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# Course of renal allograft function after diagnosis and treatment of post-transplant lymphoproliferative disorders in pediatric kidney transplant recipients

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## Abstract

**Background:** Post-transplant lymphoproliferative disease (PTLD) is a life-threatening complication in renal transplant recipients. Immunomodulatory and chemotherapeutic treatment potentially affect allograft function. The aim of this study was to evaluate graft function of pediatric kidney transplant recipients following diagnosis and standardized treatment of PTLD.

**Methods:** Patients were identified from the German Ped-PTLD registry, and data on renal function were retrospectively retrieved from patient charts. For PTLD treatment, immunosuppressive therapy was reduced and all children received rituximab (375 mg/m$^2$) for up to six doses. Two patients required additional low-dose chemotherapy. Renal allograft function was monitored by consecutive measurements of estimated glomerular filtration rate (eGFR) at defined time points. Follow-up was up to 60 months after PTLD.

**Results:** Twenty patients were included in this cohort analysis. Median time from transplantation to PTLD was 2.4 years. Histopathology showed monomorphic lesions in 16 and polymorphic in 4 patients. Two patients experienced PTLD relapse after 2 and 14 months. Range-based analysis of variance showed stable allograft function in 17 of 20 patients (85%). Mean eGFR increased during early treatment phase. One patient experienced graft rejection 5.3 years after diagnosis of PTLD. Another patient developed recurrence of primary renal disease (focal-segmental glomerulosclerosis) and lost his renal allograft 3.8 years post-transplant (2.0 years after PTLD diagnosis).

**Conclusion:** Treatment of PTLD with rituximab with or without low-dose chemotherapy in combination with reduced immunosuppression, mostly comprising of an mTOR

**Abbreviations:** AZA, azathioprine; CNI, calcineurin inhibitor; CSA, cyclosporine A; DLBCL, diffuse large B-cell lymphoma; EBV, Epstein-Barr virus; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; EVR, everolimus; FSGS, focal-segmental glomerulosclerosis; HLA, human leukocyte antigen; KTx, kidney transplantation; mCOMP, modified cyclophosphamide, vincristine, methotrexate, prednisone; MMF, mycophenolate mofetil; MRI, magnetic resonance imaging; mTOR, mammalian target of rapamycin; PTLD, post-transplant lymphoproliferative disease; TAC, tacrolimus.

inhibitor-based, calcineurin inhibitor-free regimen, is associated with stable graft function and favorable graft survival in pediatric renal transplant patients.

**KEYWORDS**
immunosuppression, pediatric kidney transplantation, post-transplant lymphoproliferative disease, renal allograft function, rituximab

## 1 | INTRODUCTION

Post-transplant lymphoproliferative disorders (PTLD), first described in 1968 in recipients of kidney transplants, is a severe complication after solid organ transplantation.[1,2] In the era of modern post-transplant immunosuppressive strategies, 1–2% of all pediatric kidney transplant recipients are affected by this potentially fatal complication.[3,4] Kidney transplantation (KTx) is the preferred treatment option for children with end-stage renal disease (ESRD). More than 10,000 pediatric renal transplantations have been performed in the last 20 years in the United States alone. Long-term patient survival to date exceeds 80% at 10 years post-transplant.[5,6] Since PTLD in childhood is usually an early event occurring within the first two years post-transplant during the period of intense immunosuppression, the impact of immunosuppression on PTLD pathogenesis is well accepted. The cumulative incidence of PTLD increases with age and time post-transplant.[7-9] Therefore, PTLD significantly contributes to morbidity in long-term survivors of KTx, making prevention and early diagnosis of this complication a pivotal issue during long-term follow-up.[10,11]

The 2016 revision of the 2008 World Health Organization classification for lymphoid malignancies[12] separates PTLD into four major categories with B cell–derived polymorphic or monomorphic PTLD, mainly diffuse large B-cell lymphomas, constituting the most frequent subtypes. The accepted first-line treatment consists of reduction in immunosuppression, which may partly restore immune responses and hereby induce complete remission in some patients, although balancing immune reconstitution versus the risk of graft rejection is challenging. If reduction of immunosuppression is deemed impossible or insufficient, further therapy is required. The monoclonal anti-CD20 antibody rituximab is used routinely for all CD20-positive PTLD patients with promising results, either alone or in combination with cytotoxic chemotherapy.[13-15] Patients refractory to rituximab in combination with mild chemotherapy, patients with central nervous system involvement or patients with rare PTLD subtypes such as T-Non-Hodgkin's lymphoma or classical Hodgkin-type PTLD require specific treatment including chemotherapy with or without radiotherapy.[16-18] In a recent retrospective analysis of pediatric Hodgkin-type PTLD, 2-year overall survival was 86% after treatment with chemotherapy with or without radiotherapy.[19]

Graft rejection and loss of graft function are severe concerns against reduction of maintenance immunosuppressive therapy during treatment for PTLD. Data on renal allograft function in pediatric PTLD survivors are scarce. In a monocentric pilot study, we have demonstrated previously that renal allograft function after PTLD diagnosis remains stable during and after treatment with rituximab.[20] We now extended this analysis to a multicenter cohort of pediatric renal transplant patients treated for B-cell PTLD between the years 2004 and 2013. The aim of our study was to evaluate the course of renal allograft function after the first kidney transplantation and post-transplant lymphoproliferative disease for up to five years.

## 2 | PATIENTS AND METHODS

The study population consisted of 20 pediatric renal transplant recipients of six major university hospitals. Patient's data were recorded in the prospective German pediatric PTLD (Ped-PTLD) registry. The registry was approved by the institutional review boards of all contributing centers. Written informed consent was obtained from all parents/guardians to participate in the registry, with assent from patients when appropriate for their age. Inclusion criteria were history of renal transplantation during childhood and adolescence, biopsy-proven CD20+ PTLD, treatment with reduced immunosuppression and rituximab alone or in combination with low-dose chemotherapy, minimum follow-up of 12 months after PTLD diagnosis. The latter criterion excluded one patient with complete response to PTLD treatment, who was lost to follow-up due to immediate relocation abroad. Median age at transplantation was 7.5 years (range, 0.8 years to 15.3 years). All patients were transplanted between April 1999 and March 2011, while PTLD was diagnosed between February 2004 and February 2013. The primary renal diseases requiring transplantation were renal dysplasia ($n$ = 3), focal-segmental glomerulosclerosis (FSGS) ($n$ = 2), congenital nephrotic syndrome ($n$ = 2), Jeune syndrome ($n$ = 2), atypical hemolytic-uremic syndrome ($n$ = 2), and other ($n$ = 9). Eight patients were female and twelve male. Patient characteristics are shown in Table 1.

Post-transplant immunosuppressive regimen was based on cyclosporine A (CSA) in 8 patients and tacrolimus (TAC) in 12 patients. The calcineurin inhibitor (CNI) was combined with mycophenolate mofetil (MMF) in 11 patients, everolimus in 2 patients, and steroids in 18 patients. In all but one patient (patient #19), the immunosuppressive therapy was changed to an mTOR-based regime after PTLD diagnosis.

Data for calculation of renal function (creatinine, height, weight) were retrieved retrospectively from the patients records according to the following schedule: prior to PTLD ($n$ = 13), less than 6 months

**TABLE 1** Patients characteristics and histopathology of post-transplant lymphoproliferative disease, treatment regime and outcome

| Patient #ID | Onset of PTLD | Age at kidney Tx (years) | Gender | Kidney Tx to PTLD interval (months) | Polymorphic / monomorphic PTLD | Histopathology | PTLD treatment | Relapse |
|---|---|---|---|---|---|---|---|---|
| #1[a] | late | 13.6 | Female | 31 | Polymorphic | polymorphic B-cell PTLD | RIT×6 | no |
| #2[a] | early | 13.0 | Male | 8 | Monomorphic | DLBCL | RIT×6 | no |
| #3[a] | early | 12.5 | Male | 5 | Monomorphic | B-cell lymphoma, not further specified | RIT×6 | no |
| #4[a] | early | 0.8 | Female | 11 | Monomorphic | DLBCL | RIT×6 | no |
| #5 | early | 2.9 | Female | 8 | Polymorphic | polymorphic B-cell PTLD | RIT×6 | no |
| #6[a] | late | 8.8 | Male | 26 | Monomorphic | plasmablastic lymphoma | RIT ×6 | no |
| #7[a] | late | 3.5 | Male | 94 | Monomorphic | Burkitt lymphoma | RIT×4mCOMP×6 | no |
| #8[a] | early | 6.1 | Male | 6 | Monomorphic | DLBCL | RIT×6 | no |
| #9 | early | 15.3 | Male | 7 | Monomorphic | DLBCL | RIT×6 | no |
| #10 | early | 8.3 | Male | 6 | Monomorphic | DLBCL | RIT×6 | no |
| #11 | late | 4.3 | Male | 83 | Monomorphic | DLBCL | RIT×6 | yes 14 months after PTLD |
| #12 | late | 11.5 | Female | 39 | Monomorphic | DLBCL | RIT×5 mCOMP×6 | yes 2 months after PTLD |
| #13 | late | 3.8 | Male | 71 | Polymorphic | polymorphic B-cell PTLD | RIT×6 | no |
| #14 | late | 10.2 | Female | 78 | Monomorphic | DLBCL | RIT×6 | no |
| #15 | late | 6.7 | Male | 21 | Polymorphic | | RIT×6 | no |
| #16 | late | 2.7 | Female | 50 | Monomorphic | DLBCL | RIT×5 | no |
| #17 | early | 14.1 | Male | 10 | Monomorphic | DLBCL | RIT×6 | no |
| #18 | early | 1.8 | Female | 10 | Monomorphic | DLBCL | RIT×6 | no |
| #19 | very early | 3.4 | Male | 6 | Monomorphic | DLBCL | RIT×6 | no |
| #20 | early | 14.2 | Female | 7 | Monomorphic | DLBCL | RIT×6 | no |

Abbreviations: mCOMP, modified cyclophosphamide, vincristine, methotrexate, prednisone; PTLD, post-transplant lymphoproliferative disease; RIT, rituximab; Tx, transplantation. DLBCL, diffuse large B-cell lymphoma.

[a]Data of those patients included in Kanzelmeyer et al 2018.

after PTLD diagnosis ($n$ = 16), and 6 months ($n$ = 13), 12 months ($n$ = 17), 24 months ($n$ = 15), 36 months ($n$ = 14), 48 months ($n$ = 11), and 60 months after PTLD diagnosis ($n$ = 10). Estimated glomerular filtration rate (eGFR) was calculated according to the Schwartz formula.[21] Changes in eGFR during the follow-up period were calculated in percentage in comparison with the eGFR prior to manifestation of PTLD (baseline). All patients were monitored for acute or chronic rejection episodes as well as complete graft loss or re-transplantation, general medical condition, PTLD relapse, and overall survival. In addition, seven of 20 patients were monitored for donor-specific HLA antibodies (DSA). DSA were measured with the LAB Screen® Single Antigen assay, One Lambda, Meerbusch, Germany.

Data are given as mean ±standard deviation or $n$ (%) as appropriate or, if not normally distributed, as median (range). Differences of eGFR among the subgroups treated with a CNI-free or a CNI-based immunosuppressive regimen, those who received or did not receive chemotherapy in addition to rituximab and those with early-onset (<1-year post-transplant) versus late-onset PTLD (≥1-year post-transplant) were compared with the non-parametric Mann-Whitney $U$ test. The eGFR data at the different assessment time points were analyzed by range-based analysis of variance. All $p$-values <.05 were defined as statistically significant. Analyses were performed with the EBM SPSS® statistics software, version 25, AMOK, NY, USA.

## 3 | RESULTS

Twenty patients were identified from the Ped-PTLD registry who met the inclusion criteria (B-cell PTLD after KTx, survival for at least 1 year after PTLD diagnosis) for the current study. Diagnosis of PTLD was confirmed by histopathology and classified according to the WHO classification from 2008.[12] In 19 study subjects, possible tumor infiltration of the transplanted kidney was evaluated by magnetic resonance imaging after PTLD diagnosis. In 2 of these patients (10%; patient #3 and #8), a tumor infiltration was detected. The study cohort included 5 different histological types (Table 1). Sixteen of 20 patients (80%) suffered from monomorphic PTLD, while 4 patients (20%) had polymorphic PTLD. Tumors from 13 patients with monomorphic PTLD were classified as diffuse large B-cell lymphoma (DLBCL). The other three patients had plasmablastic lymphoma, Burkitt lymphoma, or B-cell lymphoma not further specified. The mean time to PTLD diagnosis was 2.4 ± 2.5 years (range, 0.4 years to 7.8 years). The mean patient age at PTLD diagnosis was 10.3 ± 4.8 years (1.8 to 16.7 years). Eleven patients (55%) developed an early-onset PTLD and 9 patients (45%) late-onset PTLD.

### 3.1 | Outcome after PTLD

Two patients (patients #11 and #12) showed a recurrence or progression of late-onset PTLD 14 and 2 months after primary PTLD diagnosis, respectively. Both patients were diagnosed as DLBCL by histopathology. They survived after second-line oncological treatment. No non-PTLD malignancies were recorded during the follow-up period. Overall patient survival up to 60 months after PTLD diagnosis was 100%.

### 3.2 | Treatment of PTLD

Treatment of PTLD consisted of a reduction in immunosuppressive therapy first line in all study patients. The immunosuppressive therapy in relation to the elapsed time since diagnosis of PTLD is shown in Table 2. Five patients participated in the prospective Ped-PTLD Pilot 2005 trial; the others received a similar treatment protocol outside of this trial. All patients with $CD20^+$ PTLD received three weekly administrations of rituximab (375 mg/m$^2$ body surface area (BSA)) followed by evaluation of early response. In case of complete or partial remission defined as more than 25% reduction in tumor volume, patients continued to receive rituximab every 3 weeks for a total of six administrations. Both patients with stable or progressive disease were switched to a moderate chemotherapy regime (vincristine 1.5 mg/m$^2$ BSA on day 1, cyclophosphamide 600 mg/m$^2$ BSA on day 1, prednisone 2 mg/kg body weight on days 1–5, and methotrexate 300 mg/m$^2$ BSA on day 15; repeat every 28 days for a total of six courses (mCOMP regime).

According to these criteria, 17 of twenty patients (85%) received the anti-CD20 antibody rituximab (375 mg/m$^2$ BSA) for a total of six doses, two patients (10%; patient #12 and #16) got five cycles of rituximab and one patient (5%; patient #7) received four cycles of rituximab. Furthermore, two of these patients (patients #7 and #12) required six cycles of the mCOMP chemotherapy regime in addition.

### 3.3 | Graft function after diagnosis of PTLD

Figure 1 shows the course of eGFR values of all individual study subjects over time. The mean eGFR at the last assessment prior to diagnosis of PTLD was 62.5 ± 23.5 ml/m (range 27 to 105; $n$ = 13 subjects) and directly after PTLD diagnosis 60.1 ± 24.4 ml/m (range 28 to 116; $n$ = 16). At 6 months, the mean eGFR increased to 72.2 ml/m ± 35.0 ml/m (range 35 to 162; $n$ = 13). The mean eGFR decreased to 59.2 ml/m ± 23.3 ml/m (range 35 to 106) ($n$ = 17) at 12 months, and remained stable at 24 months (60.7 ml/m), 36 months (59.5 ml/m), and 48 months (58.9 ml/m). The final mean eGFR in this analysis was 50.4 ± 24.0 ml/m (range 18 to 85; $n$ = 10) at 60 months after PTLD diagnosis. Range-based analysis of variance showed no significant changes in eGFR at 6 months, 1, 2, 3, 4, or 5 years after diagnosis of PTLD.

Immunosuppressive therapy of all study subjects in relation to the elapsed time since diagnosis of PTLD is shown in Table 2. All patients were on a CNI-based immunosuppressive regimen prior to diagnosis of PTLD. After a switch to an mTOR-based immunosuppressive regime in 15 of 20 patients, three of them required a change back to a CNI-based immunosuppression during follow-up, whereas the graft function of the remaining 17 patients was not

**TABLE 2** Immunosuppressive therapy in relation to the elapsed time since diagnosis of post-transplant lymphoproliferative disease

| Patient #ID | Prior to PTLD | <6 months after PTLD | 6 months after PTLD | 12 months after PTLD | 24 months after PTLD | 36 months after PTLD | 48 months after PTLD | 60 months after PTLD |
|---|---|---|---|---|---|---|---|---|
| #1 | CSA EVR | SIR steroids | SIR steroids | SIR steroids | SIR steroids | SIR steroids | SIR steroids | SIR |
| #2 | CSA steroids MMF | CSA steroids MMF | steroids MMF | steroids MMF | SIR steroids MMF | SIR steroids MMF | SIR steroids MMF | SIR steroids MMF |
| #3 | TAC steroids MMF | TAC steroids MMF | SIR steroids | SIR steroids | SIR steroids | SIR steroids MMF | MMF | TAC MMF |
| #4 | CSA steroids MMF | CSA steroids MMF | SIR steroids MMF | SIR steroids MMF | SIR steroids | SIR steroids | EVR | SIR steroids MMF |
| #5 | TAC steroids | TAC steroids | steroids | SIR steroids | SIR steroids | SIR steroids | SIR steroids | SIR steroids |
| #6 | TAC steroids | TAC steroids MMF | SIR steroids | SIR steroids | EVR steroids | EVR steroids | EVR steroids | SIR |
| #7 | CSA steroids MMF | CSA MMF | steroids | SIR steroids | SIR steroids | SIR steroids | SIR steroids | SIR |
| #8 | CSA steroids MMF | CSA steroids MMF | SIR steroids MMF | SIR steroids MMF | SIR steroids MMF | SIR steroids MMF | SIR | SIR steroids MMF |
| #9 | TAC steroids MMF | steroids MMF | steroids MMF | steroids MMF | steroids MMF | steroids MMF | EVR steroids MMF | EVR steroids MMF |
| #10 | CSA steroids MMF | SIR steroids | ND | ND. | ND. | ND | ND | ND |
| #11 | CSA steroids | CSA | ND | ND | EVR steroids | EVR steroids | ND | EVR steroids |
| #12 | CSA steroids | steroids | EVR steroids | EVR steroids | TAC steroids | TAC steroids | TAC steroids | TAC steroids |
| #13 | TAC MMF | MMF | steroids MMF | steroids MMF | steroids MMF | steroids MMF | steroids MMF | ND |
| #14 | TAC steroids MMF | steroids MMF | ND | TAC steroids MMF | TAC steroids MMF | ND | ND | . ND |
| #15 | TAC steroids others | TAC | ND | TAC | TAC | TAC | ND | ND |
| #16 | TAC EVR steroids | EVR steroids | EVR steroids | EVR | ND | EVR | EVR steroids | EVR steroids |
| #17 | TAC steroids MMF | TAC steroids MMF | steroids MMF | steroids MMF | EVR steroids MMF | EVR steroids MMF | TAC EVR | TAC EVR |
| #18 | TAC steroids AZA | TAC steroids AZA | ND | ND | CSA steroids MMF | ND | ND | CSA steroids MMF |
| #19 | TAC steroids MMF | steroids MMF | CSA steroids MMF | CSA steroids MMF | CSA steroids MMF | CSA steroids MMF | ND | CSA steroids MMF |
| #20 | TAC steroids | ND | EVR steroids | EVR steroids | ND | EVR steroids | ND | EVR steroids |

Abbreviations: AZA, azathioprin; CSA, cyclosporine A; EV, everolimus; MMF, mycophenolate mofetil; PTLD, post-transplant lymphoproliferative disease; SIR, sirolimus; TAC, tacrolismus.

compromised. In Figure 2, changes of eGFR in comparison with the level prior to PTLD diagnosis expressed as means are shown for the subgroups of patients who received CNI-based (n=7) or CNI-free immunosuppressive therapy ($n$ = 13). Three years after PTLD diagnosis, a statistical significant decrease of eGFR was observed between these two subgroups (Mann-Whitney U test, $p$ = .037). eGFR remained stable in patients on CNI-free immunosuppression, while it significantly decreased in patients on CNI-based therapy. At 5 years after PTLD, diagnosis change in eGFR compared to pre-PTLD values was similar in both groups.

Oncological treatment in the study subjects after diagnosis of PTLD is shown in Table 1. All patients were treated with 3 to 6 cycles of rituximab. Two patients required additional chemotherapy according to the mCOMP scheme whereas the other 18 patients went into remission by rituximab only. In Figure 3, changes of eGFR in comparison with the level prior to PTLD diagnosis expressed as means are shown for the subgroup of patients who received only rituximab versus those who additionally were treated with mCOMP chemotherapy. No difference of statistical significance was observed at any time between these two subgroups (Mann-Whitney $U$ test, $p$ > .25 at all timepoints.

Eleven patients were diagnosed with PTLD less than one year after transplantation (early onset) and 9 patients more than one year (late onset; Table 1). In Figure 4, changes of eGFR in comparison with the level prior to PTLD diagnosis expressed as means are shown for of patients with early-onset versus late-onset PTLD. No difference of statistical significance was observed at any time between these two subgroups (Mann-Whitney $U$ test, $p$ > .25 at all timepoints).

## 3.4 | Graft loss after diagnosis of PTLD

Two patients (10%) lost their kidney transplant in the post-PTLD course (patients #3 and #8). They suffered from graft rejection (patient #8) and recurrence of focal-segmental glomerulosclerosis (FSGS; patient #3), respectively. Despite adequate immunosuppressive treatment, patient #3 lost his graft 3.8 years after transplantation and 2.0 years after PTLD diagnosis. Patient #8 lost his kidney transplant 5.8 years after transplantation and 5.3 years after PTLD diagnosis. Both patients had early-onset PTLD. The remaining 18 kidney grafts were functioning at the last follow-up. In patient #3, successful re-transplantation was performed after 1.8 years of hemodialysis following the loss of his first kidney graft. The eGFR values during hemodialysis were excluded from the data analysis.

## 3.5 | Donor-specific HLA antibodies

Two of seven patients (29%), who were monitored for development of HLA-DSAs, developed de novo DSAs after treatment for PTLD. Patient #5 developed DSA against HLA-A2 (class 1) and HLA-DQ8 (class 2) 5 years after diagnosis of PTLD, this patient showed a decrease in GFR. In patient #7, DSAs against HLA-A2 (class 1) and

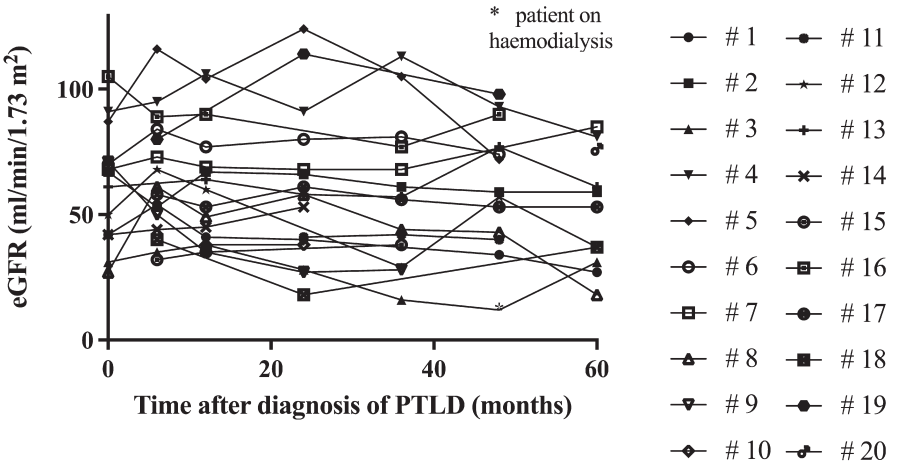


**FIGURE 1** Estimated glomerular filtration rate (eGFR) as calculated by Schwartz formula in relation to elapsed time after diagnosis of post-transplant lymphoproliferative disease (PTLD). Each symbol represents the course of eGFR of an individual patient

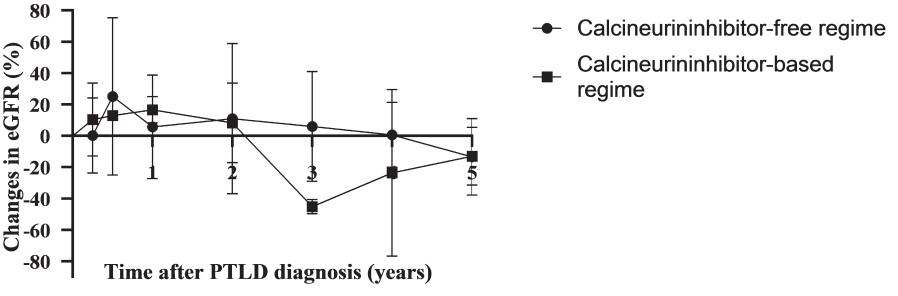


**FIGURE 2** Percentage changes in estimated glomerular filtration rate (eGFR) in PTLD patients treated with or without a calcineurin inhibitor (CNI) as maintenance immunosuppressive agent. Data represent mean ±standard deviation of each group

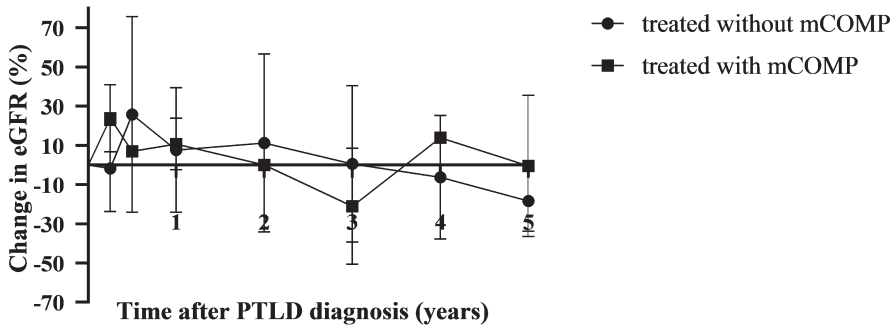


**FIGURE 3** Percent changes in estimated glomerular filtration rate (eGFR) in PTLD patients treated with rituximab and mCOMP compared to those with rituximab only. Data represent mean ±standard deviation of each group

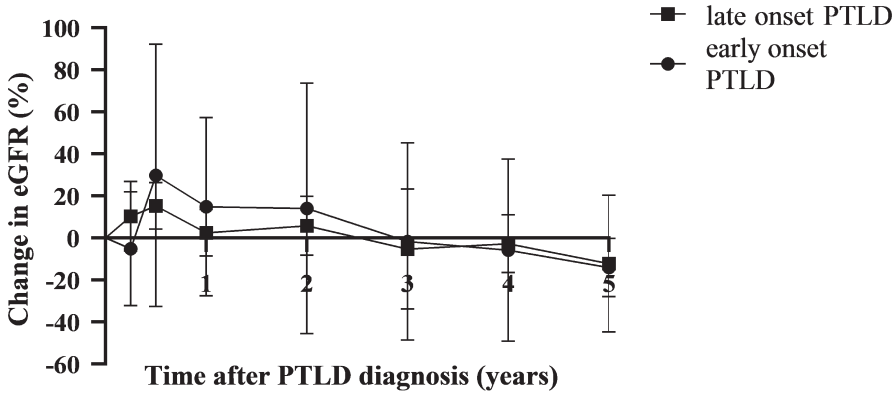


**FIGURE 4** Percent changes in estimated glomerular filtration rate (eGFR) in patients diagnosed with PTLD <and ≥ 1 year after transplantation, respectively. Data represent mean ±standard deviation of each group

HLA-DR7 (class 2) were diagnosed 3 years after PTLD diagnosis; however, this patient experienced stable to improved graft function.

## 4 | DISCUSSION

In our multicenter study, we analyzed renal graft function in 20 pediatric PTLD patients treated with rituximab alone or in combination with moderate chemotherapy. This is the largest cohort reported for graft function after a relatively uniform therapy regimen. While eGFR improved in most patients early after treatment for PTLD, there was a return to pre-PTLD values in most patients during the first follow-up year. Kidney function remained stable in the majority of patients during 4-year follow-up even though more than half of them remained on a CNI-free immunosuppressive regimen. Two patients experienced graft loss; one of them was successfully re-transplanted without recurrence of PTLD.

Children treated for ESRD have a significant increase in mortality compared to the general pediatric population. For such patients, kidney transplantation is the preferred renal replacement therapy. It provides many benefits over dialysis that include a significant survival advantage by extending life expectancy for children with end-stage kidney disease by many decades.[22-25] Therefore, pediatric patients with ESRD are even more than adults in urgent need to maintain the function of their graft to assure their uncompromised mental and physical development.

Successful treatment of PTLD aims at two major goals: to achieve complete remission of this lymphoproliferative malignancy as well as to avoid transplant rejection and to maintain the patient´s organ graft function. These therapeutic goals are sometimes difficult to combine. PTLD is generally believed to be a consequence of a relative immunodeficiency state secondary to immunosuppressive medications. Immunosuppressive therapy results in depressed T-cell function, which predisposes patients to viral infections and lymphoid proliferations. It is widely accepted that upon recognition of PTLD maintenance immunosuppression should be reduced, since PTLD occurs when immunosuppression creates conditions for failure of immune surveillance.[26] It has to be taken into account that a reduction of immunosuppression may lead to graft rejection, and careful titration of immunosuppression is required in these cases.[27] Hurwitz et al.´s retrospective analysis of 335 pediatric patients revealed that complete withdrawal of immunosuppressive therapy in their cohort of 19 PTLD patients reduced overall mortality, but was complicated by high rates of graft rejection (55%).[28]

In our study, all patients were on CNI-based immunosuppression prior to PTLD diagnosis. During treatment and follow-up, most patients were switched and remained on CNI-free immunosuppressive regimen, while 7 patients either continued CNI-based immunosuppression or were converted during follow-up. One patient of each subgroup developed a relapse suggesting that the risk of relapse may not be related to the composition of immunosuppressive maintenance therapy after adequate PTLD treatment although numbers are too small to draw definitive conclusions. Although no patient was primarily excluded due to early death of PTLD we observed a remarkably favorable course of PTLD among this limited number of patients, thus results should be verified in future clinical trials.

We could not detect any adverse impact of the reduction or modification of the maintenance immunosuppressive therapy on eGFR in our cohort as part of the PTLD treatment regime. In fact, eight of 20 patients showed an improvement in eGFR after completion of PTLD treatment (month 6). Although this increase in eGFR did not reach statistical significance, this may be attributed to either beneficial effects of rituximab on the alloimmune response against the renal allograft, stricter adherence to treatment by frequent hospital visits, beneficial effects of fluid management during administration of PTLD therapy, or improvement of the general medical condition. Infiltration of the graft by PTLD cells may occasionally contribute to function impairment at diagnosis and recovery during treatment. Also, cessation or reduction of CNI treatment may have contributed to eGFR improvement due to reduced renal toxicity. After comparing subgroups according to the composition of the immunosuppression regime (CNI-free versus CNI-based) or treatment with rituximab and mCOMP chemotherapy versus rituximab alone, respectively, no statistically significant difference in eGFR course could be demonstrated. In this retrospective analysis, however, we could not elucidate whether switch back to CNI-based immunosuppression may have been the result of an unstable graft function. Although the analysis is hampered by the small number of patients, this suggests that an initial modification of the immunosuppressive maintenance regimen, followed by rituximab or rituximab in combination with moderate chemotherapy with a consecutive immunosuppressive therapy according to the clinical requirements, seems to be a safe therapeutic regime for PTLD in regard to maintain a stable graft function in children.

In our cohort, only one patient (5%) lost his graft due to chronic allograft rejection 5.8 years after transplantation and 5.3 years after PTLD diagnosis, which is in accordance with recent reports.[23,25,29] A second patient developed recurrence of FSGS affecting the transplanted kidney and leading to graft loss.

The clinical spectrum of our cases of PTLD differed slightly from what is known: The median age at the time of PTLD was 10.3 years and therefore slightly higher than reported by others, the interval between transplantation and PTLD diagnosis was less than 12 months in only 55% of our pediatric PTLD cohort, with a mean of 2.5 years and therefore longer than reported in literature.[9,20,23,30]

Eleven patients in our study cohort were treated with an mTOR inhibitor (everolimus or sirolimus) as maintenance immunosuppression without CNI between 12 and 48 months after PTLD diagnosis. No significant difference of their eGFR course could be detected in our study compared to a CNI-based regimen, and none of those children experienced renal graft loss. These observations support recently published data that the introduction of everolimus as immunosuppressive agents after diagnosis and treatment of PTLD might be associated with a stable renal graft function.[31]

Despite providing the largest cohort on long-term renal graft function after PTLD in children, our study is hampered by the limited number of patients available. Data on graft function were retrieved retrospectively, leaving room for possible selection bias. Determination of eGFR by Schwartz formula is a widely accepted method for evaluating graft function; however, more objective measures like cystatin c or radionuclide clearance may be employed in future prospective evaluations.

## 5 | CONCLUSION

In conclusion, we presented data of a multicenter study performed in six university hospitals analyzing renal graft function in 20 cases of pediatric B-cell PTLD following PTLD diagnosis and treatment. Early improvement of graft function is observed in a substantial portion of patients. Reduction of immunosuppression including switch to a CNI-free regimen in conjunction with rituximab with or without moderate chemotherapy followed by mTOR inhibitor-based maintenance immunosuppressive therapy seems to be a safe therapeutic regime for pediatric KTx patients with PTLD. Resumption of CNI late in the post-PTLD course does not seem to influence relapse risk and may help to stabilize graft function. The results of this study should be explored in future larger multinational cohorts.

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### CONFLICT OF INTEREST

The authors have no conflict in interests to declare.

### AUTHOR CONTRIBUTIONS

HZ and BMK designed the research, analyzed the data, and wrote the manuscript. NK, AB, BH, CMK, BT, MM, MP, and LP provided patient data and helped drafting the manuscript. All authors read and approved the final version of the manuscript. The data that support the findings of this study are available from the corresponding author upon reasonable request.

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