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Original Article

Characteristics and Prognosis of Lymphoproliferative Disorders Post-Renal Transplantation in Living versus Deceased Donor Allograft Recipients

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ABSTRACT. In this study, we compared the features and prognosis of post-transplantation lymphoproliferative disorders (PTLD) occurring in living donor recipients with those of deceased donor kidney transplant patients. A comprehensive search was performed for finding studies reporting data of PTLD in living and deceased donor renal recipients in the Pubmed and Google scholar search engines. Finally, international data from 14 different studies were included in the analysis. Overall, 122 renal recipients with PTLD were entered into this analysis. Chi square test showed that renal recipients from living donors significantly less frequently represented any remission episodes during the course of their disease (41% vs. 63%, respectively; P = 0.05). Living donor renal recipients were significantly more likely to develop metastasis in comparison with deceased donor recipients (64% vs. 23%, respectively; P = 0.035). Histopathological evaluations were comparable between the two patient groups. Survival analysis did not show any difference between the patient groups, even when patients were adjusted for the type of immunosuppression. The mortality rate of the transplant patients with PTLD was 55.3% and the 1- and 5-year patients survival rates were 50% and 37%, respectively, for the deceased donor renal recipients compared with 60% and 34%, respectively, for the living donors group. We conclude that living donor kidney transplant recipients who develop PTLD have a higher rate of metastasis and a lower rate of remission episodes. Further prospective studies with a large patient population are needed to confirm our results.

Introduction

Although renal transplantation has undergone an impressive progress and is generally considered as the treatment of choice for most end-stage kidney disease patients, it continues to have complications for both the living and/or the deceased donor graft recipients.[1,2]

Post-transplantation lymphoproliferative disorders (PTLD) represent a major diagnostic and therapeutic problem characterized by the irregular proliferation of B- or T-cells in the lymphoid tissue.[3] There are several reasons behind the observed preponderance in the inci-

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dence of lymphoma among solid organ recipients, including immunosuppression used to prevent rejection episodes such as the use of antibody induction therapy, and Epstein–Barr virus (EBV) infection.[4,5] Furthermore, the type of the transplanted organ is also a repeatedly reported factor; while the reported incidence of PTLD is lowest in renal transplant recipients (0.8–2%), the highest incidence is observed in the lung transplant recipients (up to 20%).[6-9]

Several studies have investigated the potential disparities of transplantations performed from living versus deceased donors.[10-12] However, there is no study to date that focuses on the different aspects of PTLD including clinical and histopathological features as well as prognosis of the disease with respect to the type of organ donors.

We aim in our study to characterize and compare the features and prognosis of PTLD that occur in living and deceased donor recipients.

Patients and Methods

We conducted a comprehensive search for the available data using the Pubmed and Google scholar search engines for reports of lymphoproliferative disorders occurring in renal transplant patients regarding the type of organ donor: deceased or living. The keywords used for this purpose included all possible combinations of key words related to the subject. Then, we only included studies in which data of each patient were presented separately. A standard questionnaire was developed to collect data from the different published studies. Finally, data from 14 previously published studies from various countries[9,13-25] were included in the study. The duration between transplantation and PTLD onset was defined as the period between the graft and the first signs of PTLD or diagnosis, based on the studies' approaches. Patients who presented with PTLD within the first 12 months post-transplantation were considered as an "early-onset PTLD" group, and renal graft recipients who presented with the disease beyond this time period after transplantation were categorized as a "late onset PTLD" group.

We included in our analysis 122 recipients of renal graft who developed PTLD through their treatment course. There were 70 (57.4%) recipients of living donor allografts and 52 (42.6%) recipients of deceased donor allografts. Patients' status regarding EBV infection was documented in 74 (60.7%) patients, of whom 60 (81.1%) patients were reported to be positive.

Because data used for this study were from different studies, we were not able to get all the data we needed from all the included patients. Disseminated lymphoma was diagnosed when it was declared by the authors, or when at least three different organs were involved by PTLD, reported in 81 (66.4%; 41 missing data) patients (different lymph node areas were excluded from analysis due to a lack of knowledge on how to categorize the same). Multiorgan involvement was defined as involvement of more than a certain organ as well as more than one lymphatic region, and it was found in 41 (39.8%; 19 missing data) patients.

After the diagnosis of lymphoma, all the patients received varying immunosuppressive combinations of azathioprine, prednisone, cyclosporine, mycophenolate mofetil and antithymocyte/lymphocyte globulin (ATG/ALG) and OKT3. A rather uniform approach was used to manage all PTLD patients in the included reports; the first step in almost all reports was to decrease or discontinue immunosuppressive therapy, and different regimens of chemotherapy with or without surgical interventions were also used for some of patients.

Response to treatment was defined as any favorable change in the cancer measures as well as patients' clinical conditions. Data of PTLD response to treatment were reported by authors for 75 (61.5%) patients, of whom 46 (37.7%) patients responded to anti-malignancy treatment. Remission of the disease was defined as remaining alive after the 24th month of PTLD diagnosis (all reported cases having this criterion had at least one confirmed remission episode), and no remission was defined as a patient who died within the first month post-PTLD diagnosis (there were no patients dying at the first post-transplant month). According

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to this criteria, 89 (73%) patients had data on remission, of whom 45 (50.6%) patients had at least one response to treatment, irrespective of their future disease behavior. The overall mortality was 63 (51.6% of the study population and 55.3% of the reported cases; eight missing data) patients; death due to PTLD was defined as: (1) if authors state it, (2) when patients died within 6 months post-diagnosis or (3) when patients died due to PTLD treatment complications. Overall, 43 (41.3% of the reported data; 68.3% of the whole mortality rate) patients died due to disease based on the above-mentioned criteria.

Statistical Analysis

Software used for data analyses was SPSS v.13.0. Statistical differences between patients' subgroups were performed by using the χ^2 and Fishers' exact tests for proportions and the Students t test for continuous data. Survival analysis was performed with life tables and Kaplan–Meier methods and log-rank test. All statistical tests were performed at the 0.05 significance level.

Results

We entered in this analysis 122 patients with lymphoproliferative disorders after renal transplantation. There were 63 (58.9%) male and 44 (41.1%) female patient (15 missing data). The mean age of the patients at the diagnosis of PTLD was 40.7 ± 14.6 years. The mean interval between transplantation and the diagnosis of PTLD was 24.6 ± 35.6 months, whereas the follow-up time after the diagnosis of PTLD was 30.8 ± 75.4 months.

The characteristics of the patients regarding their malignancy site are summarized in Table 1. Chi square test revealed that renal recipients from living donors had significantly less-frequent remission episodes during their disease course (41% vs. 63%, respectively; $P = 0.05$). Renal transplant recipients of living donor allograft were comparable to their counterparts of deceased donor graft recipients in their gender (59% male, both; $P = 1.0$), lymphoma cell types (89% vs. 91% B-cell, respectively; $P = 1.0$), positive EBV antibodies (89% vs. 74%, respectively; $P = 0.13$) and mortality rate (62% vs. 55%, respectively; $P = 0.566$). However,

Table 1. Characteristics of the renal transplant recipients with PTLD regarding their allograft source.

Variables	Living donor	Deceased donor	Significance	Available data
Age (year)	37.2 ± 12.8	46.1 ± 15.7	0.001	122
Pediatric; <18 years old (%)*	1 (1.5)	4 (9.1)	0.07	112
Gender: Male (%)	40 (58.8)	23 (59)	1.0	107
Time to PTLD development (months)	64.3 ± 55.9	66.1 ± 74.9	0.882	122
Multiorgan involvement (%)**	24 (39.3)	17 (40.5)	1.0	103
Disseminated PTLD (%)**	5 (11.4)	7 (18.9)	0.366	81
Hodgkin disease (%)	3 (11.5)	3 (12.5)	0.99	50
EBV status (%)	32 (88.9)	28 (73.7)	0.138	74
Remission episode (%)	21 (41.2)	24 (63.2)	0.05	89
Azathioprine-based IS*** (vs. MMF/FK-506)	40 (72.7)	40 (83.3)	0.397	103
Use of induction therapy	12 (60)	28 (68.3)	0.574	61
Early onset (within the first 12 months post-transplant)	17 (24.3)	15 (28.8)	0.678	122
Monoclonal lesions vs. polyclonal lesions (%)	1 (25)	2 (18)	1.0	15
Monomorphic lesions (%)	3 (23.1)	7 (28)	1.0	38
Lymphoma cell type B-cell (%)	16 (88.9)	21 (91.3)	1.0	41

*: Denominator for percentages is each column's group, **: according to the criteria defined in the methods section; ***IS: immunosuppression, EBV: Epstein–Barr virus.

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Table 2. Frequency of the involved organs in 82 renal transplant recipients with regard to their allograft source.

Involved organs	Living donor	Deceased donor	Significance
Orbital	0	0	
Skin	1 (2.9)	4 (8.5)	0.387
Stomach	1 (2.9)	3 (6.4)	0.632
Genitalia	1 (2.9)	1 (2.2)	1.0
CNS	6 (17.1)	6 (12.8)	0.754
Skeleton	0	0	
Spleen	0	2 (4.3)	0.505
Colon	0	2 (4.3)	0.505
Small intestine	8 (22.9)	9 (19.1)	0.785
Renal involvement	6 (17.1)	7 (14.9)	1.0
Respiratory system	3 (8.6)	4 (8.5)	1.0
Bone marrow	3 (8.6)	2 (4.3)	0.646

CNS: Central nervous system.

living donor renal recipients were significantly more likely to develop metastasis when it was definitely reported by the authors (64% vs. 23%, respectively; $P = 0.035$), but when data were re-analyzed based on the defined criteria mentioned in the methods section, multiorgan involvement (58% vs. 60%, respectively; $P = 1.0$) and disseminated PTLD (42% vs. 56%, respectively; $P = 0.366$) were equally distributed between the two patient groups regarding their donor types.

Table 2 summarizes the different organ involvements with PTLD according to their donor type. Living donor kidney transplant patients were significantly younger (median age 34.0 vs. 49.5 years) but had comparable time from transplantation to PTLD development (median 56.3 vs. 40.5 months). The histopathological evaluations were also comparable between the living and the deceased donor renal recipients with PTLD, including morphology (77% vs. 72% polymorph, respectively; $P = 1.0$) and clonality (25% vs. 18%, respectively; $P = 1.0$). The two groups were also similar in the frequency of Hodgkin and non-Hodgkin's PTLD lesions (11% vs. 12%, respectively; $P = 1.0$).

At the last follow-up, 63 (55.3%) patients were dead (eight missing data). When death irrespective of the reason was used as the final outcome, the log–rank test did not show any difference between the two groups in their survival ($P = 0.915$; Figure 1). Moreover, no statistically significant difference was observed between the groups when death due to PTLD was used as the final outcome (based on the defined criteria in the methods section; $P = 0.353$, Figure 2). To eliminate the potential impact of immunosuppression treatment on the outcome, we re-analyzed the survival of the two patient groups for patients under azathioprine-based treatment, but no significant difference in the survival of the study groups was found (Figure 3).

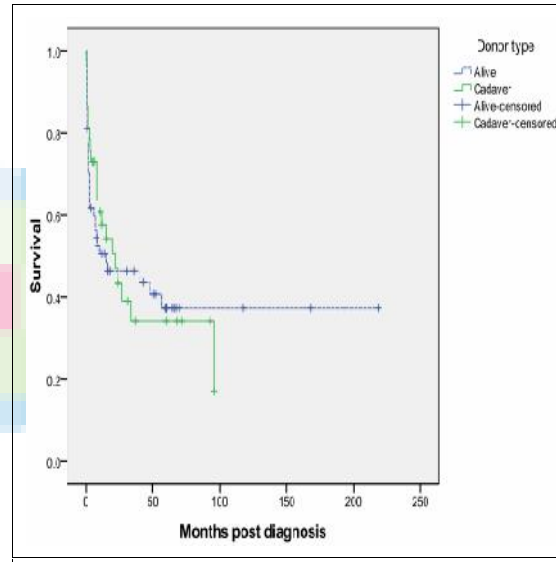

Figure 1. Survival curves of renal recipients with post-transplant lymphoproliferative disease regarding their allograft source when death irrespective of the reason is considered as the outcome.

The 1- and 5-year survival rates were 50% and

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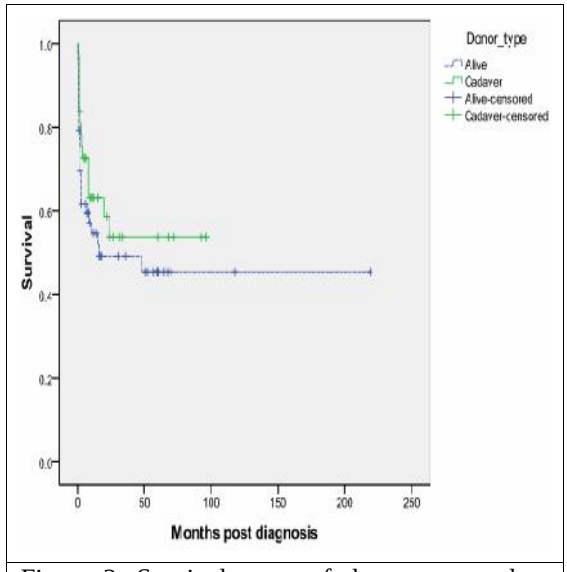

Figure 2. Survival cures of the post-transplant lymphoproliferative disease (PTLD) patients regarding their allograft source when death due to the PTLD is considered as the outcome.

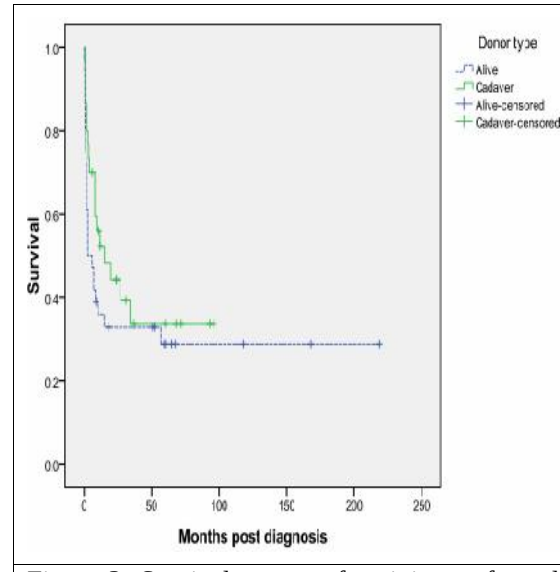

Figure 3. Survival curves of recipients of renal allograft with post-transplant lymphoproliferative disease from living versus deceased donors on azathioprine-based immunosuppression.

37%, respectively, for the deceased donor renal recipients compared with 60% and 34%, respectively, for the living donors group.

Discussion

In this study, we analyzed the existing data to discover different aspects of PTLD occurring in renal transplant recipients from living versus deceased donor sources, including histopathological characteristics (e.g., morphology and clonality), EBV infection status, involvement sites and prognostic factors. By examining previous reports,[26-33] we found several disparities of the time of presentation, risk factors and prognosis of PTLD.

In this study, we found that PTLD developing in living donor renal transplant patients had comparable histopathological features and mortality rate to those of the deceased donor renal recipients. When addressing the involvement organs, again, both the patient groups represented comparable involvement sites (Table 2). An interesting finding of this study is that although renal recipients from deceased donors developing PTLD were significantly older than those of living donor patients, the number of pediatric patients was relatively higher in the latter group, although it did not reach a significance level (P = 0.07). Moreover, the rate of author-defined metastasis was higher and the rate of remission was lower in our series of PTLD recipients from living donors. The explanation for these observations is not clear. It is well known that renal transplants from living donors have a relatively better prognosis than those of the deceased donors. Therefore, one may assume that this might be related to a better maintenance of donor cells within the allograft, including cells capable of inducing lymphomas. Malignant cells, due to the higher need for nutrients, are more susceptible to environmental stress; therefore, they can be better saved in a living donor graft, which may be due to the higher rate of metastases as well as the lower rate of remission in the recipients of grafts from living donors.

We also found that PTLD recipients of renal graft from living or deceased donors had comparable patients' outcome; although there was a narrow gap between the survival curves of both groups, it was not significant. Although different immunosuppression protocols may result in different outcomes, we found no significant difference in the survival of the study groups (Figure 3).

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The present study has some limitations. The first is the retrospective nature of data collection from different institutions, and we were, accordingly, unable to gather all data for any individual variable to have a perfect view on the whole population; for example, categorization of the histological features of the PTLD were not based on the same method; therefore, we devised some new methods to maximize inclusion of patients from the various studies. In addition, data presentation was not perfect in all the articles; for example, while some series reported very distinct data on their treatment methods or PTLD involvement sites, others presented very limited and ambiguous data. Methods of data ascertainment also varied between the different reports. For example, for evaluation of EBV infection status, some of the studies used simple serological evaluations while others used polymerrase chain reaction methods.

However, despite all these limitations, we believe that our study has several advantages over single-center reports as it used data from several centers around the world, and this strengthens our results by decreasing selection bias and/or inter-institutional disparities.

We conclude that survival of renal transplant patients who develop PTLD is not different according to the source of allografts. However, the living donor kidney transplant recipients who develop PTLD should receive more attention than the deceased donor recipients due to a higher rate of metastasis and a lower rate of remission episodes. Survival rates for both the study groups were relatively low; therefore, we recommend that all transplant patients with PTLD should receive full evaluations and should be under strict observation. Further prospective studies with a large patient population are needed to confirm our results.

References

1. Taheri S, Alavian SM, Einollahi B, Nafar M. Gender bias in Iranian living kidney transplantation program: A national report. Clin Transplant 2010;24:528-34.
2. Khedmat H, Taheri S. Ethical disputes in living donor kidney transplantation: What should we do to save lives? Saudi J Kidney Dis Transpl 2010;21:971-4.
3. Penn I, Hammond W, Brettschneider L, Starzl TE. Malignant lymphomas in transplantation patients. Transplant Proc 1969;1:106-12.
4. Malatack JF, Gartner JC Jr, Urbach AH, Zitelli BJ. Orthotopic liver transplantation, Epstein-Barr virus, cyclosporine, and lymphoproliferative disease: A growing concern. J Pediatr 1991;118:667-75.
5. Cox KL, Lawrence-Miyasaki LS, Garcia-Kennedy R, et al. An increased incidence of Epstein-Barr virus infection and lymphoproliferative disorder in young children on FK506 after liver transplantation. Transplantation 1995;59:524-9.
6. Boubenider S, Hiesse C, Goupy C, Kriaa F, Marchand S, Charpentier B. Incidence and consequences of post-transplantation lymphoproliferative disorders. J Nephrol 1997;10:136-45.
7. Boyle GJ, Michaels MG, Webber SA, et al. Posttransplantation lymphoproliferative disorders in pediatric thoracic organ recipients. J Pediatr 1997;131:309-13.
8. Gao SZ, Chaparro SV, Perlroth M, et al. Post-transplantation lymphoproliferative disease in heart and heart-lung transplant recipients: 30-year experience at Stanford University. J Heart Lung Transplant 2003;22:505-14.
9. Pourfarziani V, Taheri S, Lessan-Pezeshki M, et al. Lymphoma after living donor kidney transplantation: An Iranian multicenter experience. Int Urol Nephrol 2008;40:1089-94.
10. Bourdeaux C, Darwish A, Jamart J,et al. Living-related versus deceased donor pediatric liver transplantation: A multivariate analysis of technical and immunological complications in 235 recipients. Am J Transplant 2007;7:440-7.
11. Maluf DG, Stravitz RT, Cotterell AH, et al. Adult living donor versus deceased donor liver transplantation: A 6-year single center experience. Am J Transplant 2005;5:149-56.
12. Terasaki PI, Cecka JM, Gjertson DW, Takemoto S. High survival rates of kidney transplants from spousal and living unrelated donors. N Engl J Med 1995;333:333-6.
13. Abe T, Ichimaru N, Kokado Y, et al. Post-transplant lymphoproliferative disorder following renal transplantation: A single-center experience over 40 years. Int J Urol 2010;17:48-54.
14. Timurağaoğlu A, Uğur-Bilgin A, Colak D, etal.

[Downloaded free from http://www.sjkdt.org on Wednesday, September 28, 2016, IP: 77.253.230.104]

Posttransplant lymphoproliferative disorders in transplant recipients. Transplant Proc 2006; 38:641-5.
15. Ganne V, Siddiqi N, Kamaplath B, et al. Humanized anti-CD20 monoclonal antibody (Rituximab) treatment for posttransplant lymphoproliferative disorder. Clin Transplant 2003; 17:417-22.
16. Frías C, Lauzurica R, Vaquero M, Ribera JM. Detection of Epstein-Barr virus in posttransplantation T cell lymphoma in a kidney transplant recipient: Case report and review. Clin Infect Dis 2000;30:576-8.
17. Portell C, Nand S. Single agent lenalidomide induces a response in refractory T-cell posttransplantation lymphoproliferative disorder. Blood 2008;111:4416-7.
18. Zaltzman JS, Prasad R, Chun K, Jothy S. Resolution of renal allograft-associated posttransplant lymphoproliferative disorder with the introduction of sirolimus. Nephrol Dial Transplant 2005;20:1748-51.
19. Salama S, Todd S, Cina DP, Margetts P. Cutaneous presentation of post-renal transplant lymphoproliferative disorder: A series of four cases. J Cutan Pathol 2010;37:641-53.
20. Wasson S, Zafar MN, Best J, Reddy HK. Posttransplantation lymphoproliferative disorder in heart and kidney transplant patients: A single-center experience. J Cardiovasc Pharmacol Ther 2006;11:77-83.
21. Cockfield SM, Preiksaitis JK, Jewell LD, Parfrey NA. Post-transplant lymphoproliferative disorder in renal allograft recipients. Clinical experience and risk factor analysis in a single center. Transplantation 1993;56:88-96.
22. Hanto DW, Frizzera G, Purtilo DT, et al. Clinical spectrum of lymphoproliferative disorders in renal transplant recipients and evidence for the role of Epstein-Barr virus. Cancer Res 1981;41:4253-61.
23. Jain M, Badwal S, Pandey R, Srivastava A, Sharma RK, Gupta RK. Post-transplant lymphoproliferative disorders after live donor renal transplantation. Clin Transplant 2005;-19:668-73.
24. Mamzer-Bruneel MF, Lomé C, Morelon E, et al. Durable remission after aggressive chemotherapy for very late post-kidney transplant lymphoproliferation: A report of 16 cases observed in a single center. J Clin Oncol 2000; 18:3622-32.
25. Kerkar N, Morotti RA, Madan RP, et al. The changing face of post-transplant lymphoproliferative disease in the era of molecular EBV monitoring. Pediatr Transplant 2010;14:504-11.
26. Khedmat H, Taheri S. Early onset post transplantation lymphoproliferative disorders: Analysis of international data from 5 studies. Ann Transplant 2009;14:74-7.
27. Khedmat H, Taheri S. Late onset post transplantation lymphoproliferative disorders: Analysis of international data from 5 studies. Ann Transplant 2009;14:80-5.
28. Khedmat H, Alavian SM, Taheri S. Significance of Epstein-Barr virus infection in the outcome of renal transplant patients with lymphoproliferative disorders. Ann Transplant 2010;15: 40-4.
29. Khedmat H, Taheri S. Characteristics and prognosis of post transplantation lymphoproliferative disorders within renal allograft: Report from the PTLD.Int. Survey. Ann Transplant 2010;15:80-6.
30. Khedmat H, Taheri S. Post Transplantation lymphoproliferative disorders in renal vs. Simultaneous renal- pancreas allograft recipients: Report from PTLD. Int. Survey. Saudi J Kidney Dis Transpl 2013;24(1):1-7.
31. Izadi M, Taheri S. Significance of in Situ Hybridization Results for EBV-Encoded RNA in Post Transplantation Lymphoproliferative Disorder Setting: Report from the PTLD.Int. Survey. Ann Transplant 2010;15:102-9.
32. Khedmat H, Taheri S. Post-transplantation lymphoproliferative disorders (PTLD) localized in the central nervous system:report from an international survey on PTLD. Saudi J Kidney Dis Transpl 2013;24(2):235-42.
33. Izadi M, Fazel M, Saadat SH, Taheri S. Hepatic involvement by lymphoproliferative disorders post liver transplantation: Report from the PTLD.Int. Survey. Hepatol Int 2011 Sep;5(3):759-66.