TRANSPLANT INTERNATIONAL

Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

CNI withdrawal for post-transplant lymphoproliferative disorders in kidney transplant is an independent risk factor for graft failure and mortality

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Keywords
calcineurin inhibitor, graft survival, immunosuppression withdrawal, kidney transplant, post-transplant lymphoproliferative disorder.

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Conflicts of interest
The authors of this manuscript have no conflicts of interest.

Received: 24 March 2014
Revision requested: 21 April 2014
Accepted: 17 June 2014
Published online: 20 August 2014

doi:10.1111/tri.12375

Summary

Post-transplantation lymphoproliferative disorders (PTLD) are associated with poor patient and graft survival. The risk of rejection and subsequent graft loss are increased by the reduction of immunosuppression therapy, the cornerstone of PTLD treatment. This multicentre, retrospective, nonrandomized cohort study includes 104 adults who developed PTLD after renal or simultaneous renal/pancreatic transplantation between 1990 and 2007. It examines the effect of calcineurin inhibitor (CNI) withdrawal on long-term graft and patient survival. At 10 years postonset of PTLD, the Kaplan–Meier graft loss rate was 43.9% and graft loss or death with functioning graft was 64.4%. Cox multivariate analysis determined risk factors of graft loss as PTLD stage greater than I-II and CNI withdrawal, and for graft loss and mortality, these remained risk factors along with age over 60 years. Type and location of PTLD, year of diagnosis, and chemotherapy regime were not independent risk factors. Multivariate analysis determined CNI withdrawal as the most important risk factor for graft loss (HR = 3.07, CI 95%: 1.04–9.09; $P = 0.04$) and death (HR: 4.00, CI 95%: 1.77–9.04; $P < 0.001$). While long-term stable renal function after definitive CNI withdrawal for PTLD has been reported, this review determined that withdrawal is associated with reduced graft and patient survival.

Introduction

Post-transplant lymphoproliferative disorder (PTLD) is an uncommon complication of transplantation, making it difficult to perform prospective research. This retrospective study aimed to examine this rare heterogeneous group of lymphoid proliferations that affect less than 1–2% of kidney transplant (KTx) recipients [1]. PTLD may be nodal

and/or extranodal, restricted to the central nervous system or to the graft, or widely disseminated.

Histologically, there is a spectrum of presentation that ranges from polyclonal hyperplasia to non-Hodgkin's lymphoma, and this spectrum leads to a complex classification [2,3]. Lastly, PTLD could represent potentially life-threatening complications of solid organ transplantation [4].

PTLD is primarily of B-cell origin and is often associated with active Epstein–Barr virus infection [5,6]. In transplant recipients, poor immune control of EBV infection has been linked to a high incidence of PTLD, especially for children or adult patients who experienced a primary infection [7]. Nevertheless, if primary infection by EBV is the most important risk factor for early PTLD, late PTLD is frequently unrelated to EBV infection and is thought to be induced by the chronic allogenic stimulation of the graft [8,9].

In cases of a nonlife-threatening PTLD, treatment is initially focused on the reduction of immunosuppression (RI) [10–12]. Dose reductions of immunosuppressive drugs can improve immune surveillance against viral antigens and facilitate the clearance of proliferative cells. There is no standardization of the RI regarding which drug could be reduced first, and there is no consensus on the duration of step reduction prior to considering whether the procedure has succeeded or failed. These choices remain largely dependent on the transplant center or physician. Because CNI appears to be critical in the process of PTLD, they are frequently the first to be reduced (25–50% of baseline dosages) or withdrawn. The risk of graft rejection, which is not life-threatening and sometime manageable in KTx recipients [10,12], is counterbalanced by the potential benefit of the RI face to a severe disease, and its regression is considered to be immunosuppression-dependent. Unfortunately, complete responses following RI alone are rare [10], and the lack of response to RI is predictable in patients with older age, a bulky disease and/or an advanced disease stage [12]. A large majority of patients need additional treatment via rituximab and/or chemotherapy [13]. Lastly, with the exception of isolated kidney graft involvement by lymphoproliferation (which could be definitively cured via transplant removal [14]), the 1-year patient survival remains poor with a mortality rate of approximately 40% [15,16].

To review the effect of complete and persistent withdrawal of CNI treatment on patient and graft survival, a retrospective study involving the collaboration of eight major transplant centers during 17 years was performed. This allowed meaningful conclusions to be drawn from 104 patients, the largest series in the literature.

Patients and methods

Study population and data collected

This retrospective multicentre study was conducted in eight major French transplant centers. Inclusion criteria were as follows: (i) adult patient ≥18 years old who had received a KTx or SKPTx between January 1, 1990, and December 31, 2007, (ii) biopsy-proven PTLD, (iii) received long-term immunosuppressive therapy including a CNI. Exclusion criteria were as follows: (i) Hodgkin disease or multiple myeloma, (ii) receiving chronic dialysis at diagnosis of PTLD, (iii) conversion to mTOR at point of PTLD diagnosis.

Data were collected from medical charts during the pretransplantation period then pre- and post-PTLD diagnosis. The date and cause of death and/or graft failure were also noted. Ann Arbor staging, changes in immunosuppression regimen and specific PTLD therapies were noted.

A total of 11 006 KTx were performed in eight participating centers over 17 years, with 607 (5.5%) being simultaneous kidney/pancreas transplantations (SKPTx). PTLD was confirmed by biopsy in 109 patients (1.0% incidence in KTx, 1.1% in SKPTx). All 109 were being administered CNI at the time of PTLD diagnosis. Five patients were immediately converted to mTOR inhibitors and thus were excluded from the study due to a too small effective for significant analysis.

Diagnosis of PTLD, histopathology, and evaluation

The diagnosis of PTLD was proven by histological examination of tissue samples. All biopsies were available and examined for homogeneous classification according to the World Health Organization classification, 2008 [17]. Immunohistochemistry via immunoglobulin staining (light-chain immunoglobulin, latent membrane protein 1, zebra or Epstein–Barr nuclear antigen 2) and *in situ* hybridization for EBV Epstein–Barr early ribonucleoprotein 1 RNA were performed when possible.

PTLD treatment and immunosuppression therapy changes

The first-line treatment involved a RI therapy and (when possible) the surgical excision or reduction of tumor mass. Additional chemotherapy, mainly cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP), was started following the lack of response to RI therapy or in cases of clinically aggressive lymphoma and/or a compromise of a critical organ. Since 1997 and routinely after 2000, rituximab was administered, either alone or with chemotherapy (R-CHOP), in cases of failed RI therapy. A total of 21 patients (19.3%) were treated for PTLD before the use of rituximab.

The decision to maintain or stop the CNI at the time of the diagnosis of PTLD was at the physicians' discretion.

Patients were retrospectively assigned as "CNI withdrawal" or "CNI continuation" at the time of PTLD diagnosis. The management of the other immunosuppressive drugs was detailed for all patients (Fig. 1). Data were excluded from the statistical analysis for patients who were switched to a mammalian target of rapamycin (mTOR) inhibitors at the time of PTLD diagnosis ($n = 5$).

Renal function monitoring

Renal transplant function was assessed using serum creatinine. Glomerular filtration rate (eGFR) was estimated monthly for 6 months and thereafter at least yearly using the four-variable equation from the Modification of Diet in Renal Disease Study Group. Renal lesions were graded according to the Banff classification. Allograft failure was defined as the need for chronic hemodialysis.

Statistical analysis

Graft and patient survival were calculated from the date of PTLD diagnosis until the beginning of chronic hemodialysis or the date of death from any cause or the date of the last visit. Overall survival was determined as the lesser of these two time periods. Results are presented for all patients, including those censored due to early transplantectomy where this was feasible for complete tumor resection. The association between CNI modification and the risk of death and/or dialysis dependence was analyzed using the Kaplan–Meier and log-rank tests. A Cox multivariate model was built (univariate selection $P < 0.2$; multivariate selection $P < 0.05$) to analyze for factors associated with survival. The proportionality assumption was evaluated according to the residual analysis [13]. All of the tests were two-sided, and P-values <0.05 were considered statistically significant. The statistical analyses were performed using R software Team RDC 2010 (A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing).

Comparisons were made between the cohort of patients included in this study and a similar control population of kidney-transplanted patients in France, without PTLD. The data were extracted from the DIVAT data bank (www.divat.fr), a French prospective study of kidney transplant recipients. Patients with a cancer during their follow-up were excluded. The 104 paired controls were of a similar age (±3 years) and living with a functional kidney at the time of PTLD diagnosis of their paired case.

Results

PTLD presentation

The mean time of PTLD diagnosis after KTx was 53 ± 42 months. For the cohort, 26% were diagnosed with PTLD in the first year after transplantation (27/104), 10.1% more than 10 years after transplantation (11/104). At the time of diagnosis, PTLD was primarily nodal or mixed and of B-cell origin (Table 1). Other clinical features are presented in Table 1.

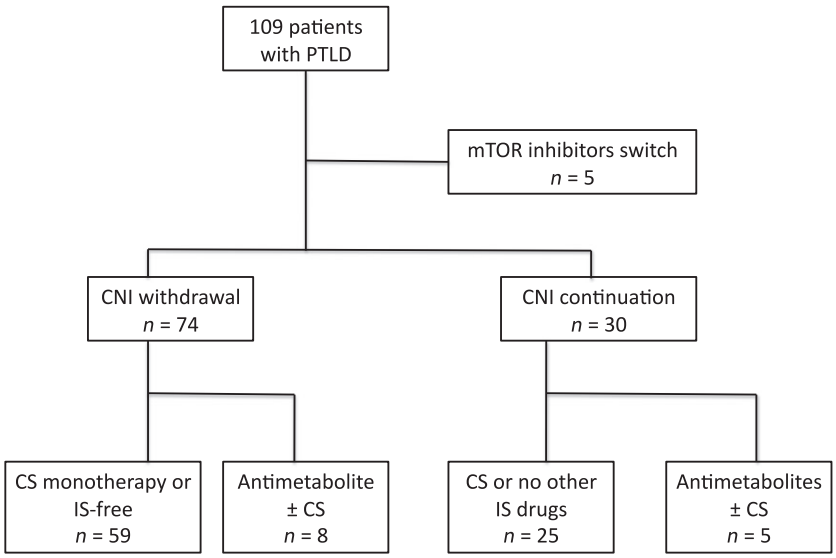

Figure 1 Immunosuppression therapy changes after the diagnosis of post-transplant lymphoproliferative disorder (PTLD) in patients with kidney or simultaneous kidney/pancreas transplantation. mTOR, mammalian target of rapamycin; CNI, calcineurin inhibitor; IS, immunosuppression; CT, corticotherapy.

Immunosuppressive regimens prior to and after PTLD diagnosis

Prior to PTLD diagnosis, 94 patients (90.4%) had received induction therapy. All patients had received CNI combined with antimetabolite agent and steroids at least during the first months after transplantation. A total of 29 patients (27.9%) experienced biopsy-proven acute cellular rejection, and all of these had received pulse steroids. Additional monoclonal antibody therapy (Orthoclone OKT3, Cilag, France) was needed in five cases.

At PTLD diagnosis, patients received CNI combined with an antimetabolite drug (86.5%) and/or steroids (57.7%). The immunosuppressive therapy was reduced in all cases after PTLD diagnosis. There was no standardized management, but two main strategies were employed (Fig. 1): complete CNI withdrawal for 74 patients (71.2%) or CNI continuation with dose reduction from 25% to 50% for 30 patients (28.8%). Additionally, azathioprine (AZA) or mycophenolate mofetil/mycophenolic acid (MMF/MPA) therapy was interrupted or reduced in most cases (75.0% and 76.1%, respectively). Steroids were stopped in 6 patients (5.8%) at the time of PTLD diagnosis, but low-dose steroid treatment (≤10 mg/d) was given to 65 patients (62.5%).

Concomitant treatment of PTLD

Further treatment of PTLD included surgery for tumor mass reduction for 30 patients and radiotherapy for 12 patients (central nervous system or cervical lymph nodes). PTLD was successfully managed using RI alone for only eight patients (7.7%). Most patients required further second-line therapy, including rituximab ($n = 58$) and/or chemotherapy ($n = 69$, CHOP regimen for 78.2% of the patients). Chemotherapy was administered as a second-line therapy after RI therapy failure for 30 patients and as a third-line therapy after RI and rituximab for 15 patients.

Patient and graft survival

Mean follow-up after diagnosis of PTLD was 35 ± 39 months (range: 12–147 months). In all, 24 patients died with a functional graft after 15 ± 25 months (range: 1 to 102 months). The causes of death were disease progression in 13 patients, infection in six patients, and miscellaneous in five patients. Graft loss was observed in 30 patients. In seven of these, graft loss through transplant nephrectomy was indicated by isolated PTLD of the kidney graft. At last follow-up, 50 patients were alive, in complete remission of their PTLD with a functional graft. At 10 years post-PTLD diagnosis, the cumulative probability of death with a functional graft and of graft failure was 64.4% (CI 95%: 49.6–74.8%). At 10 years, the probability of graft failure (death censored) was 43.9% (CI 95%: 27.4–56.6%) (Fig. 2a).

In addition, outcomes of PTLD patient are significantly worse than control patients without PTLD (Fig. 2b).

Factors influencing patient death and/or graft failure

The probability of graft failure was significantly higher for patients with CNI withdrawal than continuation (Fig. 3). Before excluding transplantectomies from the analysis, eGFR (i.e., <30 ml/min) at the time of the diagnosis was associated with a poor graft outcome. On multivariate analysis, CNI withdrawal, patient age >60 years, and stage III or IV (according to Ann Arbor classification at time of PTLD diagnosis) were independent risk factors for both patient and graft survival (Table 2). CNI withdrawal was the most important risk factor for death (HR: 4.00, CI 95%: 1.77–9.04; $P < 0.001$). After censoring patient death, only Ann Arbor stage III or IV and CNI withdrawal remained associated with poor graft survival (Table 2). The hazard ratio for graft loss was 3.07 (CI 95%: 1.04–9.09; $P = 0.04$) with CNI withdrawal.

Rejection and long-term changes in renal graft function

At the time of PTLD diagnosis, the overall mean serum creatinine level was 146 ± 65 μM and estimated glomerular filtration was 52 ± 25 ml/min. Withdrawal and continuation CNI groups did not differ in renal function at PTLD diagnosis (eGFR 48 ± 22 and 52 ± 18 ml/min, respectively, $P = 0.2$).

After PTLD diagnosis, 12 patients presented biopsy-proven acute graft rejection after a mean delay of 7 ± 3 months (CNI withdrawal, $n = 8$; CNI continuation: $n = 4$). One patient presented two episodes of acute rejection. These rejection episodes were treated with steroids in six cases, but the six other patients did not receive any specific treatment followed by graft failure within a few weeks.

After PTLD diagnosis, 30 patients experienced graft loss (CNI withdrawal, $n = 26$, 35.1%; CNI continuation, $n = 4$, 13.3%). If we exclude patients undergoing transplant nephrectomy as PTLD therapy from the analysis (CNI withdrawal, $n = 7$), the proportion of graft loss was double in the withdrawal group (25.7% vs. 13.3%). Time after PTLD to graft loss was a typical asymptotic curve after transplantation (26% in first year, 20% in second year, 54% after 2 years) with no cutoff period after which the risk of graft failure increased or decreased (data not shown). At 10 years, six patients (5.7%) had a functional graft; four of these had a creatinine clearance >30 ml/min. Among these patients, three were on low-dose steroid maintenance therapy only (<10 mg/d), and one was not on any immunosuppressive drugs.

Table 1. Clinical features of 104 kidney or kidney/pancreas transplant recipients at the diagnosis of post-transplant lymphoproliferative disorder (PTLD).

	All patients* *n* = 104	CNI withdrawal *n* = 74	CNI continuation *n* = 30
Before PTLD diagnosis			
Recipient gender male/female (% of male)	65/39 (62)	45/29 (61)	20/10 (67)
Mean recipient age at Tx, year (range)	48 (21–73)	48 (21–73)	49 (21–70)
Donor type, deceasing/living (% deceased)	101/3 (97)	72/2 (97)	29/1 (97)
First transplantation, *n* (%)	95 (91)	66 (89)	29 (97)
Transplant type, *n* (%)			
Kidney	97 (93)	68 (92)	29 (97)
Simultaneous kidney and pancreas	6 (7)	6 (8)	1 (3)
Treatment induction, *n* (%)			
Polyclonal antibodies	81 (78)	58 (78)	23 (76)
Anti-IL2 receptor MoAb	13 (12)	8 (11)	5 (17)
No induction treatment	10 (10)	8 (11)	2 (7)
Mismatch EBV (D+/R−), *n* (%)	8 (8)	6 (8)	2 (7)
≥1 Acute rejection episode, *n* (%)	30 (29)	23 (28)	7 (23)
>1 Acute rejection episode, *n* (%)	4 (4)	4 (5)	0 (0)
At the time of PTLD diagnosis			
Early/late PTLD, *n* (%)	27/77 (26)	20/54 (27)	7/23 (23)
Mean Age, year (range)	52 (22–74)	52 (24–74)	53 (22–71)
Age >60, *n* (%)	39 (37)	24 (32)	15 (50)
eGFR (ml/min per 1.73 m^2) *n* (%)			
≤29	18 (17)	15 (20)	3 (10)
30–59	59 (57)	43 (58)	16 (53)
≥60	27 (26)	16 (22)	11 (37)
Immunosuppressive therapy, *n* (%)			
Cyclosporine	73 (70.2)	55 (74.3)	18 (60)
Tacrolimus	31 (29.8)	19 (25.7)	12 (40)
MMF or MPA	50 (48.1)	34 (45.9)	16 (53.3)
Azathioprine	38 (36.5)	29 (39.2)	9 (30)
Corticosteroids	58 (55.8)	39 (52.7)	19 (63.3)
Localization/type of PTLD, *n* (%)			
Extra-nodal localization	86 (82.7)	65 (87.8)	21 (70)
Restricted to kidney graft	8 (7.7)	6 (8.8)	2 (6.7)
Restricted to pancreas graft	1 (0.9)	1 (1.3)	0 (0)
Central nervous system	10 (9.6)	8 (10.8)	2 (6.7)
Polymorphic form, *n* (%)	39 (50)	30 (51.7)	9 (45)
Ann Arbor stage I-II†, *n* (%)	77 (74)	55 (74.3)	22 (73.3)
Histological data, *n* (%)			
B phenotype	94 (90.4)	67 (90.5)	27 (90)
T or no B/no T phenotype	10 (9.6)	7 (9.5)	3 (10)
EBV-positive lymphoma (performed in 99 samples)	49 (47.1)	32 (43.2)	17 (56.7)
Treatment of PTLD, *n* (%)			
RI alone	8 (7.7)	3 (4)	5 (16.7)
RI + rituximab	15 (14.4)	9 (12.2)	6 (20)
RI + chemotherapy	26 (25)	19 (25.7)	7 (23.3)
RI + rituximab + chemotherapy	43 (41.3)	33 (44.6)	10 (33.3)
RI ± radiotherapy	12 (11.5)	10 (13.5)	2 (6.7)
Death, *n* (%)	24 (23)	21 (28)	3 (10)
Graft failure, *n* (%)	30 (29)	26 (35)	4 (13)

Data are number (%).

CNI, calcineurin inhibitor; EBV, Epstein–Barr virus; MMF, mycofenolate mofetil; MPA, mycophenolic acid; RI, reducing immunosuppression.

*Serologies known for the donor and recipient for 41 patients.

†See complete classification in the Appendix 1.

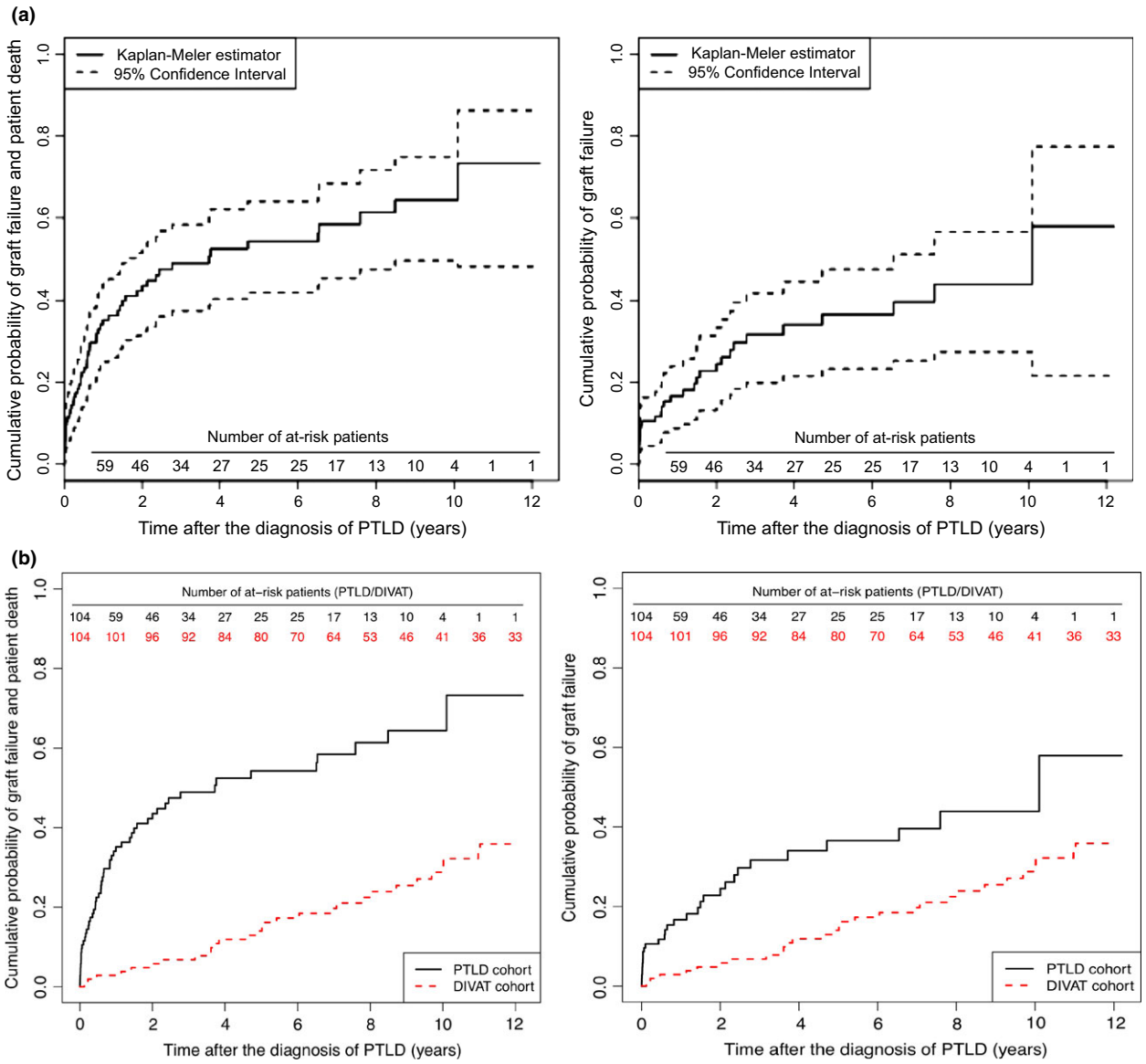

Figure 2 (a) Cumulative probability of graft failure and patient death (top left), cumulative probability of graft failure (top right) in patients with Post-transplantation lymphoproliferative disorders (PTLD) after kidney or simultaneous kidney/pancreas transplantation. The probability of graft failure or death during the 10 years following PTLD diagnosis was approximately 64.4% (CI 95% = [45.2%, 74.8%]) (left). The probability of graft failure during the 10 years following PTLD diagnosis (if deaths with a functional graft were censored) was approximately 43.9% (CI 95% = [27.4%, 56.6%]) (right). (b) The cohort was matched to a comparable kidney-transplanted patient in France without PTLD. Outcomes of PTLD patient are significantly worse than control patients without PTLD.

Discussion

This study of 104 kidney transplant recipients treated using CNI at the time of PTLD diagnosis demonstrated that a strategy using a complete and definitive withdrawal of CNI is associated with worse graft and patient survivals than a strategy with CNI reduction. CNI withdrawal was an independent risk factor for patient death and/or graft loss. The 1-year mortality rate after PTLD diagnosis in kidney transplant recipients is 30–40% [15,16,18], and the causes of death are usually directly related to PTLD progression or to infection [14]. A previous report [14] found that the risk of death with a functional graft or graft loss continued to increase after the first year post-PTLD, with a cumulative probability of 60% at 10 years.

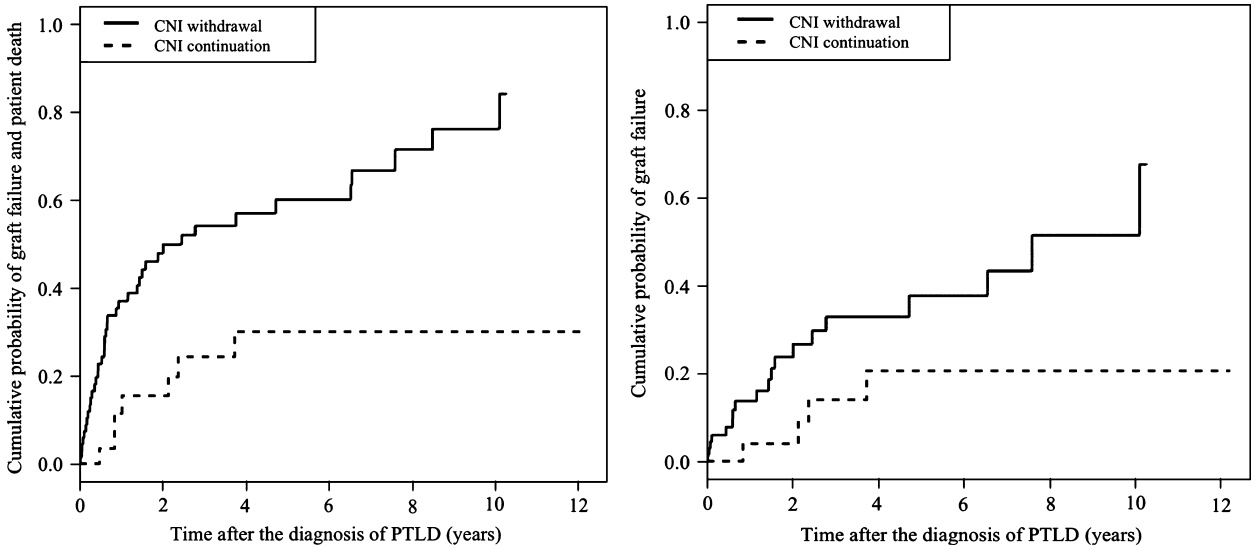

Figure 3 Left: Cumulative probability of graft failure and patient death ($P = 0.0003$); Right: cumulative probability of graft failure ($P = 0;0082$) in patients with Post-transplantation lymphoproliferative disorders (PTLD) after kidney or simultaneous kidney/pancreas transplantation via calcineurin inhibitor modification strategy. Transplantectomies were censored. Deaths with a functional graft were censored (right).

Table 2. Univariate and multivariate analysis of variables associated with graft and patient survival (transplantectomies censored).

	Patient and graft survival			Graft survival		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Univariate analysis						
CNI modification (withdrawal vs. continuation)	3.48	1.55–7.78	0.0025	2.99	1.01–8.83	0.0480
Age at PTLD diagnosis (≥60 vs. <60 years)	1.64	0.91–2.93	0.0980	1.52	0.65–3.55	0.3321
Time diagnosis PTLD (≥1 year post-transplantation vs. <1 year)	0.98	0.48–1.97	0.9514	0.59	0.24–1.44	0.2378
Acute rejection before PTLD (yes vs. no)	1.54	0.81–2.92	0.1888	1.52	0.59–3.88	0.3804
Infection before PTLD (yes vs. no)	0.71	0.40–1.28	0.2647	1.09	0.46–2.57	0.8494
Another cancer before PTLD (yes vs. no)	0.84	0.35–1.98	0.6912	0.88	0.26–2.98	0.8372
Creatinine clearance at diagnosis (<30 ml/min vs. ≥30 ml/min)	1.09	0.51–2.33	0.8315	1.10	0.37–3.26	0.8621
PTLD localization (disseminated vs. one site)	1.57	0.70–3.53	0.2654	1.97	0.58–6.70	0.2784
EBV-related PTLD (yes vs. no)	0.57	0.30–1.06	0.0745	0.65	0.28–1.49	0.2965
Phenotype (T, no B/no T vs. B)	1.26	0.53–2.99	0.5984	0.36	0.05–2.72	0.3214
Chemotherapy (yes vs. no)	2.77	1.33–5.79	0.0067	1.72	0.70–4.24	0.2433
PTLD staging (I-II vs. III-IV)	0.51	0.28–0.91	0.0240	0.41	0.18–0.95	0.0371
Year of diagnosis (after 2000 vs. before)	0.83	0.45–1.51	0.5312	0.68	0.28–1.65	0.4122
Multivariate analysis						
CNI modification (withdrawal vs. continuation)	4.00	1.77–9.04	0.0009	3.07	1.04–9.09	0.0425
Age at PTLD diagnosis (≥60 vs. <60 years)	2.08	1.15–3.77	0.0159	–	–	–
PTLD staging (I-II vs. III-IV)	0.5	0.27–0.90	0.0203	0.40	0.17–0.92	0.0315

HR, hazard ratio; CNI, calcineurin inhibitor; PTLD, post-transplantation lymphoproliferative disorders.

Therapy for PTLD is not well standardized, but in general, treatment strategies follow international recommendations [19]. For extensive disease but not critical illness, recommendations are to decrease CNI by 50%, to discontinue AZA/MMF and to maintain low-dose corticosteroids (7.5–10 mg/d); for extensive disease and critical illness, recommendations are to stop all agents except corticosteroids and initiate specific treatments via rituximab (if the proliferative cells are $CD20^+$) and/or chemotherapy. Following RI, up to 50% of cases show a reduction of the PTLD lesions [12,20] within 2–4 weeks [11], but complete responses are less frequently observed (ranging from 0 to 37%) [10,12]. Such complete remission after RI alone was observed in 8% of our cohort. Additionally, RI alone in

low-risk patients after PTLD (defined as age <50, LDH <2.5 × ULN, no hepatitis C, no liver and/or bone marrow involvement, and no B symptoms or dyspnea at presentation) resulted in good 3-year overall survival (up to 79%) [12]. Of note, in heart transplantation, survival was better for patients with RI therapy than without RI therapy independent of additional treatment [19].

The safety of RI is a major concern. The allograft rejection rate reported in the literature ranges from 17% to 32% in kidney transplant recipients after RI for PTLD [12]. Acute rejection following RI is also frequently reported in cardiac transplant recipients with PTLD [10]. In this situation, RI increases the risk of sudden death related to heart rejection [20]. In our series, despite CNI withdrawal, additional cytotoxic chemotherapy resulted in a low rate of acute rejection (3%). The negative impact of RI on graft function and graft survival can be counterbalanced via chemotherapy, which also induces immunosuppression [21]. Another study showed that rituximab combined with RI (but without chemotherapy) was ineffective in prevention of acute rejection (45% [12]). Additionally, a recent publication suggested that the maintenance of CNI at a reduced dose appeared to be associated with a lower incidence of *de novo* anti-HLA antibodies and better control of the humoral response of the recipient [22]. Despite the risk of rejection, short-term renal function for patients with PTLD receiving RI, rituximab, and chemotherapy was similar to that of a control population [21]. Notably, this study detailed that patients with long-term kidney graft survival after CNI withdrawal for PTLD remained a minority. Two studies reported stable renal function in 36% of patients at 105 months [23] and 19% of patients at 36 months [24] for CNI-free patients.

Serre *et al.* [22] found that maintaining CNI at reduced dose after PTLD is safe and may improve renal graft outcome but did not appear to affect overall survival. In this study, patient survival was influenced by the International Prognosis Index (IPI) and the use of rituximab but not by the type of immunosuppressive regimen and the PTLD staging as independent factor was not analyzed. Our results are not in opposition, as we used different composite criteria of failure that considered patient death and graft loss.

If kidney graft rejection becomes irreversible, a subsequent transplantation could be a safe option. Interestingly, the outcome of retransplantation, generally delayed by 12–24 months after the diagnosis of PTLD, can be successful when the EBV viral load is undetectable at the time of transplantation [25–27]. The success of retransplantation without PTLD recurrence in nonkidney transplant recipients has been reported in patients receiving powerful immunosuppressive therapies [28,29]. Thus, for kidney transplant recipients, the reintroduction of immunosuppression could be safe after complete remission of PTLD and a washout period of therapeutic immunosuppression for a duration that is yet to be defined (1–2 years).

The limitations of this research, which is slightly larger than the biggest previously reported series, are related to its retrospective and nonrandomized design. While a limitation, the data are still valuable given the lack of randomized trials on the management of immunosuppression in this malignancy. Only a prospective randomized study can overcome the association of CNI withdrawal with more aggressive and bulky disease. Statistical analysis has been used to control for severity of disease, but bias cannot be eliminated. Additionally, this study population could represent a group of more aggressive PTLD than those reported elsewhere in the literature. This hypothesis is supported by two observations. First, the incidence of PTLD was lower in the present study than that reported in the French PTLD registry (2.1% at 10 years) [4] or in the United States and ANZDATA registries (1.4%) [30,31]. These discrepancies could be related to the under-representation of polyclonal benign or mononucleosis infectious-like proliferations.

Secondly, while some characteristics of the participants appeared to be similar to other reported series [4,30,31], approximately 80% of the patients in this study required additional chemotherapy (compared with 50% to 60% in the literature) [4,12]. Nevertheless, when comparisons were made between the two intervention groups of patients, the severity of disease and known prognostic factors associated with a poor prognosis [18] (such as age, EBV, and CMV serological status, the use of induction therapy and histological subtype) did not differ between the two groups. While PTLD tended to be more frequently extranodal in patients with CNI withdrawal, this difference was not statistically significant. This lack of statistical significance may be due to low power; however, this cohort is the largest series in the world literature involving multiple centers, so it remains our best available resource.

Lastly, in this series, the precise cause of graft loss was known for only 17% of patients (biopsies were performed in five patients who experienced graft loss; this rate of biopsy is similar to that performed in other studies) [22]. Furthermore, our findings cannot be extended to pediatric patients.

One current alternative to CNI withdrawal is conversion to mTOR inhibitors. However, the effect of these agents in PTLD is not clearly defined in comparison with the clearly demonstrated improvement in kidney transplant patients with squamous cell carcinoma [32,33]. After PTLD, the conversion to mTOR inhibitors was successfully reported in few cases [34,35]. Three of the five patients excluded from this study due to conversion to mTOR inhibitors and who were also treated using rituximab and CHOP, obtained complete remission with long-term graft function

(mean follow-up 37 ± 23 months with creatinine clearance of 64 ± 6 ml/min). Some experimental *in vitro* and *in vivo* findings support the use of this class of immunosuppressive agents for PTLD [36,37], but the combination of mTOR inhibitors and tacrolimus was associated with an increased risk of PTLD [38]. Current clinical evidence is insufficient for clear recommendations regarding conversion to mTOR during the early phases of PTLD management [39].

In conclusion, RI is the first-line treatment for PTLD after kidney transplantation, but the management of long-term immunosuppression remains questionable. This research has demonstrated that complete withdrawal of CNI after developing PTLD is associated with poor long-term kidney graft function; however, others have reported that maintaining CNI after PTLD diagnosis improves renal graft survival [11]. Low-risk PTLD patients could benefit from RI; CNI reduction without complete withdrawal seems to be a safe management option.

Authorship

NR, MB, YF and JD: participated in research design, writing the paper, performing the research and data analysis. AM, CD and MCM: participated in performing the research. MK, EM, AT, CL, JR and NK: participated in performing the research and data analysis.

Funding

No funding.

Acknowledgements

We thank Laura Smales, Richard and Kate Large for editing the manuscript.

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Appendix: Ann Arbor staging of lymphoma

I A single involved lymphoid region, organ, or site.
II Two or more involved lymphoid regions or one extralymphoid site and a lymphoid region on the same side of the diaphragm.
III Lymphoid regions involved on both sides of the diaphragm with or without the localized involvement of extralymphatic organs or spleen.
IV Disseminated involvement of 1 or more extralymphatic organs or tissues with or without associated lymphadenopathy.