

## Rituximab is Indispensable for Pediatric Heart Transplant Recipients Developing Post Transplant Lymphoproliferative Disorders

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### Abstract

Rituximab, an anti-CD20 agent, has been suggested as an effective strategy to deal with post transplant lymphoproliferative disorders (PTLD). In the current study, we aim to evaluate the efficacy of rituximab therapy in heart transplant population developing PTLT. A comprehensive search of the literature was performed to gather the available data on lymphoproliferative disorders occurring in heart transplant patients. Finally, data of 125 patients from 26 previously published studies were included into the study. Patients who underwent rituximab therapy had significantly worse tumoral histopathology features (P-value= 0.003).

Survival analyses showed no significant difference regarding receiving rituximab therapy for heart

recipients; however, when the analysis was repeated only including data of pediatric patients, significant beneficial effects for pediatric were found for rituximab therapy. In fact, no children undergoing rituximab therapy died during the follow up. In conclusion, this study showed that rituximab therapy in pediatric heart transplant recipients with PTLT represents surprisingly excellent results, making rituximab an indispensable agent in the management of the disease. To define feasibility of rituximab therapy in adult recipients of heart graft with PTLT, randomized controlled trials are needed.

### Keywords

Pediatrics; Heart Transplantation; rituximab

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### Introduction

The science of organ transplantation has witnessed substantial succession through the recent two to three decades, after the significant advances achieved either in the surgical techniques or introduction of highly potent immunosuppressive agents for preventing rejection episodes. These advances have provided the transplantation practice, an opportunity to experience success in transplanting different organs of the body, even critical organs like the heart, for which rather unfavorable results used to be obtained before the recent progressions. On the other hand, the widespread use of powerful immunosuppression for preventing the risk of rejection has emerged new troubles that can adversely affect patients' survival in different ways (1-3). Post transplant lymphoproliferative disorders (PTLD) are one of the most frequent and also fatal disorders that have been reported as a consequence of immunosuppressive therapy. The vulnerability to the development of lymphomas in organ transplant recipients has firstly been reported by Penn et al. (4)

in 1969, characterized by lymphoid proliferation of B- or T-cell origins in different organs. Then, after a large amount of reports from all over the world, the high incidence of PTLT among recipients of all types of organs indicated, either in adults or children, and poor outcome (5-9). Different studies have suggested that the incidence, time interval, prognosis, and presentation of PTLT vary depending on several factors including the demographics of the patients, the immunosuppression employed, and the type of organ transplanted (10-12). The reported incidence of PTLT in heart transplant recipients varies from 2% to up to 25% with higher rates in pediatric settings and EBV negative patients (13, 14).

Since the majority of PTLT lesions arise from B lymphocytes, anti-B monoclonal antibodies seem logical agents for administration; Rituximab, an anti-CD20 monoclonal antibody, has been used to treat non-Hodgkin's lymphoma, and had resulted in a favorable outcome (15). In the transplant context, this agent prevents the risk of graft rejection due to immunosuppression discontinuation, and minimizes

the systemic toxicity secondary to chemotherapy. Therefore, rituximab administration concomitant to reducing immunosuppression has been suggested as an effective strategy to deal with PTLD (16, 17). In the current study, we aim to evaluate the efficacy of rituximab therapy in a heart transplant population developing PTLD.

## Methods and material

### Approach to the study

We conducted a comprehensive search by Pubmed and Google Scholar for the available data in lymphoproliferative disorders occurring in heart transplant patients. Keywords used included “lymphoproliferative disorders + transplantation + heart + survival” “lymphoproliferative disorders + transplantation + heart + outcome” “lymphoproliferative disorders + heart transplantation + mortality” “lymphoproliferative disorder + transplantation + heart + treatment” “PTLD + heart + survival” “PTLD + heart + outcome”, and similar combination of the keywords. In cases that we were not able to achieve the full text of the articles, emails were sent to corresponding authors requesting the article. To minimize selection bias, we only included studies reporting their series of patients from single or multi center populations, and studies with any specific selection criterion were excluded from the analysis. Finally, data from 26 previously published studies from various countries (18-43) were included into the study. Patients whose PTLD presentation time was within the first 12 months post transplantation were considered as “early-onset PTLD” group, and the heart graft recipients who represented the disease beyond this time period after transplantation were categorized as “late onset PTLD” patients.

### Study population

Overall, 125 recipients of cardiac allograft were included into the study. 34 (27.2%) of the study population were patients who had been received rituximab after PTLD diagnosis while the remaining 91 (72.8%) patients had been confirmed not having gotten rituximab.

### Data standardization and terminology definition

Because of inconsistencies in the data presentation by different included reports, we had to standardize data of different measures to cumulate into a unique database. Disseminated lymphoma was diagnosed when it was declared by the authors or at least three different organs (excluding different lymph node areas) were involved by PTLD, reported in 21 (27.6%; 49 unreported) of patients. Multi organ involvement defined as involvement of more than a unique organ as well as more than one lymphatic region was diagnosed in 34 (40%; 40 unreported) patients.

## Response to treatment

Response to treatment was defined as any favorable change in the cancer measures as well as patients' clinical condition termed as “remission”, and was defined when declared by authors or when patients were alive after their 24th month of PTLD diagnosis, and no remission was defined when a patient dies within the first month post PTLD diagnosis. Please divided into two sentences when it is possible

According to the abovementioned criteria, 58 cases (78.4%) had at least one episode of remission (51 unreported). Overall mortality was 44 (46.3% of the reported cases; 30 unreported) patients.

### Statistical analysis

Software used for data analyses was SPSS v.17.0 (SPSS corp., Chicago, IL, USA). Statistical differences between patients' subgroups were performed by using  $\chi^2$  and Fishers' exact tests for proportions and the Students t test for continuous data. Survival analysis was done with life tables and Kaplan-Meier methods and log-rank test. All statistical tests were performed at the 0.05 significance level.

## Results

Overall 125 recipients of heart allograft with lymphoproliferative disorder who had a verified history of either having or not having use of rituximab therapy were entered into the analysis. The list of the studies of their patients, which were finally included into analysis are summarized in table I. There were 78 (75.7%) males and 25 (24.3%) female (22 unreported) patients. Mean age at diagnosis of PTLD was  $37.5 \pm 23.4$  years. 30 (26.5%) of the patients were at the pediatric age (12 unreported). The mean interval between transplantation and the diagnosis of PTLD was  $47.2 \pm 39.0$  months whereas follow up time after diagnosis of PTLD was  $30.4 \pm 35.8$  months.

Table II summarizes comparative data of the study population regarding the history of rituximab therapy. As can be seen, patients who undergone rituximab therapy were significantly more likely to be younger at age, having more aggressive histopathological type of lymphomas, and also none of them receive induction therapy. At the last follow, 44 (46.3%) patients were dead (30 case unreported data). Survival analyses using either ‘death irrespective of the reason’ (P-value= 0.47) or ‘death due to PTLD’ (P-value= 0.27) as the outcome showed no significant difference regarding receiving rituximab therapy for heart recipients, neither any significant difference was found for remission rates between patients who had received rituximab and patients who had not (P-value= 0.637). In order to analyze a potential disparity between children and adults with regard to response to rituximab therapy, we reanalyzed the data

for each age subgroup, separately. This time, survival analyses showed a significant beneficial effects for pediatric heart recipients with PTLD who get rituximab therapy (P-value= 0.031; figure 1), but no benefit was found for adult heart recipients with PTLD regarding rituximab therapy (P-value= 0.2). For patients with CD20 positive results, survival

analysis, showed no survival benefit (P-value= 0.95); however, we should consider that CD20 positive patients who undergone rituximab therapy had a significantly more unfavorable tumoral histopathology (11(69%) monomorphic lesions versus 5 (31%) for those who did not get rituximab).

Table I. List of the series included

Studies	Frequency	Percent
Aigner et al. [18]	1	.8
Tsai et al.[19]	2	1.6
Dotti et al. [20]	4	3.2
Poirel et al. [21]	14	11.2
Trappe et al. [22]	2	1.6
Muti et al. [23]	22	17.6
Wasson [24]	4	3.2
Vakiani et al. [25]	9	7.2
Schubert et al. [26]	6	4.8
Oertel et al. [27]	3	2.4
Buadi et al. [28]	4	3.2
Douglas et al. [29]	2	1.6
Timms et al. [30]	3	2.4
Elad et al. [31]	5	4.0
Morovic [32]	1	.8
Peraira et al. [33]	2	1.6
Manlhiot et al. [34]	2	1.6
Pitman e al. [35]	3	2.4
Windebank et al. [36]	3	2.4
Burra et al. [37]	10	8.0
His et al. [38]	2	1.6
Benkerrou et al. [39]	13	10.4
Blaes [40]	1	.8
Oertel et al. [41]	2	1.6
Zimmermann et al. [42]	1	.8
Picarsic et al. [43]	4	3.2
<b>Total</b>	<b>125</b>	<b>100.0</b>

Table II. Comparative data of the study cases and control population

Variables	Rituximab	No rituximab	Sig.	Available data
Age (yr)	30.3±24.3	40.4±22.4	0.034	113
Pediatric; <18 yr/o (%)	13 (39.4)	17 (21.3)	0.06	113
Gender male (%)	19 (73.1)	59 (76.6)	0.79	103
Time to PTLD development (mo)	44.5±39.8	48.2±38.9	0.66	118
Multi organ involvement (%)*	10 (41.7)	29 (39.3)	0.52	85
Disseminated PTLD (%) *	3 (17.6)	18 (30.5)	0.37	76
EBV status (%)	22 (81.5)	50 (75.8)	0.785	93
Remission episode (%)	20 (80)	38 (77.6)	0.53	74
Monoclonal lesions vs. polyclonal (%)	9 (90)	34 (68)	0.26	60
Lymphoma cell type B cell (%)	24 (96)	68 (90.7)	0.68	100
Morphology	1(3.1)	8 (11.6)	0.003	101
Early lesion (Plasmacytic hyperplasia)	3 (9.4)	23 (33.3)		
Polymorphic B cell lymphoma	27 (84.4)	31 (44.9)		
Monomorphic PTLD	1 (3.1)	7 (10.1)		
Hodgkin lymphoma	1(3.1)	8 (11.6)		

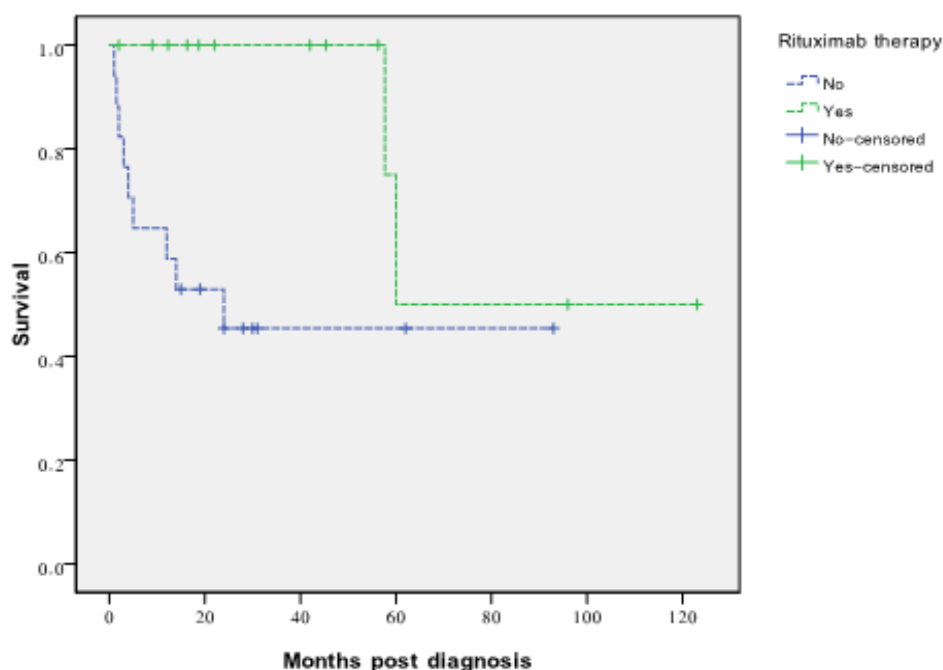


Figure I. Survival curves of pediatric heart Recipients developing PLTD ,who have undergone rituximab therapy or have not.

## Discussion

Rituximab is a chimeric anti-CD20 IgG monoclonal antibody which through its murine Fab domain binds to the CD20 antigen, a transmembrane protein located on the surface of mature B-cells. The CD20 antigen is one of regulators of transmembrane calcium conductance and cell-cycle progression

during activation of B-cells. Rituximab was firstly approved for the treatment of relapsed CD20-positive non-Hodgkin lymphomas with reported high remission rates (44); and since then, it has been widely used alone or in combination with other agents for the treatment of various hematological malignancies (45-47).

Rituximab has also been used in the management of PTLD (48). Although due to its indiscriminate attack to CD20 cell, irrespective of their status as neoplastic or normal, several serious side effects are associated with this agent administration, in a way that some authors have doubted its safety as a drug. Data on the feasibility of rituximab administration in PTLD patients is quite more limited than it is in non-transplant context. The current study which is based on cumulative data of 26 studies showed no significant beneficial effects for rituximab therapy in heart transplant recipients. Nonetheless, we should bring in mind that our analyses were not based on data achieved from a randomized controlled trial, and a selection bias in defining the patient population in our study is inevitable. For example, as it is summarized in table II, patients who had undergone rituximab therapy had a significantly worse histopathological feature of the tumor; this may in part show that why we did not observe a beneficial effect for the rituximab therapy; the drug has been used for patients of more aggressive tumors.

The most important finding of the current study is that we found that rituximab therapy is associated with a significant superior survival for pediatric heart transplant recipients. Taking a precise look at the survival curves illustrated in the figure 1, no mortality has been occurred in heart transplant children who had received rituximab during the first 4-5 years after PTLD diagnosis. This finding is of utmost importance when we consider the fact that PTLD is highly fatal in heart graft recipients compared to recipients of other organs (49). This makes rituximab an indispensable drug to manage PTLD arising in heart transplant recipients.

Findings of the current study have other clinical implications as well. Although both rituximab and chemotherapy have been approved to be used as the therapeutic options in PTLD patients, chemotherapy has been associated with high rates of toxicity related mortality. In one study over 1/4<sup>th</sup> of all PTLD patients who had undergone chemotherapy died of its associated toxicity (50). Although this fact does not diminish the importance of chemotherapy in patients with more aggressive PTLD courses, use of rituximab therapy alone or in combination with low dose chemotherapy might provide higher survival rates, both due to lowering adverse effects of chemotherapy and therapeutic effects of rituximab. This idea would be more strengthened when we consider that compared to cytotoxic chemotherapy alone, a combination of chemotherapy and rituximab in the treatment of non-Hodgkin's lymphoma is more effective (51). More specifically, a trial of six patients with PTLD has showed that a combination of chemotherapy with rituximab was associated with 100% remission rate in

their series (52); and based on this finding authors have suggested that rituximab can also sensitize tumoral cells to the effects of chemotherapy. Moreover, there are studies demonstrating high response rate to rituximab therapy in the pediatric setting (53). Consistent to our findings, Webber et al. have proposed rituximab as the first line treatment for refractory PTLD developing in pediatric solid organ recipients (54). Putting all the above mentioned data together, we recommend that all pediatric heart transplant recipients who develop PTLD to receive rituximab therapy in their anti-tumoral therapy regimens, either alone or in combination with chemotherapy. For adult recipients of heart graft, more data are needed from randomized controlled trials to confirm its beneficial effects.

This study has some limitations. These limitations are inevitable due to the nature of the PTLD. Int Surveys which includes its cases from different reports (55-71). Patients whose data were used for analysis in this study were gathered from different case reports or series, which might follow more or less inconsistent approaches. However, to deal with this problem we standardized data of different studies to be able to cumulate them all in a single database. On the other hand, our study represents the single largest patient population of heart transplant recipients with PTLD who undergone had rituximab therapy. Moreover, the very excellent outcome achieved by rituximab therapy in pediatric recipients of heart allograft with PTLD leaves rituximab a compelling agent in the management of this disease.

In conclusion, this study showed that rituximab therapy in pediatric heart transplant recipients with PTLD represents surprisingly excellent results, making rituximab an indispensable agent in the management of the disease. However, in this study we found not a comparable result for adult recipients of cardiac transplant. The rationale behind this observation, we believe, lies on the methodology of the study and the selection bias between the patients who received the rituximab or not; because patients who received the agent were significantly more likely to have worse histopathological features for the tumor. To define feasibility of rituximab therapy in adult recipients of heart graft with PTLD, randomized controlled trials are needed.

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#### **Conflict of Interest**

There is no conflict of interest associated with this study.

#### **References**

- 1.Pappas PG, Alexander BD, Andes DR, Hadley S, Kauffman CA, Freifeld A, et al. Invasive fungal infections among organ transplant recipients: results of the Transplant-Associated Infection Surveillance Networ (TRANSNET). *Clin Infect Dis*. 2010; 50(8): 1101-11.
- 2.Menon KV, Hakeem AR, Heaton ND. Meta-analysis: recurrence and survival following the use of sirolimus in liver transplantation for hepatocellular carcinoma. *Aliment Pharmacol Ther*. 2013; 37(4): 411-9.
- 3.Doesch AO, Müller S, Konstandin M, Celik S, Kristen A, Frankenstein L, et al. Malignancies after heart transplantation: incidence, risk factors, and effects of calcineurin inhibitor withdrawal. *Transplant Proc*. 2010; 42(9): 3694-9.
- 4.Penn I, Hammond W, Brettschneider L, Starzl TE. Malignant lymphomas in transplantation patients. *Transplant Proc*. 1969; 1:106-12.
- 5.Khedmat H, Taheri S. Early versus late outset of lymphoproliferative disorders post-heart and lung transplantation: the PTLD.Int Survey. *Hematol Oncol Stem Cell Ther*. 2011; 4: 10-6.
- 6.Khedmat H, Taheri S. CD20 antigen expression by lymphoproliferative disorders after kidney transplant is independently associated with a poor outcome: PTLD.Int survey. *Exp Clin Transplant*. 2012; 10: 325-31.
- 7.Khedmat H, Taheri S. Lymphoproliferative disorders in pediatric liver allograft recipients: a review of 212 cases. *Hematol Oncol Stem Cell Ther*. 2012; 5: 84-90.
- 8.Pourfarziani V, Taheri S, Lessan-Pezeshki M, Nourbala MH, Simforoosh N, Nemati E, et al. Lymphoma after living donor kidney transplantation: an Iranian multicenter experience. *Int Urol Nephrol*. 2008; 40:1089-94.
- 9.Khedmat H, Taheri S. Post-transplantation lymphoproliferative disorders (PTLD) localized in the central nervous system: report from an international survey on PTLT. *Saudi J Kidney Dis Transpl*. 2013; 24:235-42.
- 10.Penn I. De novo cancers in organ allograft recipients. *Curr Opin Organ Transplant*. 1998; 3:188-99.
- 11.Morton M, Coupes B, Roberts SA, Klapper PE, Byers RJ, Vallely PJ, et al. Epidemiology of posttransplantation lymphoproliferative disorder in adult renal transplant recipients. *Transplantation*. 2013; 95: 470-8.
- 12.Dierickx D, Tousseyn T, Sagaert X, Fieuws S, Wlodarska I, Morscio J, et al. Single-center analysis of biopsy-confirmed posttransplant lymphoproliferative disorder: incidence, clinicopathological characteristics and prognostic factors. *Leuk Lymphoma*. 2013.
- 13.Chinnock R, Webber SA, Dipchand AI, Brown RN, George JF. A 16-year multi-institutional study of the role of age and EBV status on PTLT incidence among pediatric heart transplant recipients. *Am J Transplant*. 2012; 12:3061-8.
- 14.Khedmat H, Taheri S. Heart allograft involvement by posttransplant lymphoproliferative disorders: report from the PTLT. Int survey. *Exp Clin Transplant*. 2011; 9: 258-64.
- 15.Coiffier B, Haioun C, Ketterer N, Engert A, Tilly H, Ma D, et al. Rituximab (anti- CD20 monoclonal antibody) for the treatment of patients with relapsing or refractory aggressive lymphoma: a multicenter phase II study. *Blood* 1998; 92: 1927-32.
- 16.Bonney DK, Htwe EE, Turner A, Kelsey A, Shabani A, Hughes S, et al. Sustained response to intrathecal rituximab in EBV associated Post-transplant lymphoproliferative disease confined to the central nervous system following haematopoietic stem cell transplant. *Pediatr Blood Cancer*. 2012; 58: 459-61.
- 17.Miyagi S, Sekiguchi S, Kawagishi N, Akamatsu Y, Satoh K, Takeda I, et al. Rituximab therapy and reduction of immunosuppression to rescue graft function after renal posttransplantation lymphoproliferative disorder found by macrohematuria in a pancreas and kidney transplant recipient: a case report. *Transplant Proc*. 2011; 43: 3299-301.
18. Aigner F, Boeckle E, Albright J. Malignancies of the colorectum and anus in solid organ recipients. *Transplant Int* 2007; 20: 497-504.
19. Tsai DE, Hardy CL, Tomaszewski JE, Kotloff RM, Oltoff KM, Somer BG, et al. Reduction in immunosuppression as initial therapy for posttransplant lymphoproliferative disorder: analysis of prognostic variables and long-term follow-up of 42 adult patients. *Transplantation* 2001; 71: 1076-88.
20. Dotti G, Fiocchi R, Motta T, Mammana C, Gotti E, Riva S, et al. Lymphoma occurring late after solid organ transplantation: influence of treatment on the clinical outcome. *Transplantation*. 2002; 74: 1095-102.
- 21.Poirel HA, Bernheim A, Schneider A. Characteristic Pattern of Chromosomal Imbalances in Posttransplantation Lymphoproliferative Disorders: Correlation with Histopathological Subcategories and EBV Status. *Transplantation* 2005; 80: 176-84.
- 22.Trappe R, Riess H, Babel N. Salvage Chemotherapy for Refractory and Relapsed Posttransplant Lymphoproliferative Disorders (PTLT) After Treatment With Single-Agent Rituximab. *Transplantation* 2007; 83: 912-18.
- 23.Muti G, Cantoni S, Oreste P, Klersy C, Gini G, Rossi V, et al.Cooperative Study Group on PTLTs. Post-transplant lymphoproliferative disorders:

improved outcome after clinico-pathologically tailored treatment. *Haematologica*.2002; 87(1): 67-77.

24.Wasson S, Zafar MN, Best J, Reddy HK. Post-transplantation lymphoproliferative disorder in heart and kidney transplant patients: A single-center experience. *J Cardiovasc Pharmacol Therapeut*. 2006; 11: 77- 83.

25.Vakiani E, Basso K, Klein U, Mansukhani MM, Narayan G, Smith PM, et al. Genetic and phenotypic analysis of B-cell posttransplant lymphoproliferative disorders provides insights into disease biology. *Hematol Oncol* 2008; 26: 199-211.

26. Schubert S, Renner C, Hammer M, Abdul-Khaliq H, Lehmkuhl HB, Berger F, et al. Relationship of immunosuppression to Epstein-Barr viral load and lymphoproliferative disease in pediatric heart transplant patients. *J Heart Lung Transplant*. 2008; 27: 100- 5.

27.Oertel S, Trappe RU, Zeidler K, Babel N, Reinke P, Hummel M, et al. Epstein-Barr viral load in whole blood of adults with posttransplant lymphoproliferative disorder after solid organ transplantation does not correlate with clinical course. *Ann Hematol*. 2006; 85: 478- 84.

28.Buadi FK, Heyman MR, Gocke CD, Rapoport AP, Hakimian R, Bartlett ST, et al. Treatment and outcomes of post-transplant lymphoproliferative disease: a single institution study. *Am J Hematol*. 2007; 82: 208- 14.

29.Douglas RS, Goldstein SM, Katowitz JA, Gausas RE, Ibarra MS, Tsai D, et al. Orbital presentation of post-transplantation lymphoproliferative disorder: a small case series. *Ophthalmology*. 2002; 109: 2351-5.

30. Timms JM, Bell A, Flavell JR, Murray PG, Rickinson AB, Traverse-Glehen A, et al. Target cells of Epstein-Barr virus (EBV)-positive post-transplant lymphoproliferative disease: similarities to EBV-positive Hodgkin's lymphoma. *Lancet*. 2003; 361: 217-23.

31.Elad S, Meyerowitz C, Shapira MY, Glick M, Bitan M, Amir G. Oral posttransplantation lymphoproliferative disorder: an uncommon site for an uncommon disorder. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2008; 105: 59- 64.

32.Morovic A, Jaffe ES, Raffeld M, Schrag JA. Metachronous EBV-associated B-cell and T-cell posttransplant lymphoproliferative disorders in a heart transplant recipient. *Am J Surg Pathol*. 2009; 33:149-54.

33.Peiraira JR, Segovia J, Fuertes B, Fernández JA, Escudier JM, Salas C, et al. Current induction immunosuppression and post-heart transplant lymphoproliferative disorders. *Transplant Proc*. 2003; 35: 2009-10.

34.Manlhiot C, Pollock-Barziv SM, Holmes C, Weitzman S, Allen U, Clarizia NA, et al. Post-transplant lymphoproliferative disorder in pediatric heart transplant recipients. *J Heart Lung Transplant*. 2010; 29: 648- 57.

35.Pitman SD, Huang Q, Zuppan CW, Rowsell EH, Cao JD, Berdeja JG, et al. Hodgkin lymphoma-like posttransplant lymphoproliferative disorder (HL-like PTLD) simulates monomorphic B-cell PTLD both clinically and pathologically. *Am J Surg Pathol*. 2006; 30: 470- 6.

36.Windebank K, Walwyn T, Kirk R, Parry G, Hasan A, Bown N, et al. Post cardiac transplantation lymphoproliferative disorder presenting as t(8;14) Burkitt leukaemia/lymphoma treated with low intensity chemotherapy and rituximab. *Pediatr Blood Cancer*.2009; 53(3): 392- 6.

37.Burra P, Buda A, Livi U, Rigotti P, Zanusi G, Calabrese F, et al. Occurrence of post-transplant lymphoproliferative disorders among over thousand adult recipients: any role for hepatitis C infection? *Eur J Gastroenterol Hepatol*.2006; 18(10): 1065- 70.

38.His ED, Singleton TP, Swinnen L, Dunphy CH, Alkan S. Mucosa-associated lymphoid tissue-type lymphomas occurring in post-transplantation patients. *Am J Surg Pathol*. 2000; 24(1): 100- 6.

39.Benkerrou M, Durandy A, Fischer A. Therapy for transplant-related lymphoproliferative disease. *Hematol Oncol Clin North Am*.1993; 7(2): 467- 475.

40.Blaes AH, Peterson BA, Bartlett N, Dunn DL, Morrison VA. Rituximab therapy is effective for posttransplant lymphoproliferative disorders after solid organ transplantation: results of a phase II trial. *Cancer*. 2005; 104(8): 1661-7.

41. Oertel SH, Verschuuren E, Reinke P, Zeidler K, Papp-Váry M, Babel N, et al. Effect of anti-CD 20 antibody rituximab in patients with post-transplant lymphoproliferative disorder (PTLD). *Am J Transplant*.2005; 5(12): 2901-6.

42.Zimmermann T, Hoppe-Lotichius M, Tripkovic V, Barreiros AP, Wehler TC, Zimmermann A, et al.Liver transplanted patients with preoperative autoimmune hepatitis and immunological disorders are at increased risk for Post-Transplant Lymphoproliferative Disease (PTLD). *Eur J Intern Med*.2010; 21(3): 208- 15.

43.Picarsic J, Jaffe R, Mazariegos G, Webber SA, Ellis D, Green MD, et al. Post-transplant Burkitt lymphoma is a more aggressive and distinct form of post-transplant lymphoproliferative disorder. *Cancer*. 2011; 117(19): 4540- 50.

44.Mamzer-Bruneel MF, Lomé C, Morelon E, Levy V, Bourquelot P, Jacobs F, 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(21):3622-32.
- 45.Rummel MJ, Niederle N, Maschmeyer G, Banat GA, von Grünhagen U, Losem C, et al.On behalf of the Study group indolent Lymphomas (StiL). Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. *Lancet*.2013; 381(9873): 1203-10.
- 46.Machida S, Tomizawa D, Tamaichi H, Okawa T, Endo A, Imai K, et al. Successful Treatment of Diffuse Large B-Cell Lymphoma in a Patient With Ataxia Telangiectasia Using Rituximab. *J Pediatr Hematol Oncol*. 2013.
- 47.Gray C, Kalumba K, Pati N, Peterson A, Connell TG.Successful Treatment of Refractory Immune Thrombocytopenia With Rituximab in a 10-Week-Old Infant. *J Pediatr Hematol Oncol*.2013; 35(4):174-7.
- 48.Svoboda J,Kotloff R, Tsai DE.Management of patients with post-transplant lymphoproliferative disorder: the role of rituximab.2006; 19 (4): 259–269.
- 49.Manlhiot C, Pollock-Barziv SM, Holmes C, Weitzman S, Allen U, Clarizia NA, et al. Post-transplant lymphoproliferative disorder in pediatric heart transplant recipients. *J Heart Lung Transplant*.2010; 29(6): 648-57.
- 50.Elstrom RL, Andreadis C, Aqui NA, Ahya VN, Bloom RD, Brozena SC, et al. Treatment of PTLD with rituximab or chemotherapy. *Am J Transplant*.2006; 6(3):569-76.
- 51.Ghobrial IM, Habermann TM, Ristow KM, Ansell SM, Macon W, Geyer SM, et al. Prognostic factors in patients with post-transplant lymphoproliferative disorders (PTLD) in the rituximab era. *Leuk Lymphoma*.2005; 46(2):191-6.
- 52.Hiddemann W, Kneba M, Dreyling M, Schmitz N, Lengfelder E, Schmits R, et al. Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. *Blood*.2005; 106(12): 3725-32.
- 53.Faye A, Van Den Abeele T, Peuchmaur M, Mathieu-Boue A, Vilmer E. Anti-CD20 monoclonal antibody for post-transplant lymphoproliferative disorders. *Lancet*.1998; 352(9136): 1285.
- 54.Webber S, Harmon W, Faro A, et al. Anti-CD20 Monoclonal Antibody (rituximab) for Refractory PTLD after Pediatric Solid Organ Transplantation: Multicenter Experience from a Registry and from a Prospective Clinical Trial. *Blood*.2004; 104(11): 746.
- 55.Khedmat H, Taheri S. Early onset post transplantation lymphoproliferative disorders: analysis of international data from 5 studies. *Ann Transplant*. 2009; 14(3): 74-7.
- 56.Khedmat H, Taheri S. Late onset Post Transplantation Lymphoproliferative Disorders: Analysis of International Data from 5 Studies. *Ann Transplant*.2009 ;14(4): 80-5.
- 57.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(2): 40-44.
- 58.Khedmat H, Taheri S. Characteristics and prognosis of post-transplant lymphoproliferative disorders within renal allograft: Report from the PTLD.Int. Survey. *Ann Transplant*.2010; 15(3): 80-6.
- 59.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(4): 102-9.
- 60.Izadi M, Taheri S. Features, predictors and prognosis of lymphoproliferative disorders post-liver transplantation regarding disease presentation time: Report from the PTLD.Int. survey. *Ann Transplant*. 2011 ; 16(1): 39-47.
- 61.Khedmat H, Taheri S. Post-Transplantation Lymphoproliferative disorders localizing in the adenotonsillar region: Report from the PTLD.Int survey. *Ann Transplant*. 2011; 16(1): 109-16.
62. Izadi M, Fazel M, Saadat SH, Taheri S. Hepatic involvement by lymphoproliferative disorders post liver transplantation: PTLD.Int. Survey. *Hepatol Int*. 2011; 5(3): 759-66.
- 63.Izadi M, Taheri S. Hepatitis B virus infection has no significant role on lymphoproliferative disorders post liver transplantation: PTLD. Int survey. *Ann Hepatol*. 2011; 10(3): 315-20.
- 64.Khedmat H, Taheri S. Very late onset lymphoproliferative disorders occurring over 10 years post-renal transplantation: PTLD.Int. Survey. *Hematol Oncol Stem Cell Ther*. 2011 ;4(2):73-80.
- 65.Izadi M, Fazel M, Saadat SH, Taheri S. Radiotherapy is the best treatment method in post transplant lymphoproliferative disorders localizing in brain: A review of the literature. *Ann Transplant*. 2011; 16(4): 126-33.
- 66.Izadi M, Fazel M, Saadat SH, Taheri S. Bone marrow involvement by lymphoproliferative disorders after renal transplantation: PTLD. Int. Survey. *J Cancer Res Ther*. 2012 ; 8(1): 62-7.
- 67.Khedmat H, Taheri S. Hepatitis C virus infection can affect lymphoproliferative disorders only as a cofactor for Epstein-Barr virus in liver transplant recipients: PTLD.Int survey. *Exp Clin Transplant*. 2012; 10(2): 141-7.

68. Izadi M, Taheri S. Allograft involvement by lymphoproliferative disorders after lung transplantation: report from the PTLD. Int survey. Prog Transplant. 2011; 21(4): 353-9.

69. Khedmat H, Taheri S. Post-transplantation lymphoproliferative disorders in renal vs. simultaneous renal-pancreas allograft recipients: A survey and analysis of data from the literature. Saudi J Kidney Dis Transpl. 2013 ;24(1): 1-7.

40. Khedmat H, Taheri S. Hepatic lymphomas post renal transplantation may signify worse disease behavior: analysis of data from 26 international studies. Arab J Nephrol Transplant. 2011 ;4(3): 109-16.

71. Khedmat H, Taheri S. Bone marrow involvement by lymphoproliferative disorders post liver transplantation: PTLD Int Survey. Acta Med Indones. 2012; 44(3): 207-13.