Outcomes in human T-cell leukemia virus type I carriers after hematopoietic stem cell transplantation for diseases other than adult T cell leukemia/lymphoma: a Japanese national survey

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Summary

Background Human T-cell leukemia virus type I (HTLV-1) is a retrovirus known to cause adult T-cell leukemia/lymphoma (ATL). There are few reports on hematopoietic stem cell transplantation (HSCT) for HTLV-1 carriers with diseases other than ATL.

Methods A total of 25,839 patients (24,399 adults and 1440 children) with pre-transplant HTLV-1 serostatus information recorded in the Japanese National Survey Database who had undergone their first HSCT were analyzed. We investigated the overall survival (OS), transplant-related mortality (TRM), and disease-related mortality (DRM) after HSCT in relation to HTLV-1 serologic status.

Findings Three hundred and forty-eight patients were HTLV-1 antibody carriers. The number of HTLV-1 carriers and noncarriers among adult patients who received allogeneic HSCT (allo-HSCT) or autologous HSCT (auto-HSCT) was 237/15,777 and 95/8920, respectively, and was 16/1424 among pediatric patients who received allo-HSCT. No pediatric HTLV-1 carrier recipients undergoing auto-HSCT were identified. There were no significant differences between HTLV-1 carriers and non-carriers regarding stem cell source, disease risk, or HCT-CI score prior to allo-HSCT. Multivariate analysis of OS (P = 0.020) and TRM (P = 0.017) in adult patients showed that HTLV-1 positive status was a significant prognostic factor. In children, TRM was significantly higher (P = 0.019), but OS was not significantly different. In adult patients who underwent auto-HSCT, HTLV-1 positive status was not a significant prognostic factor. In adult allo-HSCT patients, cytomegalovirus reactivation was significantly more common in HTLV-1 carriers (P = 0.001).

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Interpretation HTLV-1 antibody positivity was shown to have a poor prognosis in OS and TRM after allo-HSCT in adult patients and in TRM after allo-HSCT in pediatric patients.

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Keywords: HTLV-1; Stem cell transplantation; Diseases other than ATL

Research in context

Evidence before this study

There have been a number of reports of risk factors or higher rates of non-relapse mortality, including infection-related mortality, in transplantation for adult T cell leikemia/lymphoma (ATL) compared to other diseases, and it is expected that non-relapse mortality, especially infection-related mortality, may be higher in allogeneic hematopoietic stem cell transplantation (HSCT) for Human T-cell leukemia virus type I (HTLV-1) carriers with diseases other than ATL. There have been previous reports from the Center for International Blood and Marrow Transplant Research (CIBMTR) regarding allogeneic transplantation of HTLV-1 carriers, and the results of this study, HTLV-1 carriers performed poorly with respect to overall survival (OS), and transplant-related mortality (TRM).

Added value of this study

Although the results, including OS and TRM, were similar to the CIBMTR study in that they were poor in HTLV-1 carriers, the present study is larger than that of the CIBMTR in terms of patients analyzed, and unlike the CIBMTR's data, which are multiethnic, the present study is from a single Japanese ethnic group and reports new findings, including the results of allogeneic transplantation in children and the fact that CMV infection was more common in transplants in HTLV-1 carriers, and those patients had a poorer prognosis. This is the first large study to determine the outcomes of hematopoietic cell transplantation in Japanese HTLV-1 patients with diseases other than ATL.

Implications of all the available evidence

This study on HSCT in HTLV-1 antibody–positive patients for diseases other than ATL demonstrated that HTLV-1 antibody positivity was a factor in poor prognosis after allogeneic HSCT in both adult and pediatric patients. In adult patients who underwent autologous HSCT, HTLV-1 positive status was not a significant prognostic factor. In adult allogeneic HSCT patients, cytomegalovirus reactivation was significantly more common in HTLV-1 carriers, and their prognosis was also significantly worse.

Introduction

Human T-cell leukemia virus type I (HTLV-1) is a retrovirus known to be the cause of adult T-cell leukemia/lymphoma (ATL), a type of peripheral lymphoma that has a poor prognosis, despite chemotherapy.[1–4] Some reports indicate that HTLV-1 carriers are immunologically compromised hosts.[5,6] Furthermore, this virus is also known to cause HTLV-1–associated myelitis and uveitis.[7,8] Globally, HTLV-1 is prevalent in a limited number of regions, including Southwest Japan, Central Africa, the Caribbean, and South America.[8] Japan is a major endemic area in the world, with approximately 1 million carriers and 4000 new cases reported annually.[9]

HTLV-1 carriers have been reported to have a higher frequency of opportunistic infections such as systemic disseminated *Strongyloides stercoralis*, molluscum contagiosum, *Mycobacterium tuberculosis*, histoplasma, and other sexually transmitted infections.[10–15]

There have been a number of reports of risk factors or higher rates of non-relapse mortality, including infection-related mortality, in transplantation for ATL[16–19] compared to other diseases, and it is expected that non-relapse mortality, especially infection-related mortality, may be higher in HSCT for HTLV-1 carriers with diseases other than ATL.

On behalf of the Japan Society for Transplantation and Cellular Therapy (JSTCT) Complication Working Group, here we report the impact of HTLV-1 serological status on survival in those with HSCT for diseases other than ATL using the Transplant Registry Unified Management Program (TRUMP).[20] This is a nationwide survey database of the Japanese Data Center for Hematopoietic Cell Transplantation (JDCHCT).

Methods

Patients

There were 25,839 patients (24,399 adults and 1440 children), who had information about their serological status of HTLV-1 in the TRUMP database and who received their first HSCT between January 2007 and December 2015.

Adults were defined as those aged 16 years or older, and children were defined as those younger than 16 years of age.

Data correction

From the TRUMP database, details of HTLV-1 antibody status, patient age at transplant, sex, disease, disease risk at transplant, hematopoietic cell transplantation-comorbidity index (HCT-CI) score, stem cell sources, conditioning regimens, survival status, and cause of death were extracted.

In terms of disease, for malignant lymphoma, patients listed as having ATL were excluded.

Disease risk at transplantation was defined as non-remission at transplantation for hematologic malignancies such as leukemia and malignant lymphoma, and for myelodysplastic syndrome, EB-1 or higher was defined as high risk, and all others as low risk.

Statistical analysis

Survival analysis was performed separately for adult patients who received allo-HSCT and autologous HCST (auto-HSCT), and pediatric patients who received allo-HSCT. Overall survival (OS) after HSCT for HTLV-1 serologic status was analyzed using the Kaplan–Meier method and a log-rank test was used to compare groups. Transplant-related mortality (TRM) after HSCT for HTLV-1 serologic status was calculated by Gray's test, considering disease-related mortality (DRM) as a competing risk.

For adult allo-HSCT patients who were evaluable for incidence of graft-vs-host disease (GVHD) and cytomegalovirus (CMV) antigenemia or diseases, GVHD or CMV was assessed. The cumulative incidence of GVHD was tested with Gray's test, with pre-adult death as a competing risk. For chronic GVHD, only cases that survived more than 100 days were analyzed.

Survival analysis was performed using the Cox model for OS and the Fine–Gray regression model for TRM and DRM, and multivariate analysis was performed using the backward stepwise method. Covariates used in the multivariate analysis were HTLV-1 antibody status, age at transplant, sex, disease risk,[21–24] HCT-CI, stem cell source, disease stage at transplant, and intensity of conditioning regimen. P-values less than 0.05 were considered statistically significant.

Statistical analysis was performed using EZR[25] (EZR Ver 1.60.)

Role of the funding source

The research funds provided for this study covered the cost of English editing of the manuscript and correspondence.

Results

Patient characteristics

Among all patients, there were 348 HTLV-1 carriers. The number of HTLV-1 carriers and non-carriers in adult patients who received allo-HSCT or auto-HSCT was 237/15,777 and 95/8920, respectively, and was 16/1424 in pediatric patients who received allo-HSCT.

The median age of adult HTLV-1 carriers and non-carriers was 57 years (17–76) and 53 years (16–88), respectively, and in pediatric patients was 11 years (0–15) and 8 years (0–15), respectively. Adult allo-HSCT and auto-HSCT patients were significantly older at the time of transplantation than HTLV-1–positive patients, but there was no difference in pediatric allo-HSCT patients. (Table 1).

The number of adult HTLV-1 carriers and non-carriers for each disease was 80/7511 in acute myeloid leukemia (AML), 133/6673 in malignant lymphoma (ML), 34/3265 in plasmacytic neoplasm, 30/2885 in acute lymphoblastic leukemia (ALL), 31/2178 in myelodysplastic syndrome (MDS), 8/446 in chronic myeloid leukemia (CML), 5/539 in aplastic anemia, and 11/570 in others.

The number of pediatric HTLV-1 carriers and non-carriers in each disease was 3/684 in ALL, 6/394 in AML, 2/170 in MDS, 2/76 in congenital metabolic disease, and 3/100 in others.

The number of adult HTLV-1 carriers and non-carriers with auto-HSCT in each disease was 58/4782 in ML, 32/3200 in plasmacytic neoplasm, 5/27 in AML, and 0/35 in others.

No pediatric patients who were HTLV-1 carriers had received auto-HSCT in the TRUMP database.

There were no significant differences in stem cell sources, disease risk, or HCT-CI score before HSCT between HTLV-1 carriers and non-carriers (Table 1).

Survival outcomes

Allo-HSCT in adults

Median OS in adult allo-HSCT recipients was 358 days (0–3249) and 437 days (0–3477) for HTLV-1 antibody–positive and –negative patients, respectively, with OS rates of 40.7% and 50.2% at 3 years post-transplant (P = 0.003). The hazard ratio (HR) of the OS was 1.30 (95% CI, 1.096–1.549, P = 0.003; Table 2 and Fig. 1A).

Among HTLV-1 antibody–positive patients, causes of death were due to primary disease in 40 patients, infection in 31, lung injury/interstitial pneumonia in 12, acute GVHD in 8, multiorgan failure (MOF) in 6, hemorrhage in 6, chronic GVHD in 5, veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) in 4, renal failure in 3, viable tissue in 3, thrombotic microangiopathy (TMA) and acute respiratory distress syndrome (ARDS) and secondary malignancy in 2 patients each, and cardiomyopathy a in 1 patient (Table S1).

Cumulative incidence of TRM at 100 days and 1 year after allo-HSCT was 17.5% vs 12.1% and 31.0% vs 23.6% in HTLV-1 antibody–positive and –negative patients (P = 0.001), respectively, and the HR was 1.41 (95% CI, 1.144–1.743, P = 0.001). In terms of DRM, the

Variables	Total number	HTLV-1 (+)	HTLV-1 (–)	P-value
Adult patients with allo-HSCT	**16,014**	**237**	**15,777**	
Median age (range)	49 years (16–88)	54 years (17–76)	49 years (16–88)	**<0.001**
Gender				0.549
Male	9465 (59.1%)	136 (57.4%)	9329 (59.1%)	
Female	6542 (40.9%)	100 (42.2%)	6442 (40.8%)	
Unknown	4	1	3	
Diseases				**<0.001**
AML	7308 (45.6%)	75 (31.6%)	7233 (45.8%)	
ML	1966 (12.3%)	75 (31.6%)	1891 (12.0%)	
MDS	2206 (13.8%)	31 (13.1%)	2175 (13.8%)	
ALL	2908 (18.2%)	30 (12.7%)	2878 (18.2%)	
CML	454 (2.8%)	8 (3.4%)	446 (2.8%)	
AA	537 (3.4%)	5 (2.1%)	532 (3.3%)	
MPN	237 (1.5%)	2 (0.8%)	235 (1.5%)	
Others	398 (2.5%)	11 (4.6%)	387 (2.5%)	
Disease risk[a]				0.692
Low risk	9008 (56.3%)	130 (54.9%)	8878 (56.3%)	
High risk	7006 (43.7%)	107 (45.1%)	6899 (43.7%)	
HCT-CI				0.542
0	10,686 (66.7%)	132 (55.7%)	9354 (59.3%)	
1–2	4381 (27.4%)	74 (31.2%)	4307 (27.3%)	
≧3	2079 (13.0%)	29 (12.2%)	2050 (13.0%)	
Stem cell source				0.248
CB	4603 (28.7%)	60 (25.3%)	4543 (28.8%)	
Others	11,411 (71.3%)	177 (74.7%)	11,234 (71.2%)	
Conditiong regimen				**0.001**
MAC	9513 (59.4%)	116 (48.9%)	9397 (59.6%)	
RIC	6501 (40.6%)	121 (51.1%)	6380 (40.4%)	
Pediatric patients with allo-HSCT	**1440**	**16**	**1424**	
Median age (range)	8 years (0–15)	11 years (0–15)	8 years (0–15)	0.471
Gender				0.803
Male	833 (57.8%)	10 (62.5%)	823 (57.8%)	
Female	607 (42.2%)	6 (37.5%)	601 (42.2%)	
Diseases				**0.039**
AML	400 (27.8%)	6 (37.5%)	394 (27.7%)	
ALL	687 (47.7%)	3 (18.8%)	684 (48.0%)	
MDS	172 (11.9%)	2 (12.5%)	170 (11.9%)	
Congenital metabolic disease	78 (5.4%)	2 (12.5%)	76 (5.3%)	
Others	103 (7.2%)	3 (18.8%)	100 (7.0%)	
Disease risk[a]				0.417
Low risk	999 (69.4%)	13 (81.3%)	986 (69.2%)	
High risk	441 (30.6%)	3 (18.8%)	438 (30.8%)	
HCT-CI				0.897
0	1158 (80.4%)	12 (75.0%)	1146 (80.5%)	
1–2	212 (14.7%)	3 (18.8%)	209 (14.7%)	
≧3	68 (4.7%)	1 (6.3%)	67 (4.7%)	
Stem cell source				0.285
Sib-PB	95 (6.6%)	2 (12.5%)	93 (6.5%)	
Others	1345 (93.4%)	14 (87.5%)	1331 (93.5%)	
Conditiong regimen				0.774
MAC	1086 (75.4%)	13 (81.3%)	1073 (75.4%)	
RIC	354 (24.6%)	3 (18.8%)	351 (24.6%)	

(Table 1 continues on next page)

Variables	Total number	HTLV-1 (+)	HTLV-1 (−)	P-value
(Continued from previous page)				
Adult patients with auto-HSCT	**8385**	**95**	**8290**	
Median age (range)	57 years (16–81)	59 years (27–79)	57 years (16–81)	0.005
Gender				0.676
Male	4946 (59.0%)	54 (56.8%)	4892 (59.0%)	
Female	3439 (41.0%)	41 (43.2%)	3398 (41.0%)	
Diseases				0.538
ML	4840 (57.7%)	58 (61.1%)	4782 (57.7%)	
Plasmacytic neoplasm	3232 (38.5%)	32 (33.7%)	3200 (38.6%)	
AML	283 (3.4%)	5 (5.3%)	278 (3.4%)	
Others	30 (0.4%)	0 (0%)	30 (0.4%)	
Disease risk[a]				0.730
Low risk	6032 (71.9%)	67 (70.5%)	5965 (72.0%)	
High risk	2328 (27.8%)	28 (29.5%)	2300 (27.7%)	
Unknown	35 (0.4%)	0 (0%)	35 (0.4%)	
HCT-CI				0.474
0	6304 (75.2%)	65 (68.4%)	6249 (75.4%)	
1–2	1640 (19.6%)	23 (24.2%)	1617 (19.5%)	
≧3	380 (4.5%)	6 (6.3%)	374 (4.5%)	
Unknown	51 (0.6%)	1 (1.1%)	50 (0.6%)	

Abbreviations: HTLV-1, human T-cell leukemia virus type 1; AML, acute myeloid leukemia; ML, malignant lymphoma; MDS, myelodysplastic syndrome; ALL, acute lymphoblastic leukemia; CML, chronic myeloid leukemia; AA, aplastic anemia; MPN, myeloproliferative neoplasms; HCT-CI, hematopoietic cell transplantation-comorbidity index; CB, cord blood; MAC, myeloablative conditionig regimen; RIC, reduced intensity conditioning regimen; sib-PB, periperal blood from sibling donor. Statistical significance is indicated by a bold. [a]Low risk of disease risk defined as benign diseases and malignant disease in compleat responce (CR) status; High risk was defined as any malignant diseases status in non-CR and EB 1–2 of MDS.

Table 1: **Patient characteristics.**

cumulative incidence of DRM at 100 days and 1 year after allo-HSCT was 5.56% vs 4.04% and 13.6% vs 13.7% in HTLV-1 antibody–positive and –negative patients (P = 0.672), respectively (Table 2 and Fig. 2A).

In the multivariate analysis in terms of OS and TRM, the HR was 1.24 (95% CI, 1.042–1.478, P = 0.016) and 1.35 (95% CI, 1.345–1.089, P = 0.002). This demonstrates that being an HTLV-1 carrier is a negative risk factor for survival outcomes (Table 2).

Incidents of non-infectious TRM, such as acute GVHD, VOD/SOS, and TMA, were significantly higher in adult HTLV-1 carriers who received allo-HSCT compared with HTLV-1 non-carriers (P = 0.002; Fig. 2D and E).

In adult allo-HSCT patients, there was no significant difference in OS among patients younger than 50 years of age and those older than 50 years of age, but there was a higher percentage of HTLV-1–positive patients for TRM. On the other hand, in the group of patients older than 50 years, HTLV-1–positive patients showed a significantly lower OS and higher risk of TRM (Figure S1).

Allo-HSCT in children

The median OS in adult allo-HSCT recipients was 608.5 (35–2171) and 823.5 (0–3432) days for HTLV-1 antibody–positive and –negative patients, respectively, with OS rates of 49.1% and 67.1% at 3 years post-transplant (P = 0.318). The risk to OS for patients with HTLV-1 antibodies had a HR of 1.46 (95% CI, 0.692–3.080, P = 0.321; Table 2 and Fig. 1B).

The causes of death among patients with HTLV-1 antibodies were primary disease in 2 patients, infection in 3 patients, cerebral hemorrhage in 1 patient, and myocardial damage in 1 patient.

Cumulative incidence of TRM at 100 days and 1 year after allo-HSCT were 6.2% vs 6.6% and 18.8% vs 11.7% in HTLV-1 antibody–positive and –negative patients (P = 0.050), respectively, and the HR was 2.39 (95% CI, 1.021–5.612, P = 0.045). In terms of DRM, the cumulative incidence of DRM at 100 days and 1 year after allo-HSCT was 0% vs 3.6% and 6.2% vs 14.1% in HTLV-1 antibody–positive and –negative patients (P = 0.583), respectively (Table 2 and Fig. 2B).

In the multivariate analysis, HTLV-1 positive status was not a significant factor for OS, but was a significant risk factor for TRM with an HR of 2.58 (95% CI, 1.166–5.699, P = 0.019; Table 2).

Cumulative TRM due to infection was significantly higher in pediatric patients with HTLV-1 antibodies (P = 0.018; Fig. 2F and G).

Auto-HSCT in adults

The median OS in adult auto-HSCT recipients was 1075 (20–2911) and 795.5 (0–3441) days for HTLV-1

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	P-value	HR	95% CI	P-value
Adult patients						
OS						
HTLV-1						
Positive	1.30	1.096–1.549	0.03	1.24	1.042–1.478	0.016
Age						
16–35	1.00	–	–	1.00	–	–
36–49	1.24	1.155–1.330	<0.001	1.18	1.101–1.269	<0.001
50–59	1.73	1.613–1.846	<0.001	1.48	1.385–1.588	<0.001
60–69	2.21	2.062–2.362	<0.001	1.71	1.596–1.835	<0.001
70-	3.77	3.190–4.462	<0.001	2.59	2.185–3.069	<0.001
Gender						
Male	1.25	1.197–1.313	<0.001	1.18	1.122–1.232	<0.001
Disease risk*						
Low risk	0.40	0.378–0.414	<0.001	0.45	0.425–0.466	<0.001
HCT-CI						
score 3	1.00	–	–	1.00	–	–
score 1–2	0.73	0.678–0.777	<0.001	0.81	0.758–0.869	<0.001
score 0	0.52	0.491–0.556	<0.001	0.65	0.607–0.690	<0.001
Stem cell source						
Non-CB	0.69	0.661–0.727	<0.001	0.84	0.798–0.881	<0.001
Conditioning						
RIC/NMA	1.33	1.269–1.389	<0.001			
TRM						
HTLV-1						
Positive	1.41	1.144–1.743	0.001	1.35	1.345–1.089	0.002
Age						
16–35	1.00	–	–	1.00	–	–
36–49	1.29	1.176–1.416	<0.001	1.24	1.128–1.359	<0.001
50–59	1.89	1.732–2.065	<0.001	1.67	1.527–1.825	<0.001
60–69	2.42	2.219–2.647	<0.001	1.95	1.777–2.130	<0.001
70-	4.71	3.862–5.734	<0.001	3.34	2.729–4.077	<0.001
Gender						
Male	1.29	1.216–1.370	<0.001	1.19	1.176–1.327	<0.001
Disease risk*						
Low risk	0.62	0.581–0.651	<0.001	0.45	0.426–0.469	<0.001
HCT-CI						
score 3	1.00	–	–	1.00	–	–
score 1–2	0.68	0.621–0.736	<0.001	0.75	0.692–0.821	<0.001
score 0	0.47	0.438–0.512	<0.001	0.58	0.540–0.633	<0.001
Stem cell source						
Non-CB	0.72	0.675–0.763	<0.001	0.81	0.757–0.857	<0.001
Conditioning						
RIC/NMA	1.30	1.223–1.372	<0.001			
DRM						
HTLV-1						
Positive	1.05	0.768–1.434	0.761			
Age						
16–35	1.0	–	–	1.00	–	–
36–49	1.18	1.056–1.314	0.003	1.11	0.994–1.237	0.065
50–59	1.51	1.354–1.676	<0.001	1.24	1.112–1.379	<0.001
60–69	1.93	1.720–2.134	<0.001	1.41	1.259–1.570	<0.001

(Table 2 continues on next page)

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	P-value	HR	95% CI	P-value
(Continued from previous page)						
70-	2.44	1.767–3.381	<0.001	1.61	1.158–2.227	0.004
Gender						
Male	1.15	1.071–1.242	<0.001			
Disease risk*						
Low risk	0.25	0.235–0.274	<0.001	0.45	0.250–0.293	<0.001
HCT-CI						
score 3	1.00	–	–	1.00	–	–
score 1–2	0.82	0.732–0.924	<0.001	0.92	0.816–1.030	0.144
score 0	0.62	0.556–0.689	<0.001	0.76	0.682–0.848	<0.001
Stem cell source						
Non-CB	0.71	0.660–0.771	<0.001	0.90	0.828–0.971	<0.001
Conditioning						
RIC/NMA	1.287	1.196–1.385	<0.001	–	–	–
Pediatric patients						
OS						
HTLV-1						
Positive	1.46	0.692–3.080	0.321			
Age	1.01	0.992–1.033	0.227			
Gender						
Male	1.03	0.858–1.241	0.737			
Disease risk*						
Low risk	0.26	0.220–0.317	<0.001	0.28	0.232–0.337	<0.001
HCT-CI	1.27	1.161–1.383	<0.001	1.24	1.139–1.359	<0.001
Stem cell source						
Sib-PB	2.60	1.954–3.471	<0.001	1.97	1.475–2.637	0.001
Conditioning						
RIC/NMA	0.66	0.519–0.841	<0.001			
TRM						
HTLV-1						
Positive	2.39	1.021–5.612	0.045	2.58	1.166–5.699	0.019
Age	1.02	0.992–1.055	0.15			
Gender						
Male	1.03	0.784–1.356	0.830			
Disease risk*						
Low risk	0.45	0.346–0.594	0.500	0.50	0.376–0.656	<0.001
HCT-CI	1.35	1.199–1.521	<0.001	1.32	1.162–1.499	<0.001
Stem cell source						
Sib-PB	2.54	1.683–3.842	<0.001	1.99	1.282–3.091	0.002
Conditioning						
RIC/NMA	0.80	0.569–1.132	0.210			
DRM						
HTLV-1						
Positive	0.76	0.188–3.037	0.692			
Age	1.00	0.976–1.030	0.832			
Gender						
Male	1.01	0.787–1.295	0.939			
Disease risk*						
Low risk	0.20	0.158–0.261	<0.001	0.21	0.163–0.271	<0.001
HCT-CI	1.15	1.006–1.318	0.041			

(Table 2 continues on next page)

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	P-value	HR	95% CI	P-value
(Continued from previous page)						
Stem cell source						
Sib-PB	2.40	1.598–3.607	<0.001	1.73	1.148–2.612	0.009
Conditioning						
RIC/NMA	0.57	0.409–0.808	0.001			

Abbreviations: HTLV-1, human T-cell leukemia virus type 1; HCT-CI, hematopoietic cell transplantation-comorbidity index; CB, cord blood; RIC, reduced intensity conditioning regimen; NMA, Non Myeloablative conditioning regimen; sib-PB, periperal blood from sibling donor. *Low risk of disease risk defined as benign diseases and malignant disease in compleat responce (CR) status; High risk was defined as any malignant diseases status in non-CR and EB 1–2 of MDS.

Table 2: **Survival analysis of adult and child patients with allogeneic hematopoietic stem cell transplantation.**

antibody–positive and –negative patients, respectively, with OS rates of 69.4% and 75.0% at 3 years post-transplant (P = 0.172). The risk to OS for patients with HTLV-1 antibodies had an HR of 1.22 (95% CI, 0.665–2.249, P = 0.517; Table 2 and Fig. 1C).

Among patients with HTLV-1 antibodies, causes of death included death from the primary disease in 20 patients, infection in 4, secondary malignancy in 3, interstitial pneumonia in 2, and myocarditis, renal failure, and hemorrhage in 1 patient each.

Cumulative incidence of TRM at 100 days and 1 year after allo-HSCT was 2.17% vs 1.77% and 3.29% vs 4.24% in HTLV-1 antibody–positive and –negative patients (P = 0.052), respectively, and the HR was 1.48 (95% CI, 0.843–2.61, P = 0.17). In terms of DRM, the cumulative incidence of DRM at 100 days and 1 year after allo-HSCT was 5.56% vs 2.17% and 13.6% vs 9.01% in HTLV-1 antibody–positive and –negative patients (P = 0.103), respectively (Table 2 and Fig. 2C).

In the multivariate analysis for OS, TRM, and DRM, HTLV-1 antibody possession was not a significant risk factor in adult auto-HSCT patients.

Acute GVHD and chronic GVHD in adult allo-HSCT patients

The number of adult allo-HSCT patients evaluable for GVHD was 224/14,914 HTLV-1 positive or negative patients with acute GVHD and 176/12,948 for chronic GVHD.

The cumulative incidence of acute GVHD at 100 days after transplantation in HTLV-1 positive or negative patients was 61.5% vs 60.9% (P = 0.165) and for grade II–IV acute GVHD was 13.6% vs 13.0% (P = 0.106). (Fig. 3A and B).

There was also no difference in the cumulative overall incidence of chronic GVHD in adult allo-HSCT patients who survived at least 100 days after transplantation; 40.6% vs 40.4% (P = 0.073) in HTLV-1 antibody–positive or –negative patients (Fig. 3C).

Incidence of CMV infection in adult allo-HSCT patients

Patients who could be evaluated for CMV infection included 130 and 6691 HTLV-1–positive and –negative patients, respectively. There were no significant differences between transplants of HTLV-1–positive and HTLV-1–negative patients with respect to the prevalence of CMV antibodies in patients (P = 0.163) and donors (P = 0.592) prior to transplantation (Table S2).

In adult allo-HSCT patients, the cumulative incidence of CMV antigenemia and CMV infection at 1 year post-transplant was 76.2% vs 65.9% (P = 0.001) in HTVL-1–positive or –negative patients, with a HR of

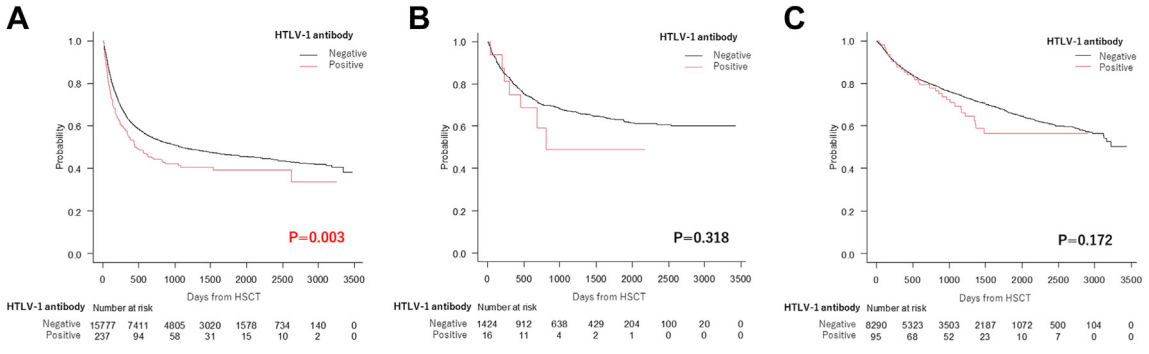

Fig. 1: **Overall survival (OS).** (A) OS in adult patients with allogeneic hematopoietic stem cell transplantation (allo-HSCT). (B) OS in child patients with allo-HSCT. (C) OS in adult patients with autologous HSCT.

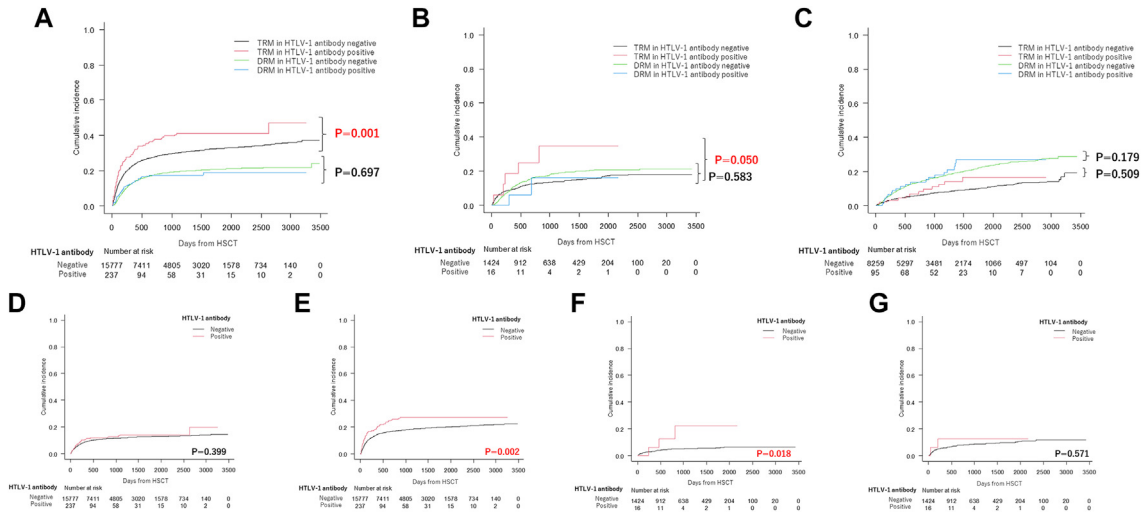

Fig. 2: **Transplant-related mortality (TRM) and disease-related mortality (DRM)**. (A) TRM/DRM in adult patients with allogeneic hematopoietic stem cell transplantation (allo-HSCT). (B) TRM/DRM in child patients with allo-HSCT. (C) TRM/DRM in adult patients with autologous HSCT. (D) Infectious TRM in adult patients with allo-HSCT. (E) Non-infectious TRM in adult patients with allo-HSCT. (F) Infectious TRM in pediatric patients with allo-HSCT. (G) Non-infectious TRM in pediatric patients with allo-HSCT.

1.391 (95% CI: 1.120–1.728, P = 0.0028), and a significantly higher risk of developing the disease in HTLV-1–positive patients (Fig. 4).

In the group with CMV infection, being HTLV-1–positive patients were significantly worse with respect to OS (HR: 1.36, 95% CI: 1.041–1.778, P = 0.0244), while in the group without CMV infection, there was no significant difference in survival outcomes (Fig. 5).

In our analysis population, four HTLV-1–negative patients died of CMV pneumonia and four patients died of CMV enteritis. No HTLV-1–positive patients died from CMV infection.

Discussion

This is the first large study to determine the outcomes of hematopoietic cell transplantation in Japanese HTLV-1 patients with diseases other than ATL. There have been previous reports from the Center for International Blood and Marrow Transplant Research (CIBMTR) regarding allogeneic transplantation of HTLV-1 carriers, and similar to the results of this study, HTLV-1 carriers performed poorly with respect to OS, and TRM.[26] However, the present study is larger than that of the CIBMTR in terms of patients analyzed, and unlike the CIBMTR's data, which are multiethnic, the present study is from a single Japanese ethnic group and reports

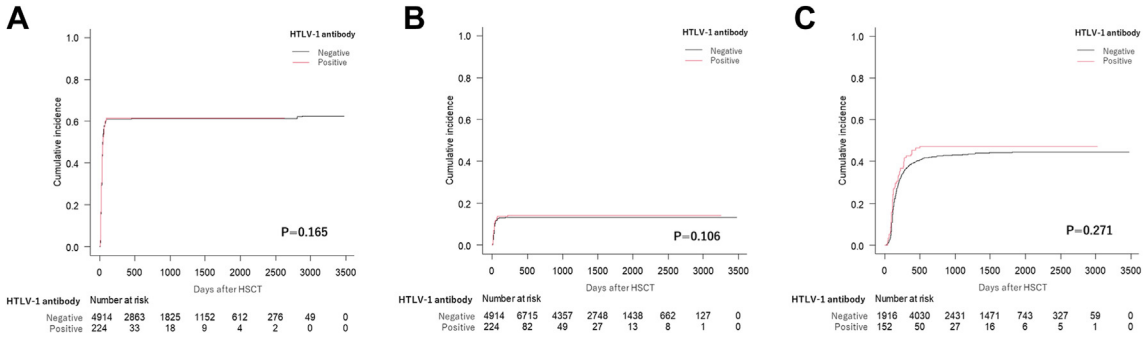

Fig. 3: **Cumulative incidence of acute and chronic graft-vs-host disease (GVHD) in adult patients with allogeneic hematopoietic stem cell transplantation**. (A) Cumulative incidence of acute GVHD (any grade). (B) Cumulative incidence of acute GVHD (≥ grade II). (C) Cumulative incidence of chronic GVHD.

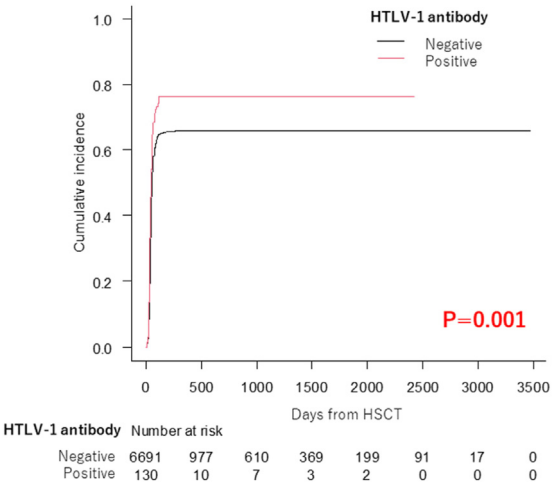

Fig. 4: Cumulative incidence of cytomegalovirus antigenemia or infection.

new findings, including the results of allogeneic transplantation in children and the fact that CMV infection is significantly increased. The positivity rate for HTLV-1 antibodies in the population in this study was 1.34%, which was not significantly different from the positivity rate for antibodies in a national survey in Japan.[8]

In this study, patients who were positive for HTLV-1 antibodies had a significantly poorer prognosis with allogeneic transplantation, particularly adults. As expected, cumulative transplant-related mortality was significantly higher in HTLV-1 antibody–positive patients in allogeneic transplantation, suggesting a possible association with HTLV-1 infection.

Antibody transfer from the mother of HTLV-1 carriers is thought to occur in infants. While in many cases immunity disappears or disappears within 12 months, it has been reported that antibody titers increase again within 12 months in some of the carrier's children.[27] On the other hand, according to reports of in vivo

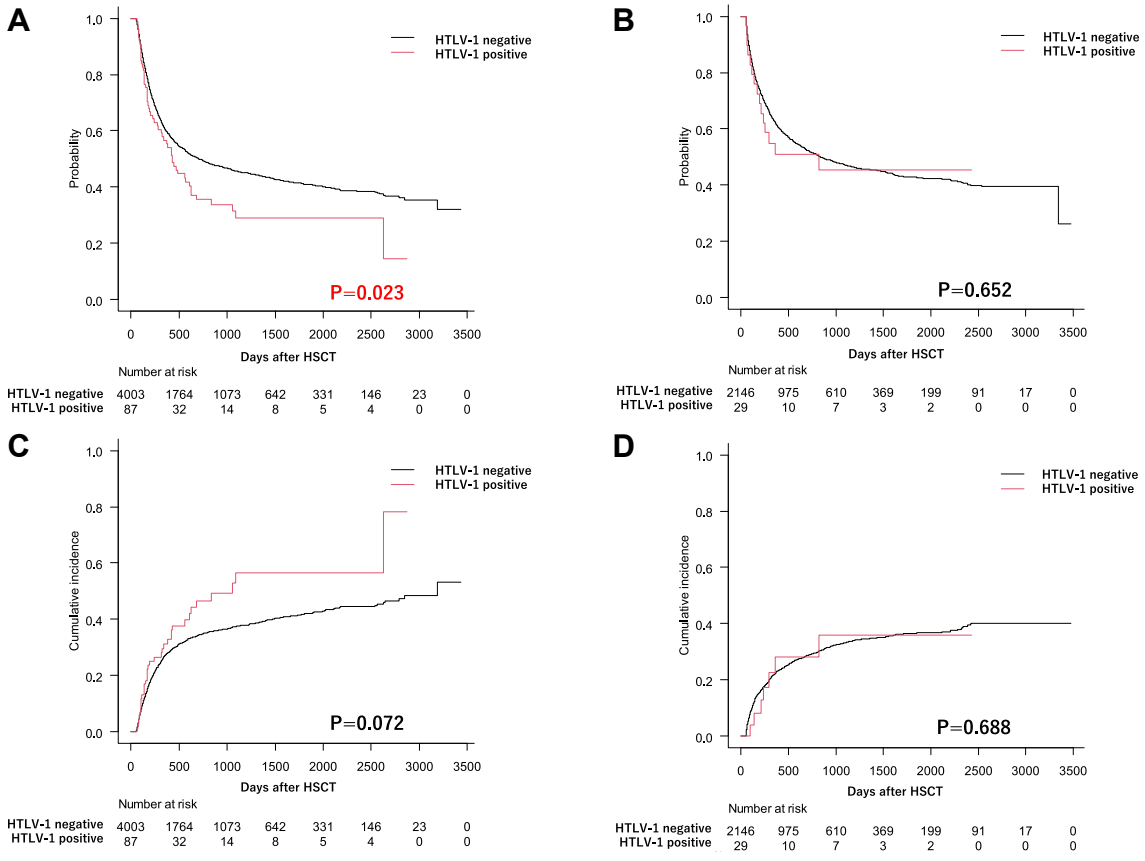

***Fig. 5:* Effect of HTLV-1 infection on post-transplant OS and TRM in patients with or without CMV reactivation**. The landmarks for CMV onset are survival for at least 50 days after transplantation. (A) Comparison of OS in patients with CMV reactivation (B) Comparison of OS in patients without CMV reactivation (C) Comparison of TRM in patients with CMV reactivation (D) Comparison of TRM in patients without CMV reactivation.

experiments in rats,[28] HTLV-1 antibody transfer from the placenta is unlikely, and the occurrence of HTLV-1 antibody positivity before the weaning period may be due to breast milk infection. In any case, in this registry data, there is no discrimination regarding the interpretation of positive HTLV-1 antibodies in children younger than 1 year, which is considered a limitation of the registry data.

Because of reports of a higher risk of opportunistic infections in HTLV-1 carriers[13] and speculation that deaths from infections may be higher in HSCT in HTLV-1 antibody–positive patients, this study was further analyzed by classifying TRM into infectious and non-infectious categories. Infectious TRMs were not significantly more common in adult allogeneic transplant recipients with HTLV-1 antibodies, and, of note, were significantly more common in non-infectious TRMs. On the other hand, infectious TRMs were significantly more common in children. However, non-infectious TRMs may have included those triggered by infectious diseases such as ARDS and MOF; therefore, caution is required when interpreting the results, and this is considered a limitation of an analysis based on registry data. In addition, the number of HTLV-1-positive pediatric patients was small, which is also a limitation of this study.

In terms of patient background, despite the relatively older age of the HTLV-1–positive patient group, it is possible that this may have influenced the higher non-infectious TRM rate compared to the HTLV-1–negative patient group, which includes many patients who used MACs as conditioning regimens for HSCT.

Adult allo-HSCT patients who were HTLV-1 positive were not at risk for the development of acute GVHD grade II or higher or grade III or higher. This tendency was also true for chronic GVHD. A report of allo-HSCT in patients with chromosomally integrated Human herpesvirus 6 showed an increased risk of developing GVHD,[29] but this was not the case in HTLV-1 carriers.

In adult allo-HSCT patients, the risk of developing CMV antigenemia and CMV infection was higher in HTLV-1–positive patients. Given the previously reported high risk of CMV antigenemia in allogeneic transplantation for ATL,[3,30,31] allogeneic transplantation for HTLV-1–infected patients may itself be a risk for CMV and may be associated with immunodeficiency associated with HTLV-1 infection, moreover, HTLV-1–infected patients with CMV reactivation had a poorer prognosis.

In children, the higher incidence of infectious TRM in HTLV-1 carriers may have been due to a lower frequency of non-infectious transplant-related complications, which may have been expected because of the lower risk of organ damage and other complications compared to adults.

In an analysis of auto-HSCT for non-Hodgkin's lymphoma and multiple myeloma in human immunodeficiency virus (HIV)-positive patients using the same TRUMP data, OS was significantly worse in HIV-positive patients, especially in non-Hodgkin's lymphoma.[32] In our study, survival outcomes such as OS, TRM, and DRM after auto-HSCT were not significant factors for patients who were HTLV-1 positive and this differed from those with HIV. Since auto-HSCT results in patients with HIV reported higher relapse rates than in HIV-negative patients, and our study did not find a difference in survival outcomes in HTLV-1–positive patients who received auto-HSCT (limited to malignant lymphomas), it is possible that more cases of highly malignant HIV-related lymphomas were included for patients with HIV.

The number of HTLV-1 carriers has been gradually decreasing in Japan in recent years, and this is thought to be due to the decrease in breast milk infection by abstinence from breastfeeding, but on the other hand, the increase in horizontal infection through sexual intercourse has become an issue.[33] However, we believe that the results of the impact of HTLV-1 infection on allo-HSCT outcomes in diseases other than ATL are important findings. The results of this study may also be useful when considering HSCT in regions outside of Japan with high infection rates.

There are several limitations to this study. As mentioned above, the small number of patients who were HTLV-1 antibody positive (approximately 1% of the total), especially pediatric patients with allo-HSCT, suggests caution in interpreting the results. Particular attention should be paid to the interpretation of HTLV-1 antibodies in infants younger than 1 year of age, where it is difficult to distinguish between transitional and acquired immunity. There is also no detailed virus-specific information on the proviral loads in HTLV-1–positive patients. Another limitation is that it is not possible to distinguish whether the HTLV-1 infection was transmitted vertically or horizontally, and patients with smoldering ATL may be included. This registry contains no information on HTLV-2 infection and the incidence of HTLV-1–related diseases such as HAM/TSP.

In conclusion, this study on HSCT in HTLV-1 antibody–positive patients for diseases other than ATL demonstrated that HTLV-1 antibody positivity was a factor in poor prognosis after allo-HSCT in both adult and pediatric patients.

Contributors

N.N., H.N. A.U., and M.O. designed the research, organized the project, and wrote the paper. N.N. and H.N. performed the statistical analysis. N.N., T.E., S.M., K.I., Y.K., K.M., Y.M., N.U., A.I., N.D., and Y.O. gathered the data. N.N., H.N., S.F., A.S., R.S., A.U., and M.O. wrote the first draft of the paper. All the authors contributed to the final version.

Data sharing statement

The data of this study are not publicly available due to ethical restrictions that it exceeds the scope of the recipient/donor's consent for research use in the registry. Data may be available from the corresponding author upon reasonable request and with permission of the JSTCT/JDCHCT.

Declaration of interests

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2023.100902.

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