58.9)	15.6	10.6 (10.35-10.78)	
Disease status at transplantation								
CR	2 (13.3%)	2 (13.3%)	2 (50.0%)	2 (13.3%)	0 (0%)	0 (0%)	0 (0%)	
PR	5 (33.3%)	2 (13.3%)	1 (6.7%)	1 (6.7%)	3 (20.0%)	1 (6.7%)	1 (6.7%)	
Others	3 (20.0%)	1 (6.7%)	1 (6.7%)	1 (6.7%)	1 (6.7%)	0 (0%)	1 (6.7%)	
Conditioning regimen								
MAC/RIC	5 (33.3%)/5 (33.3%)	5 (33.3%)/0 (0%)	2 (13.3%)/2 (13.3%)	4 (26.7%)/0 (0%)	1 (6.7%)/3 (20.0%)	1 (6.7%)/0 (0%)	2 (13.3%)/0 (0%)	
1 st line Chemotherapy								
CHOP/Non-CHOP	8 (53.3%)/2 (13.3%)	3 (20.0%)/2 (13.3%)	3 (20.0%)/1 (6.7%)	2 (13.3%)/2 (13.3%)	3 (20.0%)/1 (6.7%)	1 (6.7%)/0 (0%)	2 (13.3%)/0 (0%)	
GVHD prophylaxis								
Cyclosporine	8 (53.3%)	5 (33.3%)	4 (26.7%)	4 (26.7%)	2 (13.3%)	1 (6.7%)	2 (13.3%)	
Tacrolimus	2 (13.3%)	0 (0%)	0 (0%)	0 (0%)	2 (13.3%)	0 (0%)	0 (0%)	
ATG	5 (33.3%)	2 (13.3%)	2 (13.3%)	1 (6.7%)	3 (20.0%)	1 (6.7%)	0 (0%)	
Chimerism at 1 month								
Complete/Mixed	7 (46.7%)/3 (20.0%)	2 (13.3%)/3 (20.0%)	3 (20.0%)/1 (25%)	2 (13.3%)/2 (13.3%)	3 (20.0%)/1 (25%)	0 (0%)/1 (6.7%)	1 (6.7%)/1 (6.7%)	
Engraftment, ANC/PLT, days (median, range)	10 (100%)/9 (90%)	3 (20.0%)/3 (20.0%)	4 (26.7%)/3 (20.0%)	3 (20.0%)/3 (20.0%)	4 (26.7%)/4 (26.7%)	0 (0%)/0 (0%)	2 (13.3%)/2 (13.3%)	
Onset of aGVHD/ cGVHD	14 (8-24)/16 (8-47)	11 (11-22)/10(10-26)	14 (8-22)/17 (8-35)	11 (11-15)/10(10-14)	11 (9-15)/14 (9-34)	0 (0%)/0 (0%)	22 (19-24)/33 (19-47)	
Relapse	2 (13.3%)/1 (6.7%)	1 (6.7%)/1 (6.7%)	0 (0%)/0 (0%)	1 (6.7%)/1 (6.7%)	2 (13.3%)/1 (6.7%)	0 (0%)/0 (0%)	0 (0%)/0 (0%)	
Overall survival, months (median, range)	6 (40.0%)	3 (20.0%)	2 (13.3%)	2 (13.3%)	2 (13.3%)	1 (6.7%)	2 (13.3%)	
Relapse free survival, months (median, range)	15.7 (1.5-156.0)	13.0 (0.6-151.9)	98.9 (11.3-156.0)	44.1 (0.64-97.0)	12.6 (1.46-41.2)	2.2	2.0 (1.9-2.5)	
	12.3 (0.7-118.3)	4.5 (0.6-151.9)	98.9 (3.1-118.3)	39.9 (0.64-97.0)	12.3 (1.46-41.2)	1.32	1.3 (0.7-2.0)	

PTCL: Peripheral T-cell lymphoma; NOS: peripheral T-cell lymphoma, not otherwise specified; AITL: angioimmunoblastic T-cell lymphoma; ALCL: anaplastic large cell lymphoma; alloSCT: allogeneic stem cell transplantation; autoSCT: autologous stem cell transplantation; EBMT: European Blood and Marrow Transplantation; CR: complete remission; PR: partial remission; MAC: myeloablative conditioning; RIC: reduced intensity conditioning; CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisone; ATG: anti-thymoglobulin; ANC: absolute neutrophil count; PLT: platelet; aGVHD: acute graft-versus-host disease; cGVHD: chronic graft-versus-host-disease.

Figure 5E). Among various subtypes of PTCL, patients with PTCL, NOS showed long RFS and OS compared to other subtypes (Figure 4B, $p=0.041$ and Figure 5B, $p=0.074$). It is also worth noting that patients with NK/T-cell lymphoma showed significantly inferior RFS (HR=5.186, 95%CI=0.877-30.669, $p=0.070$) and OS (HR=17.444, 95%CI=2.577-118.094, $p=0.003$). The limited role of alloSCT in NK/T-cell lymphoma has been recently reported by Kim *et al.* (18), and our data supports their findings.

Another focus of interest was the intensity of conditioning regimen. Conditioning regimen for lymphomas has traditionally been MAC in nature, but this entails higher risk of TRM and GVHD (16). In recent years, alloSCT with RIC has gained popularity based on acceptable RFS and OS, but the major pitfall is the higher relapse rates (4, 19-21). In our cohort, there were no differences in survival and GVHD incidence according to conditioning intensity, but RIC showed lower 1-year TRM rates (RIC, 10.5% *vs.* MAC, 26.1%). Since many patients undergoing alloSCT are associated with physical debilitation from extensive chemotherapy, RIC can be a good option even for younger patients.

Lastly, there were 4 patients undergoing haplo-identical stem cell transplantation (haplo-SCT) in our cohort (Table VII). Neutrophil and platelet engraftment were observed in all 4 patients and the median RFS was 11 months. None of them experienced TRM. In general, approximately 30% of patients have matched sibling donors. Additional 40-50% of patients have matched unrelated donors (MUDs), but 20-30% of the patients require an alternative donor. In particular, in the treatment setting of lymphoma where 'planned' alloSCT is often not possible, there is a higher chance that the immediately available donor is not a matched one. Recently, the Center for International Blood and Marrow Transplant Research reported that the outcomes of haplo-SCT in patients with non-Hodgkin's lymphoma were comparable to those achieved with alloSCT from MUD (22, 23). Specifically, haplo-SCT showed a similar 3-year TRM (15% *vs.* 13%), 2-year incidence of relapse (37% *vs.* 40%), 3-year PFS (48% *vs.* 48%), 2-year OS (61% *vs.* 62%) and 100-day incidence of grade II-IV acute GVHD (27% *vs.* 25%) compared to alloSCT from MUD. Although very few patients underwent haplo-SCT in our cohort, our results also support the previous studies about feasibility of haplo-alloSCT in the setting of non-Hodgkin's lymphoma (24).

One of the most obvious pitfalls of this study is its retrospective nature. As such, there may be selection bias for patients who underwent alloSCT. In addition, although 42 patients with mature T and NK cell neoplasms undergoing alloSCT is not a small number considering the rarity of the disease, there are perhaps too few patients to draw statistically powerful conclusions. Thus, our results should be cautiously interpreted and confirmed by further studies with a larger number of patients.

Table VII. Long term survivors.

	Age at Dx	Age at alloSCT	Dx	No. of previous treatment before alloSCT	mEBMT Score	Disease status before alloSCT	Previous Auto SCT	Month from Dx to alloSCT	Age of donor	Conditioning	Infused CD-34	GVHD prophylaxis	Chimerism at 1 month	Relapse	TRM	Onset of GVHD (Acute/Chronic)	RFS /OS (month)
1	29	30	Primary cutaneous gamma-delta T cell lymphoma	5	4	CR2	Yes	14.93	26	BuFlu ATG7	6.39	CSA based	Complete	No	No	SIL2G1 /No	32.00/ 32.00
2	21	22	T-lymphoblastic lymphoma /leukemia	2	2	CR1	No	11.71	52	BuFlu PTCy	5.99	Tacrolimus based	Mixed	Yes	No	S2L0G0 /No	4.25 7.11
3	28	29	T-lymphoblastic lymphoma /leukemia	1	2	CR1	No	7.89	57	TBI/FluPTCy	4.88	Tacrolimus based	NA	No	No	S2L0G0 /No	19.68 19.68
4	32	33	T-lymphoblastic lymphoma /leukemia	4	5	Persis -tence	No	20.50	60	TBI/FluPTCy	3.37	Tacrolimus based	NA	No	No	S3L0G0 /Yes	11.25 11.25

Dx: Diagnosis; alloSCT: allogeneic stem cell transplantation; mEBMT: modified European Blood and Marrow Transplantation; AutoSCT: autologous stem cell transplantation; CD34: cluster of differentiation 34; GVHD: graft-versus-host disease; TRM: treatment related mortality; RFS: relapse free survival; OS: overall survival; CR1: first complete remission; Bu: busulfan; Flu: fludarabine; TBI: total body irradiation; PTCy: post transplant cyclophosphamide; NA: not applicable; CSA: cyclosporine; S: skin; L: liver.

Figure 4. Kaplan-Meier curves of relapse-free survival of PTCL patients. (A) History of previous autoSCT; (B) subtype of PTCL; (C) disease status at alloSCT; (D) 1st line chemotherapy including cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) vs. Non-CHOP; (E) CR1 duration, <6 vs. ≥ 6 months. PTCL: Peripheral T-cell lymphoma; AITL: angioimmunoblastic T-cell lymphoma; ALCL: anaplastic large cell lymphoma; CR: complete response; PR: partial response; autoSCT: autologous stem cell transplantation; alloSCT: allogeneic stem cell transplantation; NOS: not otherwise specified.

Figure 5. Kaplan-Meier curves of overall survival of PTCL patients. (A) History of previous autoSCT; (B) subtype of PTCL; (C) disease status at alloSCT; (D) 1st line chemotherapy including cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) vs. Non-CHOP; (E) CR1 duration, <6 vs. ≥ 6 months. PTCL: Peripheral T-cell lymphoma; autoSCT: autologous stem cell transplantation; alloSCT: allogeneic stem cell transplantation; AITL: angioimmunoblastic T-cell lymphoma; ALCL: anaplastic large cell lymphoma; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; NOS: not otherwise specified.

In conclusion, alloSCT represents a viable treatment option in patients with certain subtypes of mature T and NK cell neoplasms, given that some patients experience a long durable remission. Our results suggest that if alloSCT is considered, the outcomes are best when this treatment is used earlier and when disease is well controlled prior to transplant. Finally, the use of RIC can mitigate the toxicity concerns traditionally associated with alloSCT in patients with lymphoma without compromising the outcomes.

Conflicts of Interest

The Authors have no conflicts of interest to disclose in relation to this study.

Authors' Contributions

Conceptualization, JMB; methodology, formal analysis, EHJ and JMB; investigation, data curation, all authors; supervision, JMB; writing-original draft preparation, EHJ and JMB; writing-review and editing, all Authors.

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