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Survival of Post-Transplant Lymphoproliferative Disorder after Kidney Transplantation in Patients under Rapamycin Treatment

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ABSTRACT

Background: One of the important causes of mortality and morbidity in kidney transplanted patients is Post Transplant Lymphoproliferative Disease (PTLD), which is due to immunosuppression therapy and viral activity. It seems that Rapamycin, with dual antineoplastic and immunosuppressive effects, may have a pivotal role in the treatment of PTLD patients and preserving transplanted kidneys.

Methods and Materials: Twenty patients with PTLD were enrolled. Immunosuppressive therapy was reduced or ceased, and Rapamycin was initiated at the time of PTLD diagnosis. We evaluated the effects of switching immunosuppressive drugs to Rapamycin on graft status, the response of tumor, and 6, 12 months, and 5-year survival in patients.

Results: PTLD remission was achieved in 14 patients, while six patients died; no relapse was detected in recovered patients. The median of PTLD free time was 25 months, and the mean overall survival in patients with PTLD treated by Rapamycin was 84.8 (95% CI=61.3-108.23).The five-year survival rate was 67%, 12 months survival was 73.8%, and six months' survival was 80%. The response rate to Rapamycin and immunosuppression reduction alone was 46.6%. Four out of 13 Diffuse Large B-Cell Lymphoma patients achieved a complete response just only after the reduction of immunosuppressive drugs and the consumption of Rapamycin.

Conclusion: The present study demonstrated the effectiveness of conversion from immunosuppressive medication, particularly of Calcineurin inhibitors to Rapamycin in PTLD patients. However, more research is needed to confirm the Rapamycin effect on patients with PTLD.

Keywords: Rapamycin; Post-transplant lymphoproliferative disorders; Renal transplant M-TOR inhibitors; Lymphoma

INTRODUCTION

In recent years, more efficient immunosuppressive regimens have improved the survival of transplanted patients and allografts. However, these managements have drawbacks such as increasing the risk of cancers, for example, Post Transplant Lymphoproliferative Disease (PTLD)[1-3]. PTLD encompasses a heterogeneous group of

lymphomas, and it is the abnormal proliferation of lymphoid and Plasma cells after a solid organ transplant or hematopoietic stem cell transplant. Impaired immune surveillance resulting from immunosuppression therapy and activation of oncogenic viruses especially EBV have a pivotal role in PTLD[4, 5].

The incidence of PTLD in patients who underwent kidney transplants is 1-5%, which is 2-15 times the normal population. It is potentially a fatal disorder in which the proportion of mortality and loss of allograph is high. (3, 6-8) Based on histopathology, the World Health Organization (WHO) classified PTLD into four subtypes, including early lesions, monomorphic PTLD, polymorphic PTLD, and classical Hodgkin lymphoma[5].

In terms of PTLD management after kidney transplant, the first step and the backbone of the approach is to stop or decrease immunosuppression drugs, especially Calcineurin inhibitors (CNIs) such as Cyclosporine and Tacrolimus[5]; However, the complete disruption of these immunosuppressants brings concerns regarding kidney rejection and reduced patients' survival. On the other hand, merely reducing immunosuppresses is not enough, and it is necessary to add other medications.

Rituximab, alone or combined with other drugs, has FDA approval for the treatment of non-Hodgkin lymphomas that are CD20 positive, and it is the current standard of care[5]. Despite this implication, the statistics show that the rate of mortality and morbidity are high[9, 10].

Improving the survival and outcome of PTLD patients is a big challenge for the health care systems. Meanwhile, some drugs were introduced for the treatment of patients with PTLD, for example, phosphatidylinositol 3-kinase inhibitors and mammalian target of Rapamycin (mTOR) inhibitors.(5) M-TOR inhibitors such as Rapamycin and Everolimus with dual functions; antitumor and immunosuppression, are evaluated in some articles and have shown a positive effect on saving grafts and managing PTLD in vivo and vitro studies[11, 12].

This study is the updated analysis of a previous report by Ashrafi et al. on 13 patients[13]. We followed previous patients (n=13) and extended the number of patients to 20 cases. Moreover, we included the data from 20 PTLD patients who underwent a kidney transplant. The aim of this study was to evaluate the effect of conversion to Rapamycin on the patients and renal allograft survivals, as well as, regression tumor.

MATERIALS AND METHODS

A retrospective study was performed on twenty patients that were diagnosed with PTLD after kidney transplantation at Isfahan University of Medical Sciences between 2007 to 2018. All enrolled patients were consuming immunosuppression drugs when PTLD was diagnosed. The immunosuppressive medications prescribed to kidney transplant recipients consisted of tacrolimus, cyclosporine, azathioprine, prednisone, and Mycophenolate Mofetil. Average serum cyclosporine before PTLD diagnosis was determined. Also, previous exposure to Anti-thymocyte globulin was recorded.

Histologic examination confirmed the presence of PTLD in all cases. All patients were staged according to the Ann Arbor staging system. For all of them Computed tomographic (CT) scans of the chest, abdomen, and pelvis, complete blood count, and serum chemistries were performed. Other evaluations such as bone marrow biopsies, CT scans of brain , bronchoscopy and gastrointestinal endoscopy were carried out on the basis of clinical indication and the type of lymphoma. Restaging was performed by CT scans at various intervals after management. Biopsies were tested for EBV if it could be feasible .Biopsy specimens failed to be tested for EBV in some case, which was mainly because of inadequate sample volume and lack of access to the test and biopsy. Besides, some patients had been referred to our center after cancer staging , which limits the detection of EBV using biopsies.

In all patients, immunosuppression drugs were converted to Rapamycin at the time of diagnosis of PTLD, followed by chemotherapy, chemotherapy ± Rituximab, Rituximab weekly for four consecutive weeks, radiation therapy, or simply observation, depending on the histologic subtype and staging of PTLD.

For all the patients prescribed 2 mg/day Rapamycin except for one individual who took 3 mg/day, and

two patients, receiving chemotherapy, who took 1 mg/day at the time of the PTLD diagnosis.

The patients were followed up after four weeks. If there was no response or the tumor progressed, the patient received a 4-week course of Rituximab or chemotherapy or chemotherapy ± Rituximab.

If the patient still showed no response to the second modality, they received the third modality, which consists of chemotherapy or Rituximab with chemotherapy. Concerning response evaluation, complete response (CR) was determined by the disappearance of all active symptoms and tumor, and reduction of all lymphadenopathies (target or non-target) to <10mm. Partial response (PR) was determined by at least a 50% reduction in bi-diameter of the detectable lesion without any new lesion. Progressive disease (PD) was established by the occurrence of new lesions or ≥25% increase in tumor size in one or more lesions . Finally, stable disease (SD) was determined by an insufficient reduction to classify as per PR and insufficient increase to classify as per PD, considering the smallest sum diameters. Time to failure was the interval between the initiation of therapy to progressive disease, relapse or death.

Overall survival (OS) or patient's overall survival was defined as the time from PTLD diagnosis to the patient's death from any cause or last visit of the patient.

Regarding the status of a transplanted kidney during the study, Graft survival was defined as the time between the diagnosis of PTLD in transplanted patient's PTLD and the end of the follow-up period or date of patient's death or commencement of dialysis whichever occurred first.

The study respected the Helsinki declaration, and was approved by the Isfahan University of medical sciences Review Board (No. IR.MUI.REC. 396016).

Statistical analysis

The data was analyzed using Statistical Package for Social Sciences version 22.0. Categorical data were presented as numbers (%), and continuous data as mean ± SD and median and IQR when the distribution of the data was not normal. $P<0.05$ was considered significant. We used the survival curves generated via the Kaplan-Meier method to show the survival of patients from the time of PTLD diagnosis until the last visit.

RESULTS

Totally, 20 PTLD patients comprising of 16 males and 4 females, mean age 45.45±12.7 years at last visit were enrolled. Table 1 shows the characteristics of PTLD patients at the time of diagnosis. The mean time between the first sign and diagnosis of the PTLD was 3.3 months, and the mean interval between transplantation and the PTLD diagnosis was about 75.4 months.

The EBV infection was detected in three patients' tumors; 5 patients were negative for the EBV of tumors, and in rest of all, the EBV detection was not possible because either the specimens were not available or the technique lacked sufficient sensitivity.

The diffuse large B-cell lymphoma was seen in 13 patients, Burkett lymphoma (BL) in 2 cases, Malt lymphoma in one patient, and Hodgkin lymphoma (HL) was detected in four patients. The most frequent sign or symptoms among the patients were lymphadenopathies in 11 and fever in 8 patients. CMV infection was detected in 3 patients after PTLD, and relapse of PTLD was not detected in any patients (Table 2).

LDH (80% of those tested), B-cell histology (80%) and presence of B-symptoms disease (74%) were also reported. Seven patients (35%) had early PTLD(≤ 1 year) , and 65% of patients had late PTLD(>1 year). Eight (40%) developed PTLD >10 years after transplant.

The time between reducing immunosuppression and the beginning of the second treatment was 3.5 months, and between the second and third treatment was 4 months. The duration of responses was two months for the first treatment, 1.5 months for the second treatment and two months for the third treatment .

During the last visit, PTLD remission was achieved in 14 patients, and six patients died. With the PTLD diagnosis for patients were administered Rapamycin at a dose of 1- 2–3 mg/ day . In the first stage of treatment, complete response was detected in 7

patients, partial remission in 1, 1 patient died and, among all patients, 2 patients received radiotherapy. Of the two patients who died, one of the patients who had Hodgkin disease, and the other had diffuse large B-cell lymphoma. In both cases, they died while receiving chemotherapy; however, the first died after 1.5 months, and the second after six months of administration of Rapamycin, due to sepsis. Twelve patients received secondary treatment, including weekly Rituximab (375 mg/m2 weekly x 4 weeks) in four of them, chemotherapy in another four, and Rituximab and cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) in the final four patients. Three patients who received a second treatment modality died. One of them died due to Mycobacterium tuberculosis infection one month after achieving CR. The second passed away when he was receiving R-CHOP because of sepsis. The third person died 24 months after receiving second modalities due to sepsis. One patient received R-CHOP as a third treatment challenge and died 27 months after diagnosis PTLD due to the progression of the disease (Table 3). The median duration of PTLD free time was 25 months. The response rate to Rapamycin alone was 25 %.

Moreover, the graft was rejected in 2 patients and was functional in 18 patients at the time of the last visit or death. The median graft survival after PTLD diagnosis was 24 months.

Out of 13 DLBCL patients, four showed complete response only after the reduction of immunosuppressive drugs and the consumption of Rapamycin. Two out of four female patients had undergone kidney transplants due to Systematic Lupus Erythematosus (SLE), who were diagnosed with DLBCL after 3 and 10 months after transplantation, respectively. They were in stage 4 with ECOG PS (Eastern Cooperative Oncology Group Performance Score) of 0 -1, low- intermediate risk IPI (International Prognostic Index), extra nodal involvement graft kidney, and kidney respectively. Two other patients were in stage1 with low-risk IPI, ECOG PS of 0 -1. All patients (100%) achieved complete remission after the median time of 12 weeks and they have been in complete remission until the last visit. It seems Rapamycin was the effective therapy in the prevention of graft loss in 50% of these four patients.

Graft loss happened in 2 patients; one returned to hemodialysis three months after the start of Rapamycin administration, and subsequently went under kidney transplantation, with a functional graft in the last visit. Another one returned to hemodialysis after 40 months from being on Rapamycin.

Figure one shows the Kaplan Meier curve of the PTLD patients from diagnosis to last visit (120 months). The mean overall survival in patients with PTLD treated by Rapamycin was 84.8 (CI=61.3-108.23). The five-year survival rate was 67 % (8 patients). 12 months survival 73.8 % (16 patients) and 6 months' survival was 80 % (n=17).

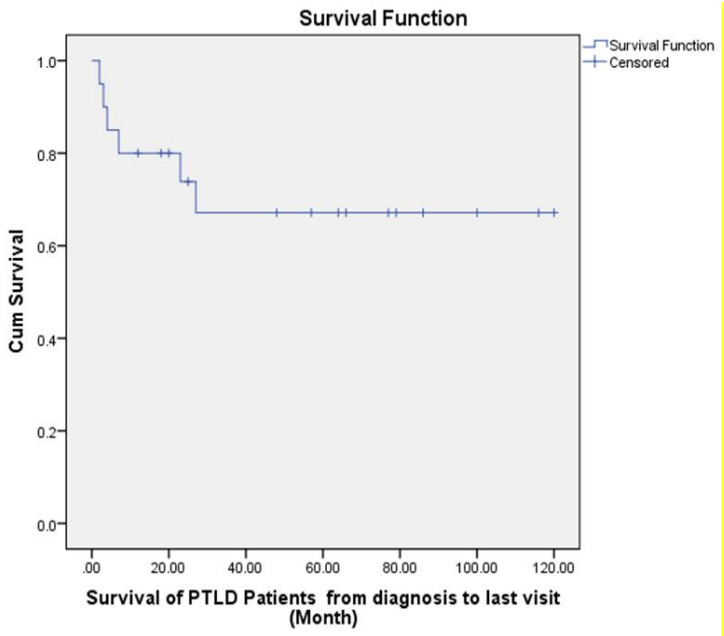

Figure 1. Graft survival of all 20 patients

Table 1. Patients demographic and PTLD characteristics

Variable	Mean ± SD
Age at PTLD (years)	42.55 ± 13.18
Age at transplant (years)	36.35 ± 12.47
Male – N (%)	16 (80%)
Etiology of primary kidney disease	
High Blood Pressure	2(10%)
Diabetes	2(10%)
Glomerulonephritis†	5(25%)
Systemic lupus erythematosus	2(10%)
Other Causes†	5(25%)
Unknown	4(20%)
Pre-transplant dialysis –N (%)	18 (90%)
Dialysis duration, months	16.40 ± 18.89
Creatinine, mg/dL at PTDL diagnosis	1.39 ± 0.44
Creatinine, mg/dL at last visits	2.31 ± 2.14
eGFR, mL/min/1.73 m2 at PTLD diagnosis	60.02 ± 17.73
eGFR, mL/min/1.73 m2 at last visit	57.83 ± 35.64
Disease duration before Transplant- Median (IQR)	30 (72)
Original immunosuppressive regimen N (%)	
Cyclosporine/Mycophenolate Mofetil/Prednisolone	13 (65%)
Cyclosporine /Azathioprine /Prednisolone	4 (20%)
Tacrolimus/Mycophenolate Mofetil/Prednisolone	3 (15%)
CNI minimization/ withdrawal N (%)	
Minimization	1(5%)
Withdrawal	19 (95%)
Anti-thymocyte globulin N (%)	
Rabbit	2 (10%)
Horse	2 (10%)
Graft status at last visit N (%)	
Functional Kidney	18 (90%)
Failure/Dialysis	2 (10%)
Number of renal Transplant N (%)	
One	16 (80%)
Two	4 (20%)

† IgA Nephropathy and Chronic Glomerulonephritis
††Alport , Reflux Nephropathy, Chronic Pyelonephritis, Chronic Renal Failure
PTLD: Post-transplant lymphoproliferative disorders; SD: standard deviation
CNI: Calcineurin inhibitor

Table 2. Clinical characteristics of PTLD patients

Variable	Median (IQR)
Time from Transplant to PTLD diagnosis/Month	40.50(134.75)
Time from renal transplant to diagnosis of PTLD -N (%)	
Early PTLD / Late PTLD	7(35%)/13(65%)
PTLD signs – N (%)	
Lymphadenopathy	
Cervical	3 (15%)
Axillary	6 (30%)
Submandibular	2 (10%)
Pelvic Mass (Lymphadenopathy)	1 (5%)
Fever	7 (35%)
Abdominal Pain	2 (10%)
Dyspnea	1 (5%)
Melena, Hematemesis	1 (5%)
Histological classification, N (%)	
Diffuse large B cell	13(65%)
Burkitt lymphoma	2(10%)
Malt lymphoma	1(5%)
Hodgkin	4(20%)
Previous History Malignancy, N (%)	1 (5%)
Duration patient is PTLD free in month	25 (71)
EBV status of PTLD, N (%)	
Positive	3 (15%)
Negative	5 (25%)
Unknown	12 (65%)
EBV in donor, N (%)	
Negative	18(90%)
Unknown	2(10%)
EBV in patients at the time of transplantation, N (%)	
Negative	17(85%)
Unknown	3(15%)
CMV post PTLD, N (%)	
Negative	15(75%)
Positive	3(15%)
Unknown	2(10%)
PTLD status at last visit – N (%)	
Complete Remission	14 (70%)
Dead	6 (30%)
Rapamycin, Duration of administration in months.	19.5(50.25)

Table 3. Clinical course and PTLD treatment

	Complete Remission	Partial - response	No-response	Death
First Modality - N=20				
Rapamycin	4	0	11	2 †
Rapamycin/ Rituximab	0	1	0	
Rapamycin/ Chemotherapy	3	0	1	
Second Modality - N= 12				
Weekly Rituximab	3	0	1	3 †
Rituximab/Chemotherapy	2	1	1	
Chemotherapy	4	0	0	
Third Chemotherapy - N= 1				
R-CHOP + Rapamycin	0	0	1	1 † †

† Due to sepsis and infection, † †Due to progression tumor, R-CHOP: Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone

DISCUSSION

This study was conducted to evaluate the effect of Rapamycin on survival among 20 renal-transplanted patients diagnosed with PTLD. We found that the conversion of immunosuppressive regimens to Rapamycin allowed regression of PTLD. Rapamycin-based therapy can provide maintenance of kidney allograft function and it seems that a positive effect on patients' survival [5].

In respect of PTLD management, the cornerstone of PTLD treatment is the minimization of immunosuppression. The method to decrease immunosuppresses and make a balance between treatment PTLD and Renal function preservation has remained uncertain in the management of lymphoma after renal transplants[5]. A rapamycin-based regimen has been reported to minimize the incidence of malignancy compared to previous immunosuppressive combinations[14-16]. In addition, switching from CNIs to Rapamycin has been shown to affect PTLD regression positively[7, 17-19]. The small number of patients and the heterogeneous presentation and management of PTLD complicates the accurate analysis of outcome-related predictive factors[17]. In this study, 4 (26.6%) out of 15 patients who were switched from CNIs and other maintenance immunosuppression to Rapamycin only accessed complete remission and did not experience any relapses. The response rate to the Reduction of immune suppression (RI; cessation or dose reduction of immunosuppression) alone in the previous small case series was 23% to 89% [10,20-23], whereas in a retrospective series with 42 patients was 63%. The latter also demonstrated that PTLD responds well to RI at one year follow up[10]. Our article is confirmatory of the results reported in previous smaller studies.

In terms of regression tumor and patients 'survival , in Vitro and Vivo studies have shown that switching to Rapamycin inhibits malignancy growth[11,12]. Among different studies, the response rate to treatment and patient survival varied widely[2,24,25]. In this study, the rate of tumor regression in patients was nearly 50%, which was comparable with Cheung's cohort and other large studies[9]. Interestingly, no relapses were reported over the follow-up period, and 8 patients have survived more than five years. Only one of the enrolled patients died due to tumor progression, and the rest of the fatalities were due to infection similar to Chung et al. study in which many patients died due to infection shortly after chemotherapy. (9) In a case study of a patient with PTLD, the anti-tumor potential of Rapamycin , regression of the tumor, and improvement of renal function were shown when tacrolimus and Mycophenolate Mofetil were switched to Rapamycin and prednisolone after one year of follow-up (19).On the basis of Pascual's data from across European centers which CNIs converted to m-TOR inhibitors beside other chemotherapy regimens in PTLD patients. Nearly 80% of patients reached complete remission of PTLD, and the kidney remained functional in 10/19, and the tumor relapsed in 2/19[26].

In most studies, age has been introduced as an independent and important prognostic factor[5,27,28]. In our practice, the mean age was lower than 50 years and did not correlate with the survival rate. Similarly, in a study by Tsai et al. the median age and range at diagnosis of PTLD were 45 years and 14–65 years, respectively, and higher age was considered as an independent prognostic factor that harmed the outcome[10]. However, in most of the previous studies, the age of patients was more than 50 years. These studies have emphasized that patients with older age experience more complications, including infections that decrease survival time and increase morbidity and mortality rates after transplantation [27, 28].

The role of EBV in the pathogenesis of PTLD and pre-transplant EBV mismatch (the most critical important risk factor for developing PTLD) is highlighted. However, it is demonstrated that EBV positivity is not requisite for diagnosis[2,5,29]. In our cohort, there was no discrepancy in the EBV status between donors and candidates in pre-transplant screening for EBV, most of them had negative results, and all early PTLD cases had negative EBV. In contrast, some studies have shown that there is a significant correlation between EBV tumor negativity and late PTLD with poor survival[25,30, 31]. It should be pointed out that the figure for negative-EBV PTLD

cases grew from 10% in 1990-1995 to 48% in 2008-2013[2]. Trappe et al. analyzed 70 PTLD patients and represented no association between EBV and survival or time of relapse[32]. Luskin et al. found that the EBV status had no significant impact on patient survival and response to initial PTLD therapy[2]. Some studies reported that EBV-negative PTLD was associated with inadequate response to rituximab treatment and inferior patient survival[31,33]. In our study, we could not represent any dramatic difference in the overall survival of PTLD patients with EBV-negative versus EBV-positive patients, which was due to the small sample size. In the case reports, associations with CMV have been explained as an epiphenomenon[34-36]. The proportion of CMV negative cases in our research was 85%, and the association between CMV and other prognostic factors was unremarkable.

In this cohort, 80% of patients saved their first transplanted kidney, and none of them experienced acute renal rejection. Serum creatinine level and GFR remained stable before and after PTLD and conversion to Rapamycin. Cullis et al. have reported the impact of Rapamycin on the improvement of graft function and resolving PTLD with kidney involvement[19]. Some articles pointed out the correction of creatinine and survival in this field. However, some data showed that using Rapamycin does not change or improve renal function compared to patients who did not receive PTLD. Probably, the previous finding was due to chronic graft dysfunction before starting Rapamycin[10, 37].

The strength of this study was a long follow-up and utilizing Rapamycin concurrent with the discounting of immunosuppression drugs. Some limitations should be taken into account. Retrospective design and heterogeneity of different types and stages of cancers made it difficult to compare our results with other studies. However, retrospective studies based on institutional experiences, such as our study, are still an attractive option for providing further knowledge about the role of mTOR inhibitors in preventing or treating post-transplant cancers. In addition, the number of patients with post-transplant cancers is relatively small.

CONCLUSION

It is still uncertain whether conversion to mTOR inhibitors after cancer development will have any benefit in long-term patient and graft survival in kidney transplant recipients. Our study shows that the use of Rapamycin with CNI minimization or stopping may offer a reasonable option given the relatively stable renal function, the decrease rejection rate the transplanted kidneys, and low cancer recurrence rate. However, treatment should also be individualized according to the different clinical conditions in each patient. Further studies, especially on the optimal dose of mTOR inhibitors in post-transplant solid organ tumors are required.

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