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ORIGINAL ARTICLE

Different causes of early and late-onset post transplant lymphoproliferative disorder in kidney transplantation patients after 2000

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Summary *Background:* The purpose of this study was to analyze the link between PTLD incidence and its occurrence time in patients at a single center in comparable medical environments after 2000.
Methods: Retrospectively, total 3305 kidney transplantation patients medical data were analyzed. Patients were divided into two groups based on the period from the day of kidney transplantation to the day of PTLD diagnosis. Early-onset was defined as PTLD development within two years after transplantation, whereas all other cases were categorized as late-onset PTLD.
Results: In the early-onset group, young age (0–19 years) was confirmed as a risk factor for PTLD incidence (HR 1.49, $p = 0.038$). In the late-onset group, history of anti-rejection therapy was confirmed as a risk factor (HR 1.32, $p = 0.031$). Overall survival rates were not significantly different between the two groups ($p = 0.556$). Graft survival rates were also not different between the two groups ($p = 0.549$).
Conclusion: When patients with PTLD were classified into early-onset group and late-onset group at two years, overall survival and graft survival were comparable. And patients with early-onset PTLD are more likely to be associated with EBV, the late-onset patients are more likely to be immunosuppressed.
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1. Introduction

Post-transplant lymphoproliferative disorders (PTLD) are a heterogeneous group of diseases occurring after organ transplantation. Several studies have analyzed the characteristics of PTLD after kidney transplantation,[1–10] and many have reported a bimodal incidence pattern.[1,3,11–13] However, there is no consensus yet regarding the differences between the two groups based on the PTLD onset time, including the cause of incidence. Some studies have analyzed the clinical features associated with early vs. late onset PTLD. These studies were multi-centered, population-based, cohort studies including patients who underwent kidney transplantation before the year 2000.[1,3,11–13] However, each center had a different kidney transplantation protocol, and several new medications such as immunosuppressants have come into use since then. Therefore, the purpose of this study was to analyze the association between PTLD incidence and its occurrence time, in patients at a single center, in comparable medical environments after the year 2000.

2. Methods

2.1. Patients and diagnosis

This study included all kidney transplant recipients at a single center between 1st January 2000 and 31st December 2015. A total of 3305 kidney transplantations were performed in 3178 patients over a period of 16 years. After receiving the Institutional Review Board's approval (2016-1782), medical records of the patients were retrospectively reviewed. Patients were divided into two groups based on the period from the day of kidney transplantation to the day of PTLD diagnosis. Early-onset PTLD was defined as PTLD development within two years after transplantation, whereas all other cases were categorized as late-onset PTLD. Medical data of the recipients and donors including the patient's demographic data, immunosuppressive medications, Epstein–Barr virus (EBV) serostatus, histologic findings of PTLD, and patient and graft survival were all analyzed. EBV seropositivity was diagnosed by the presence of EBV latent membrane protein (LMP-1), EBV nuclear antigen-2 (EBNA-2), or EBV-encoded small RNAs (EBERs). PTLD was diagnosed and classified by experienced pathologists after a needle biopsy or open biopsy according to the 2008 world health classification criteria.[14]

2.2. Immunosuppressive medication

All patients were given antithymocyte globulin or basiliximab as induction drugs. Specifically, antithymocyte globulin was used in all case of simultaneous pancreas transplantation. During the study period, immunosuppression was maintained by using a combination of a calcineurin inhibitor (CNI), a steroid, and antimetabolites. Tacrolimus or cyclosporine was used as the CNI. Azathioprine was used as an antimetabolite until 2008, while mycophenolate mofetil was used thereafter. Methylprednisolone was the steroid used. In case of ABO incompatibility, starting from 2011, rituximab was given for two weeks before plasmapheresis, and operation was performed after the isoagglutinin titer fell below 1:16.

2.3. Statistical analysis

The demographic data of the patients were compared between the two groups using the Mann–Whitney test or Fisher's exact test. Survivals were analyzed by the Kaplan–Meier method and compared by the Log-rank test. To identify the risk factors for PTLD, comparison between a group of patients with PTLD and another without PTLD was performed. The Cox proportional hazards model was used for this risk factor analysis. Only factors with a p-value of greater than 0.1 in the univariate analysis were used for the multivariate analysis. Statistical significance was established at $p < 0.05$. Statistical analyses were performed using the SPSS version 16.0 (SPSS Inc., Chicago, IL, USA).

3. Results

Among the 3305 kidney transplantation cases, 24 were diagnosed with PTLD (0.72%). The incidence of PTLD was checked every two years, and Fig. 1 shows the incidence pattern. The early and late-onset groups included 9 and 15 patients, respectively. The late onset PTLD group included one ABO incompatible transplantation and one secondary transplantation. The EBV seropositivity rate was higher in the late-onset group (100%) than in the early-onset group (55.6%). The proportion of patients receiving treatment for rejection was higher in the late-onset group (73.3%) compared to the early-onset group (22.2%). Lymphomas diagnosed in the early-onset group were all of the diffuse large B cell type, whereas those diagnosed in the late-onset group were diverse type and included diffuse large B cell, Burkitt, and extranodal NK/T cell lymphomas (Table 1). In the early-onset group, young age (0–19 years) was confirmed as a risk factor for PTLD incidence (HR 1.49, $p = 0.038$) (Table 2). In the late-onset group, history of anti-rejection therapy was confirmed as a risk factor (HR 1.32, $p = 0.031$) (Table 3).

Mean follow-up period was 86.71 ± 50.63 months. The overall survival rates at 5 and 10 years were both 77.8% in the early-onset group, while they were 86.7% and 78%, respectively in the late-onset group. Overall survival rates were not significantly different between the two groups ($p = 0.556$) (Fig. 2). The graft survival rates at 5 and 10 years were both 71.1% in the early-onset group, and 86.7% and 36.6%, respectively in the late-onset group. Graft survival rates were also not different between the two groups ($p = 0.549$) (Fig. 3).

4. Discussion

A consensus on the time period for division of PTLD into early and late-onset groups is yet to be reached. While some reports use two years after transplantation as the cutoff for onset time,[1,3,12,13,15,16] some other reports use one year as the cutoff.[2,6,17] Results of this study also found that the duration of post-operative onset was closer to that

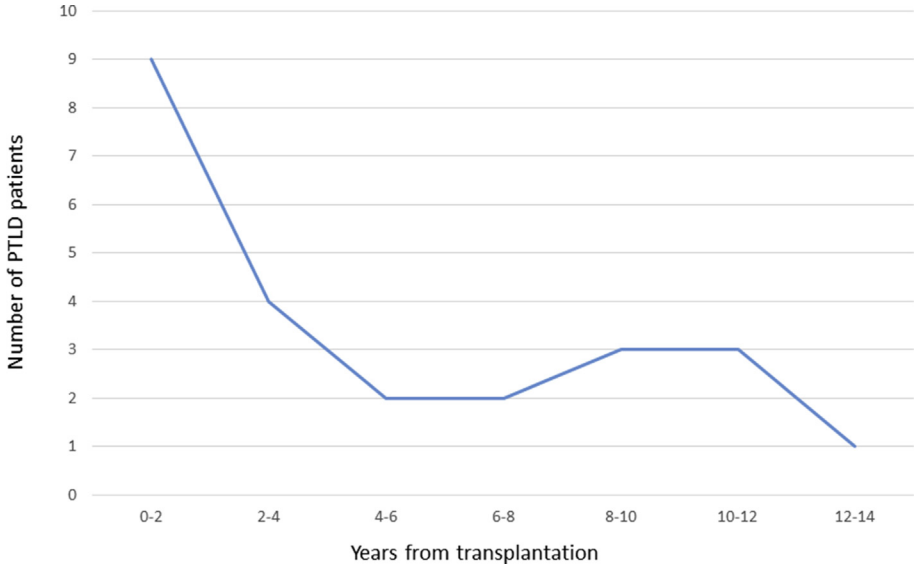

Figure 1 The incidence of PTLD based on time after kidney transplantation.

Table 1 Demographics and characteristics of kidney transplantation patients.

	Early-onset PTLD (n = 9)	Late-onset PTLD (n = 15)	Without PTLD (n = 3281)	P-value
Donor status				
Deceased (%)	4 (44.4)	4 (26.7)	807 (24.5)	0.142
Gender (%, Male)	5 (55.6)	6 (40)	2260 (68.8)	0.365
Recipient status				
Gender (%, Male)	4 (44.4)	10 (60)	1972 (60.1)	0.475
Transplantation age				0.291
0—19	4 (44.4)	4 (26.6)	92 (2.8)	
20—50	4 (44.4)	9 (60)	1884 (57.4)	
>50	1 (11.1)	2 (13.3)	1305 (39.7)	
EBV serostatus (%)				0.138
Positive	5 (55.6)	15 (100)	1152 (35.1)	
Negative	0 (0)	0 (0)	88 (2.6)	
No data	0 (0)	0 (0)	2041 (62.2)	
HLA mismatch (%)				0.231
0	0 (0)	2 (13.3)	298 (9.1)	
1—3	8 (88.9)	7 (46.7)	1972 (60.1)	
4—6	1 (11.1)	6 (40)	1011 (30.8)	
Immunosuppressants				
Calcineurin inhibitor (%)				0.096
Cyclosporine	3 (33.3)	2 (13.3)	1434 (43.7)	
Tacrolimus	6 (66.7)	13 (86.7)	1847 (56.2)	
Anti-rejection therapy (%)	2 (22.2)	11 (73.3)	306 (9.3)	0.189
Pathological features				
WHO classification (%)				
Diffuse large B cell lymphoma	9 (100)	12 (80)		
Burkitt lymphoma	0 (0)	2 (13.3)		
Extranodal NK/T cell lymphoma	0 (0)	1 (6.7)		
EBV status of the PTLD tissue (%, Positive)	8 (88.9)	9 (60)		
Graft survival rate				0.164
5 years	0.71	0.86	0.88	
10 years	0.71	0.36	0.81	
Overall survival rate				0.125
5 years	0.77	0.86	0.95	
10 years	0.77	0.78	0.92	

Table 2 Analysis of risk factors for early onset PTLD incidence among kidney transplant recipients.

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Gender				
Female	1.17 (0.35–9.98)	0.365		
Transplantation age				
0–19	1.86 (1.03–2.93)	0.004	1.49 (1.05–1.89)	0.038
20–50	1.0 (reference)		1.0 (reference)	
>50	1.91 (0.65–2.14)	0.684	1.52 (0.33–2.54)	0.873
Donor status				
Living	1.15 (0.08–3.59)	0.375		
Donor gender				
Female	1.53 (0.10–2.83)	0.461		
HLA mismatch				
0	1.0 (reference)			
1–3	1.02 (0.40–1.14)	0.563		
4–6	1.15 (0.84–1.57)	0.672		
Recipient EBV serostatus				
Negative	4.51 (2.31–7.01)	0.015	1.58 (0.44–5.70)	0.212
Calcineurin inhibitor				
Tacrolimus	1.0 (reference)			
Cyclosporine	1.25 (0.42–3.84)	0.753		
Anti-rejection therapy				
Yes	1.32 (0.85–1.78)	0.241		

Table 3 Analysis of risk factors for late onset PTLD incidence among kidney transplant recipients.

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Gender				
Female	1.35 (0.35–9.98)	0.651		
Transplantation age				
0–19	1.36 (1.06–1.93)	0.041	1.84 (0.94–5.41)	0.138
20–50	1.0 (reference)		1.0 (reference)	
>50	1.18 (0.65–2.14)	0.873	1.71 (0.53–3.57)	0.270
Donor status				
Living	0.95 (0.88–2.59)	0.482		
Donor gender				
Female	1.04 (0.71–3.83)	0.381		
HLA mismatch				
0	1.0 (reference)			
1–3	0.98 (0.60–1.14)	0.823		
4–6	1.31 (0.84–1.57)	0.746		
Recipient EBV serostatus				
Negative	1.51 (0.31–2.01)	0.185		
Calcineurin inhibitor				
Tacrolimus	1.0 (reference)			
Cyclosporine	2.14 (0.75–5.31)	0.824		
Anti-rejection therapy				
Yes	1.38 (1.85–3.25)	0.003	1.32 (1.05–2.12)	0.031

of the bimodal incidence pattern when two years was used as the cutoff onset time. Therefore, patients with PTLD onset occurring within or after two years of transplantation were categorized into early and late-onset groups, respectively. Like other reports, this study also confirmed a pattern in which the incidence of PTLD demonstrated an increasing trend in 4–6 years.[1,3] However, instead of a typical bimodal incidence pattern, we found that the

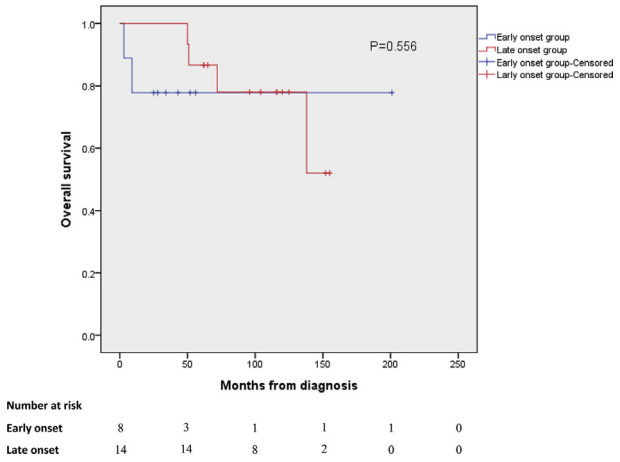

Figure 2 The overall survival rate in patients based on the time of PTLD onset.

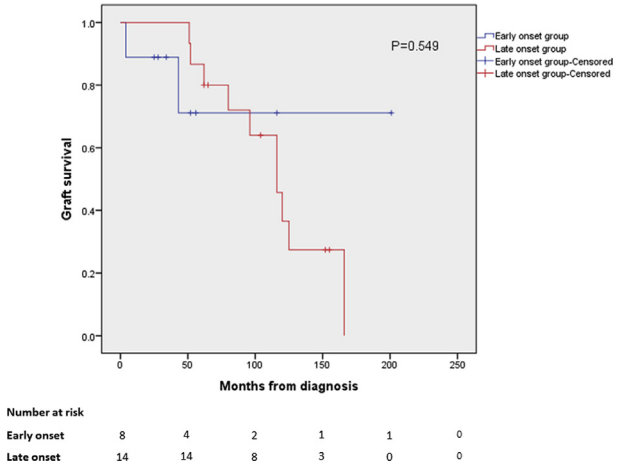

Figure 3 Graft survival rate in patients based on the time of PTLD onset.

incidence showed a slight decline in 12—14 years. This decrease seems to be due to follow up loss over long periods of time.

Data comparing the clinical features of the two groups showed that young age transplantation patients (0—19 years) were more commonly diagnosed with early-onset PTLD, suggesting that young age transplantation is a risk factor for early-onset of PTLD. EBV seronegativity is a risk factor for early-onset PTLD according to univariate analysis performed using the Cox proportional hazard model. Based on this result, we hypothesized that the early-onset of PTLD is more related to EBV than to the late-onset. It is known that EBV infection increases the probability of developing PTLD after solid organ transplantation.[18] A high proportion of young recipients are EBV seronegative at the time of transplantation, leaving them susceptible to primary infection following transplantation. In this study, the early-onset group which was relatively younger than the late-onset group showed an EBV seropositivity rate of 55.6%, which was lower than the 100% EBV seropositivity seen in the late-onset group. In agreement with this finding was the observation that the EBV positive rate in the lymphoma tissue biopsy in the early-onset group was also higher than that in the late-onset group (88.9%, 60%, respectively). The cumulative incidence rate of PTLD in our study was lower than that reported by other groups.[1,3] The low cumulative incidence rate is probably due to the higher EBV seropositivity in Koreans than in other ethnic groups, which again supports the association of early-onset PTLD incidence with EBV serostatus.[19—22]

The history of anti-rejection treatment was found to be a risk factor for development of late-onset PTLD, which is probably due to high dose exposure to immunosuppressants reducing the patient's immunity. The rates of anti-rejection treatment in the early and late-onset groups were 22.2% and 73.3%, respectively, thereby suggesting that high dose exposure to immunosuppressants is associated with late-onset PTLD. High dose exposure to immunosuppressants is distinguished from an extended exposure to cumulative immunosuppressive agents due to the prolonged duration after transplant surgery. Late onset PTLD group included one ABO incompatible (ABOi) transplantation and one secondary transplantation. The number of patients is only one each, hence statistical significance could not be elicited. However, this result indicates that exposure to high dose immunosuppressants, such as that which occurs in second transplantation or ABOi transplantation, may increase the incidence of late onset PTLD.

There was no difference in the overall and graft survival between the two groups. Compared to the survival of patients who had undergone kidney transplantation since 2000 in the same center, the prognosis was poor.[23] However, the overall survival rate is better when compared to other studies.[1,9,10,16,24] Caillard et al and Bishnoi et al have reported old age to be one of the poor prognosis factors.[6,25] The patients included in this study were by far the youngest when compared to those in other studies, which could explain the better survival rate. Moreover, all patients in this study were kidney transplant recipients after 2000, while the other studies included recipients from the 1990s. The recent developments in medications and medical conditions compared to the past may have influenced the survival rate. The limitation of this study is mainly the small number of PTLD patients. Additionally, being a retrospective study, there is a fundamental limitation in obtaining evidence. A larger prospective study will be necessary to assess the different causes for PTLD based on its onset time.

5. Conclusion

When patients with PTLD are classified into early-onset group and late-onset group at two years, overall survival and graft survival are comparable. However, there are some differences in the clinical features and risk factors for the incidence of PTLD between the two groups. While patients with early-onset PTLD are more likely to be associated with EBV, the late-onset patients are more likely to be associated with high dose immunosuppression.

Declarations of interest

None.

References

1. Maksten EF, Vase MO, Kampmann J, et al. Post-transplant lymphoproliferative disorder following kidney transplantation: a population-based cohort study. *Transpl Int*. 2016;29:483—493.
2. Ishihara H, Shimizu T, Unagami K, et al. Post-transplant lymphoproliferative disorder in kidney transplant recipients: a single-center experience in Japan. *Ther Apher Dial*. 2016;20: 165—173.
3. Quinlan SC, Pfeiffer RM, Morton LM, Engels EA. Risk factors for early-onset and late-onset post-transplant lymphoproliferative disorder in kidney recipients in the United States. *Am J Hematol*. 2011;86:206—209.
4. Franco A, Jimenez L, Sillero C, et al. Post-transplant lymphoproliferative disorders in renal transplantation: two decades of experience. *Nefrologia*. 2010;30:669—675.
5. Rausch L, Koenecke C, Koch HF, et al. Matched-pair analysis: identification of factors with independent influence on the development of PTLD after kidney or liver transplantation. *Transplant Res*. 2016;5:6.
6. Caillard S, Porcher R, Provot F, et al. Post-transplantation lymphoproliferative disorder after kidney transplantation: report of a nationwide French registry and the development of a new prognostic score. *J Clin Oncol*. 2013;31:1302—1309.
7. Rouphael B, Lankireddy S, Lazaryan A, et al. Outcomes of kidney retransplantation in recipients with prior post-transplant lymphoproliferative disorder. *Clin Transplant*. 2016;30:60—65.
8. Ferreira H, Bustorff M, Santos J, et al. Post-transplant lymphoproliferative disorder: a single-center experience. *Transplant Proc*. 2015;47:981—984.
9. Rabot N, Buchler M, Foucher Y, et al. CNI withdrawal for post-transplant lymphoproliferative disorders in kidney transplant is an independent risk factor for graft failure and mortality. *Transpl Int*. 2014;27:956—965.
10. Yoon JH, Lee S, Kim HJ, et al. Comparative analysis of post-transplant lymphoproliferative disorder after kidney transplantation versus hematopoietic stem cell transplantation. *Transpl Int*. 2014;27:721—732.
11. Caillard S, Lelong C, Pessione F, Moulin B. Post-transplant lymphoproliferative disorders occurring after renal transplantation in adults: report of 230 cases from the French Registry. *Am J Transplant*. 2006;6:2735—2742.
12. van Leeuwen MT, Grulich AE, Webster AC, et al. Immunosuppression and other risk factors for early and late non-Hodgkin lymphoma after kidney transplantation. *Blood*. 2009;114:630—637.
13. Faull RJ, Hollett P, McDonald SP. Lymphoproliferative disease after renal transplantation in Australia and New Zealand. *Transplantation*. 2005;80:193—197.
14. Harris NL, Swerdlow S, Campo E, et al. The World Health Organization (WHO) classification of lymphoid neoplasms: what's new? *Ann Oncol*. 2008;19:119.
15. Gibson TM, Engels EA, Clarke CA, Lynch CF, Weisenburger DD, Morton LM. Risk of diffuse large B-cell lymphoma after solid organ transplantation in the United States. *Am J Hematol*. 2014;89:714—720.
16. Opelz G, Dohler B. Lymphomas after solid organ transplantation: a collaborative transplant study report. *Am J Transplant*. 2004;4:222—230.
17. Ghobrial IM, Habermann TM, Macon WR, et al. Differences between early and late posttransplant lymphoproliferative disorders in solid organ transplant patients: are they two different diseases? *Transplantation*. 2005;79:244—247.
18. Ho M, Miller G, Atchison RW, et al. Epstein-Barr virus infections and DNA hybridization studies in posttransplantation lymphoma and lymphoproliferative lesions: the role of primary infection. *J Infect Dis*. 1985;152:876—886.
19. Crawford DH, Macsween KF, Higgins CD, et al. A cohort study among university students: identification of risk factors for Epstein-Barr virus seroconversion and infectious mononucleosis. *Clin Infect Dis*. 2006;43:276—282.
20. Jansen MA, van den Heuvel D, Bouthoorn SH, et al. Determinants of ethnic differences in cytomegalovirus, epstein-barr virus, and herpes simplex virus type 1 seroprevalence in childhood. *J Pediatr*. 2016;170:126—134. e121—126.
21. Ford JL, Stowe RP. Racial-ethnic differences in Epstein-Barr virus antibody titers among U.S. children and adolescents. *Ann Epidemiol*. 2013;23:275—280.
22. Dowd JB, Palermo T, Brite J, McDade TW, Aiello A. Seroprevalence of Epstein-Barr virus infection in U.S. children ages 6—19, 2003—2010. *PLoS One*. 2013;8, e64921.
23. Kwon H, Kim YH, Choi JY, et al. Analysis of 4000 kidney transplantations in a single center: across immunological barriers. *Medicine (Baltimore)*. 2016;95:e4249.
24. Einollahi B, Lessan-Pezeshki M, Nourbala MH, et al. Posttransplant lymphoproliferative disorders in kidney transplant recipients: an Iranian multicenter experience. *Iran J Kidney Dis*. 2008;2:227—233.
25. Bishnoi R, Bajwa R, Franke AJ, et al. Post-transplant lymphoproliferative disorder (PTLD): single institutional experience of 141 patients. *Exp Hematol Oncol*. 2017;6:26.