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Outcome of Rapamycin Therapy for Post-Transplant- Lymphoproliferative Disorder after Kidney Transplantation: Case Series

Farzaneh Ashrafi[1], Shahrzad Shahidi[2, 3], Zeinab Ebrahimi[4], Mojgan Mortazavi[5]

[1]Hematology Division of Internal Medicine Department, Isfahan University of Medical Sciences, Isfahan, Iran
[2]Nephrology Division of Internal Medicine Department, Isfahan University of Medical Sciences, Isfahan, Iran
[3]Kidney Disease Research Center, Isfahan, Iran
[4]Isfahan University of Medical Sciences, Isfahan, Iran
[5]Isfahan Kidney Disease Research Center, Isfahan, Iran

Corresponding author: Zeinab Ebrahimi, Isfahan University of Medical Sciences, Isfahan, Iran
Email: zebrahimi67@yahoo.com
Tel: +98 9136727880

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ABSTRACT

Background: Post-transplant lymphoproliferative disorders (PTLD) are a complication of chronic immunosuppressive therapy in solid organ transplantation with a high mortality rate . Alternative treatments such as rapamycin have been explored.

Methods: A detailed retrospective analysis was performed according to data collected from 13 patients with PTLD. At the time of PTLD diagnosis, immunosuppressive therapy was decreased and rapamycin administered. Overall survival, disease-free survival of patients and graft survival were determined.

Results: Among 590 kidney transplant recipients**,** 13 adult patients with PTLD were included in this study. The mean age of the patients was 42.15 (range: 25-58) years at the time of PTLD diagnosis, and 9 patients were male. Histology was distributed in 9 diffuse large B cell, 1 Malt lymphoma, 1 Burkitt lymphoma, 2 Hodgkin-like PTLD. The response rate to rapamycin alone was 30.8%. The mean overall survival period was 23.38 months and 11 patients are still alive. In total, 10 patients (76.9%) achieved a complete remission with functioning graft in 11 (84.6%) patients.

Conclusion: Despite the retrospective focus and limited number of patients, this study provides promising results regarding the effectiveness of stopping calcineurin inhibitors and switching to rapamycin for patients with PTLD.

Keywords: Lymphoma Therapy, Rapamycin, Transplant

INTRODUCTION

Immunosuppressive therapy in kidney transplant recipients have successfully reduced the risk of rejection after kidney transplantation, however, malignancy and post-transplant lymphoproliferative disorder (PTLD) are common complications of immunosuppressive therapy[1-5].

The overall reported incidence of PTLD varies from approximately 1% in kidney transplant recipients to 33% in intestinal or multiorgan transplant[2].

Immune status for Epstein-Barr virus (EBV) infection , the type and cumulative effect of immunosuppressive regimens are the major risk factors associated with PTLD [6]. In PTLD patients , immunosuppressive drugs inhibit the function of T cells and EBV-induced B-cell proliferation of lymphocytes [2]. The majority of PTLD histology is diffuse large B cell lymphoma [2,3]. Therefore, reduction or withdrawal of immunosuppression recommended as first-line therapy for PTLD. Other modalities of treatment such as rituximab, chemotherapy or radiation therapy and antiviral agents can be considered if necessary[2,6,7]. However, the optimal treatment strategy still remains to be determined [2]. Recent studies and recorded analyses

have confirmed that the calcineurin inhibitors (CNIs) increase the risk of EBV-related disease, whereas mammalian target of rapamycin(mTOR) inhibitors have a potent anti-proliferative effect to inhibit the growth of B cells infected by EBV, prevention and treatment of PTLD without induced graft rejection [8-10].Alternative treatment options such as therapy with mTOR inhibitors have been tried. There has been in vitro evidence that rapamycin, a new macrolide immunosuppressant drug, may reduce incidence of malignancy and inhibiting progression of PTLD without inducing rejection [4, 8, 11, 12] . Therefore, this therapeutic strategy can induce lytic EBV infection in the tumor cells via cell cycle arrest, induction of apoptosis and inhibition of interleukin-10 secretion [8].

This report documents the result of rapamycin therapy in 13 patients with PTLD after kidney transplantation.

PATIENTS AND METHODS

Thirteen patients with PTLD diagnosis who had previously undergone kidney transplantation at Isfahan University of Medical Sciences between 1990 and 2013 were identified. Of whom, 12 patients received a living-donor kidney and 1 patient underwent cadaveric-donor kidney transplant.

Immunosuppressive therapy for the kidney transplant recipients included combinations of cyclosporine or tacrolimus, azathioprine, prednisone and mycophenolate mofetil. Patients underwent clinical staging with a complete history, physical examination, blood tests (complete blood count, biochemical tests, liver tests and lactate dehydrogenase (LDH), bone marrow biopsy and computed tomography (CT) scans of the chest, abdomen and pelvis.

According to the type of PTLD, staging of disease and involved organs treatment modalities were selected. Management included a combination of immunosuppressive reduction, rituximab administration, combination of rituximab and chemotherapy administration and radiation therapy. At the time of PTLD diagnosis, all of the patients were treated with reduction in mycophenolate mofetil or azathioprine, discontinuation of cyclosporine or tacrolimus and administration of rapamycin 2 mg/day. If the patient did not respond during a period of 4 weeks, then other modalities of treatment were initiated. Rapamycin was given at a dosage of 2 mg/ day and has been continued with the same dose. Only one patient received rapamycin 3 mg/day at the time of PTLD diagnosis.

If the patient is a suitable candidate for chemotherapy, rapamycin dosage is decreased to 1mg/day.

A complete response (CR) was defined as the disappearance of all clinical disease evidence for at least 4 weeks. A partial response (PR) was defined as greater than 50% decrease in the bidimensional measurement of all disease sites and the absence of any new lesions. Progressive disease (PD) was defined as an increase of more than 25% in the size of lesion or the appearance of any new lesions. Time to failure was the interval from the initiation of therapy to progressive disease and disease relapse or death. Graft survival was defined as the time from PTLD diagnosis to death or dialysis. Overall survival was computed from the date of PTLD diagnosis to the date of death or last visit [3, 13].

Statistical Analysis:

Data were analyzed using Statistical Package for the Social Sciences (SPSS) version 16.0. Survival curves generated via the Kaplan-Meier method. For variables, the median or most frequent category was used.

RESULTS

Among 590 kidney transplant recipients, 13 patients with PTLD diagnosis enrolled in this study. The overall mean age at PTLD diagnosis was 42.15 (range: 25-58) and 69.2% of the patients were male.

Demographic features of 13 patients, etiologies of renal disease and immunosuppression protocols are summarized in Table 1. The clinical presentation of PTLD was highly variable. The median time from the first sign/symptom to the PTLD diagnosis was 2 months (range: 1-19 mos). Tissue biopsy performed to determine PTLD histology. At the time of PTLD diagnosis, creatinine levels ranged from 0.9 to 2.2 mg/dl and the mean Glomerular Filtration Rate(GFR) was 61.7 ml/min per 1.73 m2 (range: 33 – 94.44 ml/min).

Table 1: Demographic features of all patients

Patient no	Patient age	Gender	PreTransplant Disease	ATG type	ATG dose	Original immunosuppressive
1	58	M	DM			CsA,MMF,Pred
2	42	M	IgA Nephropathy			Tac,MMF,Pred
3	41	F	CGN			CsA,Aza,Pred
4	46	M	Chronic Pyelonephritis	rATG	7,000	CsA,Aza,Pred
5	51	M	unknown			CsA,MMF,Pred
6	50	M	unknown	rATG	5,000	CsA,Aza,Pred
7	25	M	CRF	hATG	175	CsA,MMF,Pred
8	37	M	unknown			CsA,Aza,Pred
9	55	M	DM			CsA,MMF,Pred
10	29	F	SLE	hATG	50	CsA,MMF,Pred
11	30	F	SLE			CsA,MMF,Pred
12	28	M	Reflux Nephropathy			CsA,MMF,Pred
13	56	F	HTN			CyA,MMF,Pred

M: male, **F:** female, **yrs:** years, **PTLD:** post transplant lymphoproliferative disorders, **DM:** diabet mellitus, **CGN:** chronic glomerulonephritis, **CRF:** chronic renal failure, **SLE:** systemic lupus Erythematosus, **HTN:** hypertension, **rATG:** rabbit antithymocyte globulin, **hATG:** horse antithymocyte globulin, **CsA:** cyclosporin A, **MMF:** mycophenolate mofetil , **Pred:** prednisolone , **Aza:** azathioprine, **Tac:** tacrolimus

Eleven (84.6%) patients were non-Hodgkin's lymphoma (NHL) and 9 (69.2%) patients expressed immunological markers of B-cell lymphoma (Table 2). Five patients had localized stage I or II disease and 8 patients had disseminated stage III or IV PTLD. B symptoms (fever, night sweats or weight loss) were

Table2: Patient characteristics at diagnosis of PTLD

Patient no	Time from Transplant to PTLD diagnosis (mos)	Time from sign/sym to PTLD diagnosis (mos)	Symptom/Sign PTLD	PTLD type	LDH (Upper limit nl:460U/l)	Disease stage	Affected sites	dose/ last level CsA at the time of PTLD diagnosis
1	16	5	fever ,cervical LAP	DLBCL	777	III B	LN	125/125
2	9	1	weight loss	DLBCL	480	IV B	Liver	0
3	144	2	cervical LAP	DLBCL	4460	VI B	Liver,bone	125/94
4	122	1	cervical LAP	Hodgkin	310	II A	LN	250/98
5	90	19	fever,axillary LAP	Hodgkin	607	III BE	LN	325/250
6	136	6	Melena haematemese	Malt lymphoma	775	I E	Stomach	100/211
7	32	1	fever,abdominal pain	Burkit lymphoma	1730	IV	LN	75/254
8	144	1	Abdominal pai	DLBCL	456	IV	Stomach pleural fluid	225/139
9	7	2	Cervical lap	DLBCL	592	I X	Parotid gland,LN	../343
10	3	3	Fever loss of weight	DLBCL	656	IV BS	Grafted kidney	800/166
11	10	1	Fever	DLBCL	590	IV	kidney	225/341
12	36	3	Fever	DLBCL	465	I BEX	Chest wall pleura	200/123
13	45	4	lap	DLBCL	502	LA	LN	375/610

DLBCL: diffuse large B cell lymphoma, **EBV:**Epstein-Barr virus,**CNI:** calcineurin inhibitor , **mos** : months , **PTLD:** post transplant lymphoproliferative disorders

CsA: cyclosporin **A , MMF:**mycophenolate mofetil , **Aza:** Azathioprine. **Tac:** tacrolimus, **LN:** Lymph node, **LAP:** lymphadenopathy

present in 61.5% patients and extranodal involvement was detected in 8 (61.5%) patients.

The age-adjusted International Prognostic Index (IPI) was used to assess the prognosis of patients with non-Hodgkin's Lymphoma. The presence of EBV in the tumor was assessed in 4 patients with PTLD. Two expressed EBV markers by immunohistochemistry or by in situ hybridization. In 9 cases, EBV could not be determined because of the absence of a specimen or lack of sensitivity of the technique. In all of the patients Rapamycin was administrated, at a dose of 2–3 mg/day at the time of PTLD diagnosis. The

treatment of the 13 patients, response and outcome data are summarized in Table3.

Table 3: outcome and response to treatment

Patient No	First treatment modality	dose Rapamycin mg/day	Response to initial treat-ment	time between RAPA therapy to initial response (mos)	Second Treat-ment modality	Response to second treat	third treatment modality	Respo nse to third treat	Duration of Rapamycin administration (mos)	Duration patient is PTLD free (mos)	patient status in last visit	State of kidney in last visit or death
1	Rapamycin	1	NR	3	Rituximab	CR			4	1	dead	Functional
2	Rapamycin	2	NR	1	Rituximab	CR			10	4	alive	Functional
3	Rapamycin , chemotherapy	2	D	6					6	0	dead	Functional
4	Rapamycin, Radiotherapy	2	NR	1	Chemo therapy	CR			51	43	alive	Functional
5	Rapamycin	2	NR	16	Chemo therapy	CR			20	2	alive	Functional
6	Rapamycin	2	NR	1	Rituximab-chemo therapy	CR			9	18	alive	Functional
7	Rapamycin	2	NR	1	Chemo therapy	CR			22	18	alive	Functional
8	Rapamycin	2	NR	2	Rituximab	NR	R-CHOP	D	2	0	dead	Failur
9	Rapamycin	2	NR	1	R-CHOP	NR			3	0	dead	Functional
10	Rapamycin	3	CR	3					21	18	alive	Functional
11	Rapamycin	2	CR	3					3	57	alive	Dialysis
12	Rapamycin	2	CR	7					67	65	alive	Functional
13	Rapamycin	2	CR	1					4	4	alive	Functional

PR: partial disease remission; **CR:**complete disease remission; **D:**death; **RAPA:** rapamycin , **NR:** no response , **R-CHOP:** rituximab-cyclophosphamide, doxorubicin, vincristine, prednisone, **mos:** months

rapamycin was effective in induction of remission in 4 patients (Table 4). All of the 4 patients presented with extranodal disease. Histological examination and immunophenotyping showed large B-cell lymphomas in these patients. One patient had involvement of the grafted organ and two were stage 4. According to age adjusted IPI-index, two patients were in low risk and 2 patient was in low intermediate risk group. These patients had an Eastern Cooperative Oncology Group Performance Score (PS) of 0 to 1. Complete remission was achieved after median time of 12 weeks. Repeated ultra sound and CT scans showed gradual regression of PTLD and resolution of lymphadenopathies in all of 4 patients. Median disease free survival was 37.5 months.

Rapamycin therapy was effective therapy in maintaining graft survival in 75% of these four patients. Creatinine level ranged increased from 1-2.2 mg/dl to 1.3-2.4 mg/dl at the last visit, the mean GFR however did not change during follow-up, and was 48.5 ml/min. Only one patient of these four lost her graft function and returned to hemodialysis three months after start of rapamycin therapy.

Response to Rapamycin Alone

Reduced immunosuppression in combination with

Eight (61.5%) patients received a second treatment modality, which included rituximab in three patients, chemotherapy in three patients, rituximab and cyclophosphamide, doxorubicin, vincristine, prednisone (R-CHOP) in two patients. Six (46.15%) patients achieved CR with rituximab or chemotherapy administration. Two patients died, one patient died due to Mycobacterium tuberculosis infection 1 month after have achieved CR, without any evidence of PTLD in autopsy and other died because of sepsis during R-CHOP therapy. One patient was treated with R-CHOP as a third treatment modality and expired because of PTLD progression 27 months after PTLD diagnosis.

In this study, 10 (76.9%) patients were considered to have CR. renal graft function remained stable in 11 (84.6%) patients from diagnosis through follow-up. At the last visit or time of death, creatinine levels ranged from 1 to 8.4 mg/dl and the mean GFR was 51.2 ml/min (range: 8–94 ml/min). In the present series, only 2 of 13 patients (15.4%) experienced graft rejection at 3 and 12 months after the PTLD diagnosis. Two

deaths were caused by infectious and two patients expired because of progression PTLD.
The mean time of duration of PTLD free was 18 months (range: 0 - 65 mos) and the median overall survival of the patients was 23.38 months (range: 2-129 mos) [Figure 1].

Table 4: Clinical data of patients with PTLD and outcome of treatment with rapamycin alone

	Patient 10	Patient 11	Patient 12	Patient13
Age at PTLD (years)/gender	29/Female	30/Female	28/Male	56/Female
Immunosuppressive treatment before PTLD	CyA,MMF, Pred	CyA,MMF, Pred	CyA,MMF, Pred	CyA,MMF, Pred
Disease stage	IV BS	IV	I BES	IA
LDH level(U/L)	656	590	465	502
IPI score	low- intermediate risk	low- intermediate risk	low risk	low risk
Histology of tumor	DLBCL	DLBCL	DLBCL	DLBCL
Treatment of PTLD	Rapamycin	Rapamycin	Rapamycin	Rapamycin
GFR at time of PTLD diagnosis (ml/min)	58	66	41	58
Last GFR (ml/min)	54.48	8	36	51.5
Interval between diagnosis of PTLD and last follow-up (months)	14	62	66	2
Interval between rapamycin therapy to CR(months)	3	3	7	1
dose Rapamycin (mg/day)	3	2	2	2
Duration of Rapamycin administration (mos)	21	3	67	4

PTLD: post transplant lymphoproliferative disorders**, CsA:** cyclosporin A**, MMF**: mycophenolate mofetil**, Pred: prednisolone, Aza:** azathioprine**, IPI,** International Prognostic Index**, DLBCL**: diffuse large B cell Lymphoma **, mos:** months

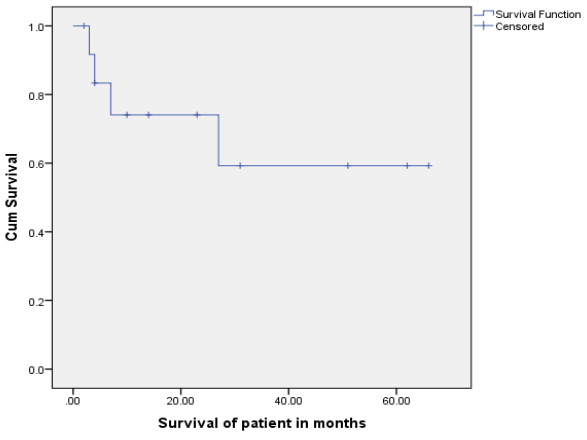

Figure1. Kaplan-Meier analysis for overall survival of all 13 patients.

DISCUSSION

Although immunosuppressive therapy has successfully reduced the risk of rejection after kidney transplantation, more aggressive immunosuppression has increased the occurrence of malignancy and PTLD [1,2,14]. Renal transplant recipients with PTLD have been managed with a variety of approaches including reduction in immunosuppression, antiviral therapy, surgical resection, chemotherapy, radiation and cellular therapy [2,3]. FDA approved Rapamycin as an immunosuppressive agent in kidney transplantation in 1999 [15]. In contrast to the CNIs, rapamycin

directly inhibits the growth of EBV^+ B cell lymphomas at doses that are therapeutically effective for prevention of graft rejection [8, 10]. Rapamycin has been utilized in the therapy of small samples of kidney transplant recipients with PTLD and have achieved a CR with low dose of this agent [16, 17]. In a series reported by Julio Pascual [18], 19 renal transplant recipients who developed PTLD were converted to PSIs (sirolimus n=16, everolimus=3). Calcineurin inhibitors (CNIs) were withdrawn in 18 patients and minimized in one patient. In this study**,** Rituximab therapy was used in 6 patients and chemotherapy with CHOP was also administered to 6 patients. Complete remission was observed in 15 patients who were maintained between 6 and 156 months. Graft function was observed in 10 patients, proteinuria reported in 3 cases and chronic allograft nephropathy reported in 2 cases.

We present the results of rapamycin implementation in the management of 13 PTLD cases which occurred among 590 kidney transplant recipients at our center between 1990 and 2013. In this series, the response rate to rapamycin alone was 30.8%. In all of 4 patients who achieved a CR with rapamycin alone, pathology of tumor was DLBCL. Overall, 4 patients are still alive without infectious complications. Eight patients required treatment with second modality treatment and 2 patients died of infection. This result suggests that rituximab or R-CHOP therapy may increase the risk of infection in patients with PTLD. Only 2 of 13 patients experienced acute rejection at 3 and 12 months after the PTLD diagnosis, respectively. In total, 10 patients (76.9%) achieved a complete remission and 9 patients are alive. No patient experienced recurrence of PTLD. The mean overall survival period was 23.38 months. These data strongly suggest that rapamycin is a safe drug to administer in the treatment of patients with PTLD. Despite the retrospective focus and limited number of patients, this study provides promising results regarding the effectiveness of stopping CNIs and switching to rapamycin for patients with PTLD, however, it is not clear whether PTLD regression due to reduced immunosuppression or the potent anti-proliferative effect of rapamycin causes it or both.

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