

Impact of human T-cell leukemia virus type 1 on living donor liver transplantation: a multi-center study in Japan

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Abstract

Background The natural history of human T-cell leukemia virus type 1 (HTLV-1), which causes adult T-cell leukemia (ATL) or HTLV-1 associated myelopathy, after liver transplantation is unclear.

Methods We conducted a nationwide survey to investigate the impact of HTLV-1 status on living donor liver transplantation (LDLT) in Japan. We analyzed the cases of 82 HTLV-1-positive recipients and six HTLV-1-negative-before-LDLT recipients who received a hepatic graft from HTLV-1-positive donors.

Results Adult T-cell leukemia developed in five recipients who ultimately died. Of these five, two received grafts from HTLV-1-positive donors and three from HTLV-1-negative donors. The 1-, 3-, and 5-year ATL development rates were 4.5%, 6.5%, and 9.2%, respectively. Fulminant hepatic failure as a pre-transplant diagnosis was identified as an independent risk factor for ATL development ($P = 0.001$). The 1-, 3-, and 5-year survival rates for HTLV-1-positive recipients who received grafts from HTLV-1-negative donors were 79.9%, 66.1%, and 66.1%, and from HTLV-1-positive donors were 83.3%, 83.3%, and 60.8%, respectively. The 1-year survival rate for HTLV-1-negative recipients who received grafts from HTLV-1-positive donors was 33.3%.

Conclusions Fulminant hepatic failure is an independent risk factor for ATL development in HTLV-1-positive recipients. Grafts from HTLV-1-positive living donors can be transplanted into selected patients.

Keywords Adult T-cell leukemia · Human T-cell leukemia virus type 1 · Living donor liver transplantation

Introduction

Human T-cell leukemia virus type 1 (HTLV-1) is a retrovirus that is endemic in southwestern Japan and causes adult T-cell leukemia (ATL) or HTLV-1 associated myelopathy (HAM) in a minority of carriers, although most carriers remain asymptomatic. HTLV-1-infected recipients who are concurrently treated with immunosuppressive drugs following organ or bone marrow transplantations might exhibit an accelerated or altered developmental course of HTLV-1-associated diseases [1]. We previously reported on the impact of HTLV-1 status in living donor liver transplantation (LDLT) as a single-center experience [2, 3]. From that study, we concluded that pre-transplant fulminant hepatic failure (FHF) is a risk factor for ATL development in HTLV-1-positive recipients [2]. HTLV-1 is vertically transmitted from mothers to infants, and the virus is maintained within the infant's family [4]. In Japan, living

donors are limited to the blood relatives or spouse of the intended recipient, except in very rare cases. Therefore, sometimes both the donor candidate and the recipient are HTLV-1 positive.

Approximately 1.1 million individuals in Japan are infected with HTLV-1 [5], and 30% of HTLV-1 carriers live in southwestern Japan. The Japan Organ Transplant Network recommends against using organs from HTLV-1-positive donors even for recipients with a pre-existing HTLV-1 infection. In contrast, most transplant centers do accept HTLV-1-positive carriers as living donors. There is a widening gap between the need for livers and the availability of livers donated by deceased individuals in most countries. The use of HTLV-1-positive donors is increasing owing to the growing disparity between organ availability and demand [6]. There are many recipients with an urgent need for transplant, especially older individuals, and, to fill this demand, livers from HTLV-1-positive donors could be considered for use in recipients who are already HTLV-1 positive.

Because Japan is located in an HTLV-1 endemic area, we collected data to report the nationwide figures on HTLV-1-positive donors or recipients who underwent LDLT. Our data show HTLV-1 transmission in a liver transplantation (LT) setting and provide important information for transplant surgeons performing LT with HTLV-1 positive donors or recipients.

Patients and methods

Recipients

As a retrospective survey, we analyzed the cases of 82 recipients who were HTLV-1 positive before LDLT and of six recipients who were HTLV-1 negative before LDLT, all of whom received hepatic grafts from HTLV-1-positive donors. These recipients underwent LDLT at the following 13 institutions prior to or during October 2014: Kyushu University (32 recipients), Kyoto University (19 recipients), Nagasaki University (12 recipients), Kumamoto University (12 recipients), Kyoto Prefectural University of Medicine (two recipients), Keio University (two recipients), Tohoku University (two recipients), Hiroshima University (two recipients), Ehime University (one recipient), National Center for Child Health and Development (one recipient), Nagoya University (one recipient), The University of Tokyo (one recipient), and Osaka City University (one recipient). This study was conducted in collaboration with the Japanese Society of Hepato-Biliary-Pancreatic Surgery and the Japanese Liver Transplantation Society. The institutional review boards of each institution

approved this study (Representative Institution: Kyushu University 25–298). The primary diagnoses requiring LDLT for the 82 HTLV-1-positive recipients were as follows: hepatitis C virus (HCV) in 33 recipients (19 had hepatocellular carcinoma, HCC), FHF in 12 recipients, primary biliary cirrhosis in seven recipients (one had HCC), biliary atresia in seven recipients, cryptogenic in six recipients (one had HCC), hepatitis B virus (HBV) in three recipients (one had HCC), autoimmune hepatitis in three recipients (one had HCC), primary sclerosing cholangitis in two recipients, and HBV + HCV with HCC, secondary biliary cirrhosis, idiopathic portal hypertension with cholangiocellular carcinoma, alcohol abuse, nonalcoholic steatohepatitis, polycystic liver disease, extrahepatic portal stenosis, graft failure, and chronic rejection in one recipient each (Table 1). The primary diagnoses requiring LDLT for the six HTLV-1-negative recipients transplanted with grafts from HTLV-1-positive donors were as follows: alcohol abuse in three, HCV in two, and FHF in one recipient(s) (Table 2).

Donors

Donors were selected from candidates who volunteered to be living donors. The donors for the HTLV-1-positive recipients were children in 39, siblings in 15, spouses in 13, parents in eight, uncles in two, siblings-in-law in two, a daughter-in-law in one, a niece in one, and a domino transplant in one case(s). The HTLV-1-positive donors for the HTLV-1-negative recipients were siblings in three, spouses in two, and a father in one case(s) (Table 2).

Graft type

The selection of graft type depended on the criteria for each institution. The graft types for the HTLV-1-positive recipients were right lobe in 36, extended left lobe in 21, left lobe in 13, right posterior sector in four, left lateral segment in two, dual graft in one, domino whole liver graft in one, and reduced S2 graft in one case(s). The graft types from the HTLV-1-positive donors for the HTLV-1-negative recipients were right lobe in five and extended left lobe with caudate lobe in one case(s).

Splenectomy

Simultaneous splenectomy during LDLT was performed under the criteria of each institution. This procedure was typically performed to decrease portal pressure or to improve pancytopenia.

Table 1 Characteristics of human T-cell leukemia virus type 1 (HTLV-1)-positive recipients at living donor liver transplantation (LDLT)

Variables	Cases (n = 82)
Recipient age (years, range)	50.2 (4 months–74 years)
Recipient gender (male, %)	37 (45.1)
Primary diagnosis	
Liver cirrhosis	
Hepatitis C/Hepatitis B/Hepatitis B + C	33/3/1
Cryptogenic/Alcohol/NASH/AIH	6/1/1/3
Fulminant hepatic failure	12
Cholestatic disease: PBC/BA/PSC/Secondary biliary cirrhosis	7/7/2/1
Others ^a	4
Recipient height (cm, range)	157 (60–183)
Recipient weight (kg)	58 (5.4–94)
MELD score (range)	19.0 (4–42)
Splenectomy (yes, %)	36 (45.6) ^b
Recipient operation time (min, range)	816 (437–1407)
Recipient blood loss (ml, range)	7934 (217–60860)
Calcineurin inhibitor (tacrolimus, %)	67 (81.7)
MMF or mizoribine (yes, %)	46 (56.1)
Donor HTLV-1 positive (yes, %)	12 (15.0) ^c
Graft (right, %)	36 (43.9)
GW/SLW ratio (%), range)	47.5 (23.6–131.5)
GW-BW ratio (%), range)	0.96 (0.44–4.97)
ABO (identical/compatible/incompatible)	49/24/9
Blood relative donor (yes, %)	64 (78.0)
Donor age (years, range)	39.7 (18–65)
Donor gender (male, %)	45 (55.5) ^d
Donor operation time (min, range)	437 (226–738)
Donor blood loss (ml, range)	541 (70–3500)

AIH autoimmune hepatitis, BA biliary atresia, BW body weight, GW graft weight, MELD model for end-stage liver disease, NASH non-alcoholic steatohepatitis, PBC primary biliary cirrhosis, PSC primary sclerosing cholangitis, SLW standard liver weight calculated by $706.2 \times \text{body surface area} + 2.4$

^a Others included polycystic liver disease, extrahepatic portal stenosis, graft failure and chronic rejection

^b Unknown in three recipients

^c HTLV-1 status was unknown in two donors

^d One patient got dual grafts from two donors

Immunosuppression regimen

Initial immunosuppression was started with either tacrolimus or cyclosporine A in combination with steroid and/or mycophenolate mofetil (MMF) or mizoribine. For the HTLV-1-positive recipients, tacrolimus was used in 67 recipients, and cyclosporine A in 14 recipients. A calcineurin inhibitor was used in all but one recipient. Steroids were used in 77 recipients. MMF was used in 44 recipients, and mizoribine in two recipients. An anti-IL-2 receptor antibody was used in 13 recipients, and rituximab was used

in five recipients. For HTLV-1-negative recipients who received HTLV-1-positive grafts, tacrolimus was used in five recipients, and cyclosporine A in one recipient. Steroids were used in all but one recipient, mizoribine was used in one recipient, and antibodies were not used in any recipients (Table 2).

Follow-up

The mean follow-up period was 1,643 days, with 360 days and 2,897 days as the 25th and 75th percentiles, respectively. Recipient survival was defined as the time period between LDLT and recipient death.

Statistical analyses

Recipient survival rates and ATL development rates were calculated by the Kaplan–Meier product-limited method. Information about the recipients was collected on their day of death when a recipient died from a disease other than ATL to calculate the ATL development rate. Variables that were included in the univariate analysis by a Fisher's exact test were recipient age, donor age, etiology of liver disease, donor HTLV-1 status, splenectomy, graft weight (GW)-standard liver weight (SLW) ratio, graft type, model for end-stage liver disease (MELD) score, recipient sex, donor sex, blood type compatibility, presence of blood relative between donor and recipient, tacrolimus or cyclosporine A use, and MMF use. For the multivariate analysis, an exact logistic regression analysis was performed. Data are expressed as means \pm standard deviation. All statistical analyses were performed using JMP 11.0 software (SAS, Inc., Cary, NC, USA). A *P*-value of <0.05 is considered significant.

Results

There were 37 male and 45 female HTLV-1-positive recipients, and their mean age was 50.2 years (range: 4 months–74 years). Their mean MELD score was 19.0 (range: 4–42), and their mean GW-SLW ratio was 47.5 (range: 23.6–131.5). Their mean GW-recipient body weight ratio was 0.96 (range: 0.44–4.97). Forty-five donors were male and 36 were female, and they had a mean age of 39.7 years (range: 18–65). One recipient was transplanted with dual grafts from male and female donors. Sixty-four (78.0%) donors were blood relatives with their recipients. Twelve of the 82 donors were HTLV-1 positive. The clinical courses of these 12 donors were uneventful after hepatectomy. No donors developed ATL or HAM after the surgery.

Table 2 Characteristics of human T-cell leukemia virus type 1 (HTLV-1) negative recipients who received grafts from HTLV-1 positive donors and their outcome after living donor liver transplantation (LDLT)

Variables	1	2	3	4	5	6
Recipient age	41	44	57	48	15	59
Recipient gender	M	M	F	M	F	M
Diagnosis	Alcohol	LC-C	Alcohol	LC-C	FHF	Alcohol
MELD	11	19	25	23	28	NA
Splenectomy	No	Yes	No	NA	No	NA
Initial CNI	TAC	TAC	TAC	CYA	TAC	TAC
Steroid	Yes	Yes	Yes	Yes	Yes	No
MMF or mizoribine	No	No	No	Mizoribine	No	No
Donor age	43	39	55	44	49	55
Donor gender	F	F	F	M	M	F
Graft	RL	RL	RL	LL + C	RL	RL
GW-SLW (%)	44.8	50.0	56.7	37.7	63.4	41.6
GW-BW (%)	0.76	1.01	1.11	0.75	1.34	0.83
ABO	Compatible	Identical	Identical	Identical	Identical	Identical
Relation to recipient	Sibling	Spouse	Sibling	Sibling	Father	Spouse
ATL	No	No	No	No	No	No
HAM	No	No	No	No	No	No
Survival time (days)	3457	59	19	22	3612	26
Alive	Alive	No	No	No	Alive ^a	No
Cause of death	–	Heart failure	Graft infarction	Graft infarction	–	Cerebral hemorrhage

ATL adult T-cell leukemia, CYA cyclosporine A, FHF fulminant hepatic failure, GW graft weight, HAM HTLV-1 associated myelopathy, LC-C liver cirrhosis type C, LL + C extended left lobe with caudate lobe graft, RL right lobe graft, SLW standard liver weight, TAC tacrolimus

^a Patient #5 underwent a re-transplantation due to chronic rejection

The HTLV-1 statuses of two of the donors were unknown. The characteristics of the HTLV-1-positive recipients and their donors at LDLT are shown in Table 1.

Adult T-cell leukemia developed in five recipients (Table 3). The intervals between LDLT and ATL development for these five recipients were 181 days, 291 days, 257 days, 823 days, and 1,315 days. Two of the ATL recipients received grafts from HTLV-1 carriers and three received them from non-carriers (Table 3). Fluorescent *in situ* hybridization revealed that the development of ATL in two of the recipients was owing to the recipient having HTLV-1 [2].

The 1-, 3-, and 5-year ATL development rates in the HTLV-1-positive recipients were 4.5%, 6.5%, and 9.2%, respectively (Fig. 1). Four recipients died despite chemotherapy owing to ATL. One recipient with ATL died of chronic rejection owing to the withdrawal of treatment with a calcineurin inhibitor [2]. The intervals between ATL development and recipient death for these five recipients were 15 days, 3 months, 5 months, 15 months, and 27 months. The overall survival rate based on recipient and donor HTLV-1 status is shown in Figure 1. The 1-, 3-, 5-, and 10-year survival rates for HTLV-1-positive recipients who received grafts from HTLV-1-negative donors were 79.9%, 66.1%, 66.1%, and 59.7%, respectively. The causes of death that were unrelated

to ATL were sepsis in 10, HCC recurrence in four, graft failure in four, graft infarction in one, and CCC recurrence in one recipient(s). We were unable to obtain follow-up data for one recipient. In contrast, the 1-, 3-, 5-, and 10-year survival rates for the HTLV-1-positive recipients who received grafts from HTLV-1-positive donors were 83.3%, 83.3%, 60.8%, and 48.6%, respectively. The three recipients whose deaths were unrelated to ATL died from post-transplant lymphoproliferative disorder (PTLD) in the brain, heart failure, and suicide (one recipient each).

Six HTLV-1-negative recipients received grafts from HTLV-1-positive donors (Table 2). Four of these six recipients died within 2 months after LDLT. Therefore, the 1-year survival rate after LDLT for these patients was 33.3% (Fig. 1). Their causes of death were graft infarction in two recipients, heart failure in one recipient, and cerebral hemorrhage in one recipient. Furthermore, one recipient underwent re-transplantation because of chronic rejection (Table 2).

Univariate analyses revealed that, in this study, both FHF as a pre-transplant diagnosis and a lack of splenectomy were risk factors for ATL development ($P < 0.001$ and $P = 0.013$, respectively; Table 4). Other factors, including donor HTLV-1 status, were not found to be

Table 3 Characteristics and outcome of recipients who developed adult T-cell leukemia (ATL) after living donor liver transplantation (LDLT)

Variables	1	2	3	4	5
Recipient age at LDLT	39	45	67	48	59
Recipient gender	F	M	M	M	F
Recipient HTLV-1	Positive	Positive	Positive	Positive	Positive
Diagnosis	FHF	FHF	FHF	FHF	FHF
MELD	23	22	22	25	32
Splenectomy	No	No	No	No	No
Initial CNJ	TAC	TAC	TAC	CYA	TAC
Steroid	Yes	Yes	Yes	Yes	Yes
MMF or mizoribine	No	No	No	No	No
Donor age at LDLT	46	56	34	20	28
Donor gender	M	F	M	M	F
Donor HTLV-1	Positive	Positive	Negative	Negative	Negative
Graft	LL	LL	RL	RL	RL
GW-SLW (%)	35.1	42.6	54.9	50.2	37.6
GW-BW (%)	0.64	0.89	1.00	0.89	0.79
ABO	Identical	Compatible	Compatible	Identical	Identical
Relation to recipient	Sibling	Sibling	Son	Son	Daughter
HAM	No	No	No	No	No
Survival time (days)	195	1273	432	2107	360
Alive	No	No	No	No	No
Cause of death	ATL	Chronic rejection	ATL	ATL	ATL

CYA cyclosporine A, FHF fulminant hepatic failure, GW graft weight, HAM HTLV-1 associated myelopathy, LL left lobe graft, RL right lobe graft, SLW standard liver weight, TAC tacrolimus

risks for ATL development. A multivariate analysis revealed that FHF was an independent risk factor for ATL development ($P = 0.001$, Table 5).

HTLV-1 associated myelopathy developed in two recipients, and both were HTLV-1 positive before LDLT. The primary diagnosis for both of these two recipients was HCV. The donor was HTLV-1-positive for one of

these two recipients [7]. A simultaneous splenectomy was performed in one recipient. The intervals between LDLT and HAM development for these two patients were 15 months and 46 months. One recipient died because of chronic rejection 8 months after HAM development, and the other was still alive 101 months after HAM development.

Fig. 1 Adult T-cell leukemia (ATL) development rate and survival after living donor liver transplantation (LDLT). Eighty-eight recipients underwent LDLT. (a) The ATL development rate in 82 human T-cell leukemia virus type 1 (HTLV-1)-positive recipients. (b) The overall recipient survival after LDLT. The HTLV-1 status was unknown in two of the donors. Follow-up data for one of the HTLV-1-positive recipients who received a graft from an HTLV-1-negative donor were not obtained

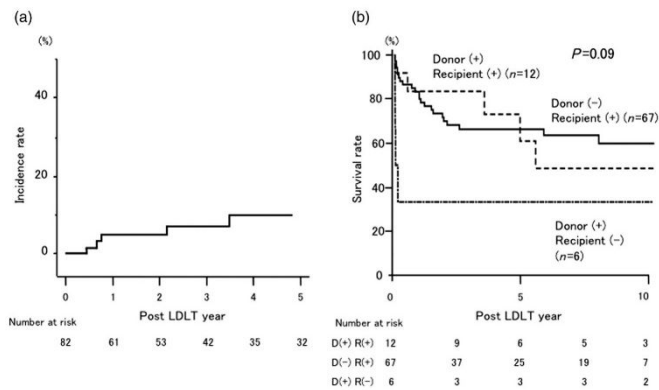


Table 4 Risk factors for adult T-cell leukemia (ATL) development: univariate analysis

Variables	Rate of ATL development	P-value
Recipient variables		
Age		
≥60 years (n = 23)	4.3%	0.66
<60 years (n = 58)	6.9%	
Sex		
Male (n = 36)	8.3%	0.47
Female (n = 45)	4.4%	
Etiology		
FHF (n = 12)	41.7%	<0.001
Others (n = 69)	0%	
MELD ^a		
≥15 (n = 56)	8.9%	0.06
<15 (n = 22)	0%	
Splenectomy ^a		
Yes (n = 35)	0%	0.013
No (n = 43)	11.6%	
Calcineurin inhibitor ^b		
TAC (n = 62)	6.5%	0.89
CYA (n = 18)	5.6%	
Donor/graft variables		
Age		
≥40 years (n = 43)	4.7%	0.54
<40 years (n = 38)	7.9%	
Sex		
Male (n = 36)	8.3%	0.47
Female (n = 45)	4.4%	
Graft ^c		
Left lobe (n = 33)	6.1%	0.83
Right lobe (n = 41)	7.3%	
GW-SLW ratio (%) ^a		
<40 (n = 33)	6.7%	0.91
≥40 (n = 45)	6.1%	
Donor HTLV-1 ^d		
Positive (n = 12)	16.7%	0.16
Negative (n = 67)	4.5%	
Donor-recipient matching		
ABO identical		
Yes (n = 48)	4.2%	0.37
No (n = 33)	9.1%	
Blood relative donor		
No (n = 17)	0%	0.12
Yes (n = 64)	7.8%	

The ATL development of one case was unknown.

^a Three cases lacked data on MELD, splenectomy, or GW-SLW ratio

^b One case was not given calcineurin inhibitor

^c Seven recipients received a right posterior sector, left lateral segment, or reduced S2 graft

^d Two cases had an unknown donor HTLV-1 status

Table 5 Risk factors for adult T-cell leukemia (ATL) development: multivariate analysis

Variables	Odds ratio	95% CI	P-value
Fulminant hepatic failure: Yes	29.6 ^a	3.58 - + INF	0.001
Splenectomy: No	0.7 ^a	0.018 - + INF	1.00

^a Median unbiased estimation

Discussion

Our cohort from the Japanese national registry is the largest cohort to date used to investigate LDLT-associated HTLV-1. Previously, based on data from a single center, we reported that both a primary diagnosis of FHF and a MELD score >15 were risk factors for ATL development [2]. In the previous report, we speculated that a pre-transplant MELD score >15 was mediated by the FHF diagnosis because all of the FHF recipients had a MELD score >15, but a multivariate analysis could not be performed owing to the relatively small number of cases. In this study, a multivariate analysis was performed using more cases than the previous report, and we revealed that only a pre-transplant diagnosis of FHF was an independent risk factor for ATL development after LDLT. Based on the data from both the previous report [2] and this study, we recommend considering the indication for LDLT in HTLV-1-positive patients with FHF before performing a LDLT because of the very high risk of mortality for these patients. Five of the six HTLV-1-positive patients with FHF in the earlier study died because of ATL development (n = 3) or because of chronic rejection after chemotherapy for ATL (n = 1) or PTLN (n = 1). In this survey, eight of the 12 HTLV-1-positive patients with FHF died; five of these patients were those previously reported. The causes of death for the three newly collected patients were graft failure, graft infarction, or ATL (one patient each).

Fulminant hepatic failure is a life-threatening condition that has a high mortality unless an urgent LT is performed. Although HTLV-1-positive recipients with FHF have a high risk of ATL development, LDLT enables such patients to survive longer than they otherwise would. Based on our findings, transplant surgeons will need to carefully weigh the potential benefits of performing a LDLT on HTLV-1-positive recipients with FHF against the established risks of ATL development or death in these recipients and evaluate each situation on a case-by-case basis.

One possible mechanism for the association between ATL development and FHF is that hepatocyte growth factor (HGF)-c-Met, the receptor of HGF, is present on ATL cells, and signaling through this pathway might augment the proliferation of HTLV-1 infected cells [2]. Furthermore, decreased numbers of natural killer cells in the peripheral

blood of FHF recipients [8] might play a pivotal role for ATL development. In this study, 11 recipients with FHF did not undergo splenectomy during LDLT. Indeed, a lack of splenectomy was a risk factor for ATL development according to the results of a univariate analysis. However, Florins et al. reported that, in sheep, splenectomy accelerated the leukemogenesis induced by bovine leukemia virus, which, like HTLV-1, is a retrovirus [9]. Therefore, they concluded that there is a potential risk for accelerating ATL onset after splenectomy in HTLV-1 carriers. Further study on the impact of the spleen for ATL development is needed. Recently, a nationwide molecular analysis using 426 ATL samples was reported from Japan [10]. The authors identified various somatic alterations in the cellular genome that largely converge on T cell receptor–nuclear factor- κ B signaling and other T-cell-related pathways [10]. Further perspective studies should confirm if these alterations are also found in FHF patients.

It is important to consider the ethical aspects of using healthy living donors for transplantation of HTLV-1-positive recipients that have FHF. Donor safety is of paramount concern in any donor surgery for LDLT. Fortunately, we found that the recipient risks do not increase the surgical risk for the donors. Furthermore, there is no donor coercion at the Japanese institutions that perform LDLT. The risk to the donor must be balanced by the benefit to the donor in terms of the survival of the recipient. Mutual affection generally motivates recipients' family members as donors, as they hoped to see their relatives survive for as long as possible.

The 5-year ATL development rate for the HTLV-1-positive LDLT recipients in this study was 9.2%, which seems to be higher than that for HTLV-1-positive individuals who did not undergo LT (3–5%) [11]. Further study is necessary to make any conclusion about why LDLT is associated with ATL development. Notably, all patients who developed ATL after LDLT died despite treatment. Advances in chemotherapy have contributed to an increase in the overall survival of patients with ATL [12]; however, complete response rates have ranged from 17 to 43% and the median overall survival times have ranged from 5 to 13 months in prospective multicenter studies in Japan [13].

Japanese centers have reported promising results for allogeneic hematopoietic stem cell transplantation [14, 15]. Additionally, treatment with mogamulizumab, a humanized anti-CC chemokine receptor 4 antibody, combined with traditional chemotherapy has been shown to induce positive responses even in cases with aggressive ATL [16]. Unfortunately, the immunosuppressive status of transplant recipients complicates ATL treatment; therefore, we have to consider whether or not we can prevent ATL development after LDLT. In the non-organ transplant setting, four risk factors have been associated with ATL development in HTLV-1 carriers,

including age greater than 40 years, high HTLV-1 proviral loads in peripheral blood, family history of ATL, and any clinical signs or symptoms [17]. There are currently no available means of preventing ATL development in patients with any of these risk factors. Our finding that FHF is the only risk factor in a LDLT setting may contribute to determining the mechanism of how ATL develops in HTLV-1 carriers.

Eighteen partial hepatic grafts from HTLV-1-positive living donors were transplanted to HTLV-1-positive ($n = 12$) or -negative ($n = 6$) recipients. Although donor HTLV-1 status was not a risk factor for ATL or HAM development in this study, the 10-year survival rates of these recipients, (48.6% for HTLV-1-positive recipients and 33.3% for HTLV-1-negative recipients), were still quite poor. Transplant teams generally will not select HTLV-1-positive donors unless they have no other choice because of life-threatening recipient conditions. One of the aims of this study was to clarify the risk of ATL or HAM development after LDLT from an HTLV-1-positive donor. Unfortunately, this risk is difficult to analyze because of the poor recipient survival rate and the relatively small number of HTLV-1-positive donors. We believe that LT should be performed in selected recipients who agree to accept these risks to rapidly obtain a life-saving organ. Additionally, it is important to consider the safety of the HTLV-1-positive donor undergoing hepatectomy. Although this study did not reveal any negative impact on the HTLV-1-positive donors after hepatectomy, careful donor follow-up is recommended to confirm that they do not develop any HTLV-1-associated disease.

To prevent or minimize the development of HTLV disease in the recipients of organs from confirmed HTLV-1-positive donors, antiviral prophylaxis therapy with zidovudine (nucleoside analog reverse transcriptase inhibitor) and raltegravir (integrase inhibitor) during a brief period after transplantation has been suggested [18, 19]. Armstrong et al. recommended HTLV-1 prophylaxis/preemptive therapy with these two inhibitors for organ transplantation, but this is still not an established approach [19].

The Japanese Ministry of Health, Labour and Welfare publically announced the following fact in December, 2014: Living donor *renal transplant* recipients who were HTLV-1 negative before the transplant and received a *renal graft* from an HTLV-1-positive donor became infected with HTLV-1. Furthermore, those recipients developed HAM rapidly with a high frequency compared with the usual HAM incident rate [20]. In these recipients, symptoms progressed to serious walking difficulty within several years after the development of HAM. Because HTLV-1 infection is relatively rare in eastern and northern Japan, until this announcement was made, transplant centers in these areas had not been cautious about donor and recipient HTLV-1 status prior to

performing living donor renal transplants. The Japan Society for Transplantation warned that to reduce the risk of unintentional transmission of HTLV-1 through renal transplantation, a serology test should be performed for all donors and recipients who plan to undergo living donor renal transplantation. Furthermore, living donor renal transplantation from an HTLV-1-positive donor or for an HTLV-1-positive recipient should be performed only after fully informed consent that highlights their increased risk of HAM development is obtained both from the recipient and the donor. Lastly, the Japan Society for Transplantation recommends that careful follow-up checks should be performed to identify the development of any HTLV-1-associated disease for any HTLV-1-positive recipient.

As we previously reported, HTLV-1 serology tests were not useful for following up on recipients who were HTLV-1-negative before the LDLT. Checking the proviral load by polymerase chain reaction is necessary to diagnose the transmission of the virus [2, 21]. It was reported that the seroconversion of the recipients receiving blood containing HTLV-1 usually occurred within 50 days after transfusion [22]. Because of their immunosuppressive status, transplant recipients could be HTLV-1 positive and develop ATL without seroconversion or their seroconversion might be delayed [1, 23].

Ramanan et al. recently reported a case of living donor-derived HAM in a renal transplant recipient [18]. Such donor-derived infection could potentially happen in the deceased donor transplant setting in the United States because of the discontinuation in 2009 of universal deceased donor organ screening for HTLV-1. The development rate of HAM in HTLV-1 carriers is 0.25% [11] in a non-transplant setting. In this study, two of the 88 (2.3%) recipients developed HAM after LDLT. Although the HAM development rate seems to be higher in the transplant setting, this result does not provide enough information to make any conclusion about why LDLT might be associated with HAM development.

The present study is subject to limitations. It is a retrospective study and has possible biases because only two institutes had recipients who developed ATL owing to the relatively small number of patients from each institute. Kyushu University Hospital experienced four ATL cases among 32 recipients, which means their ATL development rate was 12.5%, whereas, the ATL development rate at Kyoto University Hospital was 5.2% (one ATL case among 19 recipients). The other 11 institutes did not experience any ATL development, which is probably owing to differences in their recipients' primary diagnoses, and backgrounds, among other factors.

In conclusion, the outcome of HTLV-1-positive recipients who underwent LDLT was acceptable. FHF was the only identified independent risk factor for ATL development in

the HTLV-1-positive recipients. A graft from an HTLV-1-positive living donor can be safely transplanted into selected patients, but careful follow-up is recommended for the safety of the HTLV-1-infected living donor.

Conflict of interest None declared.

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