Int Urol Nephrol (2008) 40:1089–1094
DOI 10.1007/s11255-008-9377-0

NEPHROLOGY-ORIGINAL PAPER

Lymphoma after living donor kidney transplantation: an Iranian multicenter experience

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Received: 21 October 2007 / Accepted: 24 March 2008 / Published online: 1 July 2008
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Abstract
Introduction Post-transplant lymphoproliferative disorders (PTLD) are well-recognized complications in solid organ recipients. Limited data exist about the development of PTLDs in living kidney recipients. This study deals with a multicenter nationwide experience with kidney recipients from living donors.
Methods We reviewed data of PTLD patients from a total population of 6,500 patients transplanted at three different transplant centers in Iran from 1984 to 2006. We also compared their data with 2,250 normal kidney recipients of Baqiyatallah Transplant Center. Data were analyzed to determine potential correlates with the occurrence of PTLD and patient outcome.
Results Overall, 31 patients were diagnosed as having post-transplant lymphomas. The incidence of PTLD in our kidney transplant population comprised 0.47%. Sixteen (53%) PTLD patients were females, whereas 15 (47%) were males. The mean ages at transplantation and diagnosis were 37.1 and 41.9, respectively. Twelve (63%) patients died, and seven are alive. All deaths occurred within the 1st year after PTLD diagnosis. The mean time period from transplantation to diagnosis of PTLD was 64 (0.7–173) months. Localization of PTLD in the brain associated the worst outcome. Compared to non-PTLD patients, PTLD patients were significantly female predominated (51.6% vs. 32.2%; $P = 0.03$) and had lower age at transplantation (36.9 years vs. 42.9 years, respectively; $P = 0.01$). Patients under immunosuppressive regimens containing azathioprine were at higher risk for acquiring PTLDs compared to those with a MMF-containing regimen.
Conclusion PTLD is a major threat to kidney transplant recipients. Immunosuppressive agents have a significant role in developing the disease. Early detection of the disease and using more safe immunosuppresants may have beneficial effects on patient outcomes and incidence of the disease.

Keywords PTLD · Lymphoproliferative disorders · Living renal transplantation · Incidence · Iran

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Abbreviations

PTLD	Post-transplant lymphoproliferative disorder
EBV	Epstein-Barr virus
CMV	Cytomegalovirus
KTx	Kidney transplant
ATG	Antithymocyte globulin
ALG	Antilymphocyte globulin
OKT-3	Anti-T-cell receptor monoclonal antibody
AZA	Azathioprine
MMF	Cellcept: mycophenolate mofetil
CNS	Central nervous system
GI	Gastrointestinal
LUR	Living unrelated

Introduction

Post-transplant lymphoproliferative disorders (PTLD) is a serious complication of renal transplantation [1, 2]. The increasing risk of this complication among solid organ recipients was primarily recognized by Penn et al. [1] in 1969. PTLDs are considered one of the most frequent cancers occurring in kidney transplant recipients, comprising about 20% of all neoplasms [2], and result in death in up to 44% of patients [3]. Occurence of PTLD is related to the immunosuppression employed, the intrinsic characteristics of the graft recipient, viral infections and other as yet undetermined factors [4–6]. Epstein-Barr virus (EBV) seronegativity before transplantation has been found to be a powerful predictor of PTLD development [6].

Cytomegalovirus (CMV) mismatch between donor and recipient, CMV disease and the intensity, duration of prescription and cumulative dose of immunosuppression have also been identified as increasing the risk of PTLD [6].

Although several studies have reported the incidence of PTLDs in different countries, it is difficult to ascertain the precise incidence of post-transplant tumors, including lymphomas, because reporting of cancer to registries is often incomplete and probably underestimates the true cancer incidence. However, evaluating patients with post-transplant lymphomas may unveil important factors that may help us to identify high risk patients and to implement preventive policies towards reducing incidence of the disease.

This cross-sectional study examined the risk and the distribution of malignant lymphomas in recipients of living kidney allograft from a multi-center data registry. We also attempted to identify specific risk factors associated with a higher tumor risk and lower outcome for renal transplanted patients.

Patients and methods

In this retrospective cohort study, 8,000 eligible patients from three Iranian centers were reviewed for the development of PTLDs after renal transplantation. Data were obtained from our local transplant registries and spontaneous reports of eligible patients transplanted at our institutions between 1984 and 2006. For minimizing the risk of loss to follow-up, we asked authorities of transplant centers to inform us about potential PTLD patients transplanted at our centers who may attend their clinics. Incomplete medical information was clarified by telephone interviews with the corresponding physicians and/or attending their offices and searching their data registries.

We asked kidney transplant (KTx) center authorities to extract the following data from their data registries and send them to us: age, gender, type of immunosuppression, induction therapy, involvement site of PTLD and current patient status as well as dates of transplantation, start of symptoms, diagnosis of the PTLD and last follow-up.

The initial immunosuppression was defined as the post-transplant treatment at the time of discharge. Owing to center policy, this was 3 weeks after transplantation; later changes of maintenance immunosuppression were disregarded. There were two main periods of immunosuppressive regimes. The first period of immunosuppression was from 1984 onwards azathioprine (1.5 mg/kg bw/day), cyclosporin (6 mg/kg bw/day reduced to a maintenance dose of 3–4 mg/kg bw/day over a period of 3 months) and prednisolone (50 mg/day reduced to a maintenance dose of 20 mg/day). From 2001 onwards patients received triple immunosuppressive therapy consisting of mycophenolate mofetil (MMF) (2 g/day), cyclosporine and prednisolon, with the same dosages as mentioned above. To assess the relative tumor risk, our population was compared with 2,250 kidney transplant patients from

Baqiyatallah KTx data registry, which is one of the leading KTx centers in the Middle East. Induction therapy using antithymocyte globulin (ATG) or antilymphocyte globulin (ALG) was preserved in high-risk patients in the early phase of transplantation or for the treatment of acute rejection; OKT-3 was used in none of the studied populations.

Unfortunately, EBV and CMV serology was available in only 14 patients from two of the centers. All PTLD cases of these two centers were IgG positive and IgM negative for both CMV and EBV.

Statistical analysis

Software SPSS v. 13.0 was used for data analyses. Statistical differences between patient subgroups were performed by using χ^2 and Fishers' exact tests for proportions and the Student's *t*-test for continuous data. We compared distributions by the Kolmogorov–Smirnov tests. Survival analysis was done with life tables and Kaplan–Meier methods and log-rank test. Cox proportional hazard regression model was employed to determine whether the observed relations are independent. All statistical tests were performed at the 0.05 significance level.

Results

Overall, 31 patients were diagnosed as having post-transplant lymphomas. Thirty were first renal recipients, and one was the recipient of his second renal allograft. These patients were recruited from a total population of 6,500; hence the prevalence of post-kidney transplant lymphoma in our kidney transplant population comprises 0.47%. Sixteen (53%) PTLD patients were females, whereas 15 (47%) were males. The mean (SD; range) ages at transplantation and diagnosis were 37.1 (13.2; 20–66) and 41.9 (12.2; 24–67), respectively. Treatment methods included reduction or complete withdrawal of immunosuppression in 18 (58%), chemotherapy in 14 (48%), surgical intervention in 9 (30%), and radiotherapy in 3 (10%).

Overall, nine (29%) patients experienced disseminated PTLDs. Twelve (63%) patients died, and seven are alive. During their disease course, three (9.6%) experienced partial remission, but unfortunately PTLD recurred in all of them within less than 8 months. PTLD in seven patients remitted completely (mean follow-up 64 months; ranging from 9 to 218).

The mean time period from transplantation to diagnosis was 64 (0.7–173) months; the mean duration from transplantation to death was 62 (1.1–174) months; the mean time from diagnosis to death was 2.7 (0.1–10.5) months; the mean last measured creatinine was 1.8 (1.1–13). PTLD patients also had almost equivalent distribution in their age at transplantation, age at diagnosis, transplant to diagnosis time, post-transplant survival time and post-diagnosis survival time ($P > 0.05$). Above-mentioned values regarding various PTLD involvement sites were comparable (Figs. 1–3; $P > 0.05$).

Patients' survival for the PTLD group at months 12, 24, 48, 60, 120 and 180 were 86, 78, 67, 59, 43 and 36%, respectively. The localization pattern of lymphomas also had a significant impact on patient survival, with brain lymphoma as the worst location ($P < 0.001$).

Non-PTLD patients had a mean survival time of 57.0 ± 37.4 months from transplantation time, which was statistically equivalent to the mean time period between transplantation to diagnosis in the PTLD patients group (63.2 ± 54.9 months; $P = 0.390$). Compared to non-PTLD patients, PTLD patients were significantly female predominated (51.6% vs. 32.2%; $P = 0.03$) and had lower age at transplantation (36.9 ± 12.9 years vs. 42.9 ± 13.6 years, respectively; $P = 0.017$).

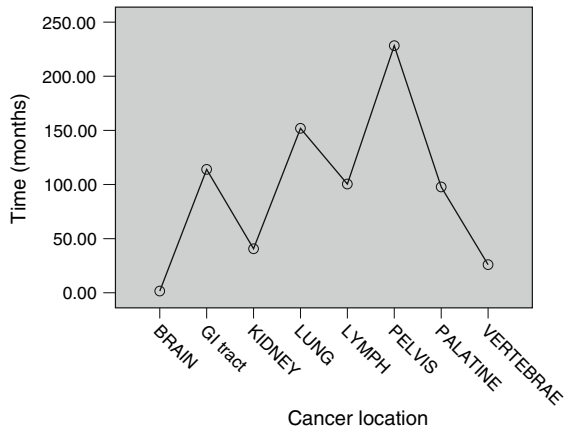

Fig. 1 Mean life time after transplantation for different cancer site involvement

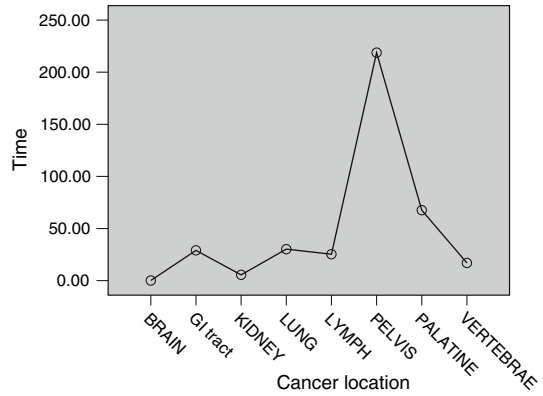

Fig. 2 Mean time period between diagnosis of PTLD and destiny

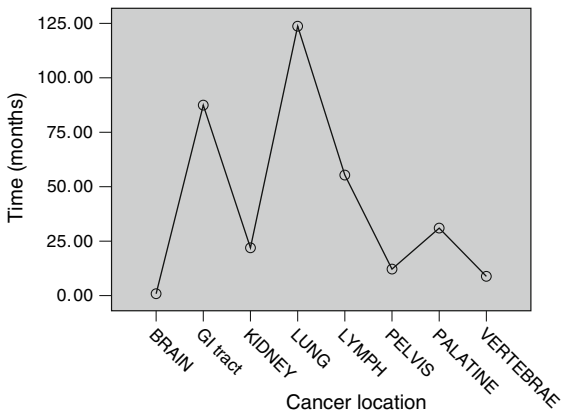

Fig. 3 Mean time period between transplantation and diagnosis of PTLD

Survival analysis using Kaplan–Meier method and log-rank test revealed that patients under immunosuppressive regimens containing azathioprine are at higher risk for acquiring PTLDs compared to a MMF-containing immunosuppressive regimen (Fig. 4). proportional hazard analysis demonstrated the independent impact of azathioprine on PTLD development (Table 1).

Discussion

In this multi-center nationwide study, we found that the overall incidence of post-transplant lymphomas among Iranian kidney recipients of living donor allograft is 0.47%, which is relatively lower than previous reports [7, 8]. It is speculated that the risk of lymphoma during the first post-transplant year is 20-

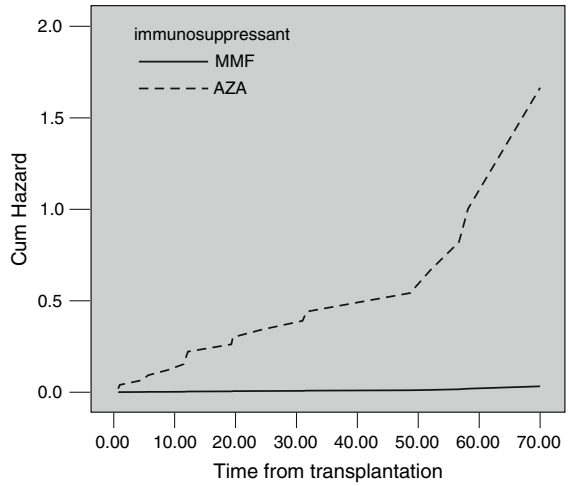

Fig. 4 Proportional hazard for development of PTLD in recipients on immunosuppressive regimens

fold higher after kidney transplantation than that in the general population [7]. Unfortunately, we have no evidence about the incidence of lymphomas among the Iranian general population; thus, we cannot compare our results with those in the general population.

The cumulative incidences of lymphomas in the 1st 1 and 2 years post-kidney transplant in our study population were 0.1 and 0.15%, comprising 22.5 and 35.5% of all the PTLD cases, respectively. This shows that lymphomas in kidney allograft recipients occur on a decreasing per year basis with the highest rates in the 1st year post-transplantation.

The relationship between lymphoma frequency and recipient characteristics has been highlighted in several reports [8–10]. However, controversy exists with respect to the role of the recipients' age and gender on the development of PTLDs. Dharnidharka et al. [7] found a higher risk for males in developing PTLDs, whereas another study from Canada [11] detected a protective effect of male gender on the condition. In this study, we found that PTLDs significantly occur in females; however, when we re-analyzed the data using time-dependent methods and after adjustment for other risk factors, we found no additional risk of developing PTLDs in females (Table 1). Moreover, using bivariate analyses and corroborating to a fair number of studies [6, 7], we found that compared to non-PTLD patients, patients in the PTLD group had significantly lower age, although several other authors reported contrasting findings with a higher incidence of PTLD among

Table 1 Proportional hazards model evaluating independent impact of immunosuppressive regimens on PTLD development

Variables	Standard error	Sig.	Exp (B)	95.0% CI for exp(B)	
				Lower	Upper
Gender of recipients	0.495	0.536	0.736	0.279	1.942
Age at transplantation	0.019	0.836	0.996	0.959	1.034
Immunosuppressant	0.591	0.000	0.022	0.007	0.069

older patients [12–16]. However, proportional hazard analysis after adjustment for other risk factors showed that age is not an independent contributing factor in developing PTLD (Table 1).

The preferential localizations of lymphoma in our population of living kidney allograft recipients were the gastrointestinal (GI) tract, peripheral lymph nodes, kidneys, lung and brain, respectively. Most previous authors evaluating PTLD incidence in kidney recipients also reported that GI tract localization of PTLD is the most frequent involvement location [8, 17]; however, controversial reports also exist with lymph nodes and the allograft as the most common involvement sites [2, 18].

Corroborating with a number of previous studies, we also found that cancer localization was strongly associated with patient survival [8, 16]. In our PTLD population, CNS localization of lymphoma represented the worst outcome, which is in accordance with previous studies [15, 19]. In a study by Opelz and Döhler [8], localization of cancer in the lung was reported as the most fatal after disseminated lymphoma.

We also found that mean survival time for non-PTLD kidney recipients was not significantly higher than mean time between transplantation and diagnosis of PTLD in this group. This confirms that a possible relatively lower average survival for our patients could not rationalize the observed low incidence of PTLD in our patients. Moreover, according to our previous studies, mean survival time for our patients was not lower than that reported from other countries [20].

In this study, it was found that renal allograft recipients on azathioprine-based immunosuppression are at extremely higher risk for development of PTLD (Table 1, Fig. 4); this finding is in contrast with previous reports, in which a triple immunosuppressive regimen including MMF was considered to have the highest imposing impact on the post-transplant malignancies [21]. One reason for this observation can be related to the higher doses of cyclosporine administered to kidney recipients under azathioprine-based immunosuppression in our centers.

As seen above, our findings in this cross-sectional multi-center study were in accordance with previous reports studying the issue; however, controversies also exist to some extent regarding the studies' results. Differences seen in our study compared to others may be related to the difference between studies in their type of transplantations. The majority of reports on the incidence of PTLD worldwide are from cadaveric kidney recipients. In fact, the first major study investigating PTLD in living kidney transplant patients was reported by Jain et al. in 2005 [17]; in this study, the overall incidence of PTLD was 0.52%, which is comparable to our result. Moreover, findings, they demonstrated that localizations of lymphoma in the GI tract and peripheral lymph nodes are the major involvement sites for the occurrence of PTLD in living kidney recipients. The reason behind discrepancies seen between living and deceased donor kidney transplantation could potentially be explained by the imposed selection in donors. In almost all countries with a living donor transplantation policy, donors should be comprehensively healthy, and even minor health problems will exclude them from donation; moreover, there may be more thorough legislations for living unrelated (LUR) donors' selection; for example, in Iran, LUR donors should be younger than 35.

To the best of our knowledge, the current study deals with the largest living donor kidney transplant population that assesses PTLD up until now. This study also revealed some invaluable data about PTLD and its correlates in living kidney recipients. A limitation of the present study is that some valuable information such as data of seroprevalence of antiviral antibodies (e.g., anti-EBV and CMV antibodies) and incidence of rejection episodes before and after PTLD diagnosis were not available for patients of two of the studied centers.

In summary, the analyses suggest that the incidence of PTLD among Iranian renal recipients is low. Moreover, being female and having younger ages at the time of transplantation are risk factors for development of PTLD. Furthermore, compared to patients using MMF-based therapy, patients under azathioprine-based immunosuppression represented significant hazards for PTLD occurrence; this observation might be a consequence of the higher doses of prescribed cyclosporine in the latter patient group.

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