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A single-centre experience of post-renal transplant lymphoproliferative disorder

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Abstract Post-transplant lymphoproliferative disorder (PTLD) complicates 1 to 10% of all transplantations. Previous clinicopathological studies of PTLD have been limited by small numbers, short follow-up times, outdated data, heterogeneity of pooled solid-organ transplant results, and selective inclusion of early-onset disease. We therefore undertake here a retrospective analysis and identify all cases of PTLD that complicated renal transplantation at the Princess Alexandra Hospital between 30 June 1969 and 31 May 2001. Tumour samples were subsequently retrieved for pathological review and for Epstein–Barr virus-encoded RNA in situ hybridisation (EBER-ISH). Of 2,030 renal transplantation patients, 29 (1.4%) developed PTLD after a median period of 0.5 years (range 0.1 to 23.3 years). PTLD patients were more likely to have received cyclosporine (76% versus 62%, $P < 0.05$), tacrolimus (10% versus 2%, $P < 0.05$) and OKT3 (28% versus 10%, $P < 0.01$). As the burden of immunosuppression increased from dual, to triple, to OKT3 therapy, the risks of early onset, extensive-stage, polymorphic, Epstein–Barr virus (EBV)-associated and fatal PTLD progressively increased. The majority of patients presented with an extranodal mass (45%), were afebrile (76%), and had stage-IV disease (60%). EBER-ISH was positive in 58%. Actuarial 5-year disease-free survival was 53.7%. The independent predictors of mortality on multivariate Cox regression were polymorphic histology (HR 7.4, 95% CI 1.5–37) and an international prognostic index (IPI) > 1 (HR 2.7, 95% CI 1.1–6.8). Compared with other treatments, chemotherapy was associated with higher survival rates (100% versus 18% at 3 years, $P = 0.0001$). In conclusion, PTLD is more likely, occurs earlier, and is more often fatal, in the setting of intensive immunosuppression. Nevertheless, excellent long-term outcomes are achievable with early recognition and institution of appropriate treatment.

Keywords Epstein–Barr virus · OKT3 · Organ transplantation · Post-transplant malignancy · Renal transplantation

Introduction

Post-transplant lymphoproliferative disorder (PTLD) is the commonest malignancy that complicates solid-organ transplantation after skin cancers [27]. It has been hypothesised that this complication arises from a combination of impaired immune tumour surveillance from anti-rejection therapy, chronic antigenic stimulation by the allograft, and Epstein–Barr virus(EBV)-induced lymphoproliferation [11, 12, 28]. Compared with malignant lymphomas in the general population, PTLD has been reported to occur 20 to 100 times more frequently in some transplant populations [33, 37, 38, 39] and to be associated with a very poor clinical outcome, with median survival times ranging between 5 and 14 months [22, 28]. However, these series have generally been limited by small numbers, short follow-up times, the pooling of heterogeneous data between multiple overseas transplant units, the reporting of cases prior to the advent of newer immunosuppressive agents, the combining of all solid-organ transplant data, the reporting of outcomes in the context of experimental or novel therapies, and/or inclusion of only early-onset PTLD (within several years of transplantation). The aim of the present study was to determine the histopathological findings, clinical course, and therapeutic outcomes of all patients who developed PTLD following renal transplantation at a single Australian centre.

Patients and methods

Patients

We undertook a retrospective chart review to identify all cases of PTLD that complicated renal transplantation at Princess Alexandra Hospital between 30 June 1969 and 31 May 2001. The clinicopathological features of the patients with PTLD were recorded and compared with those of the remainder of the transplant population. Affected patients were staged according to the Ann Arbor classification [5] following detailed clinical evaluation, chest radiography, bone marrow biopsy and aspiration, and, in most cases, computed tomography of the abdomen, pelvis, chest and head. Risk stratification was carried out by use of the International Prognostic Index (IPI) [1], based on age, tumour stage, serum lactate dehydrogenase concentration, performance status and number of extra-nodal disease sites.

Immunosuppressive protocols

Before 1983, standard immunosuppression was achieved with azathioprine 2 mg/kg and prednisone 0.3 mg/kg daily. Cyclosporine (4 mg/kg b.d.) was administered on a trial basis from 1983 on, and, routinely, as part of a three-drug regimen at a dose of 2.5 mg/kg b.d. with diltiazem) in combination with azathioprine and prednisone after December 1984. In January 1995, mycophenolate mofetil (1 g b.d.) replaced azathioprine. A small number of patients also received tacrolimus as part of a clinical trial between 1998 and 2001. The first-line treatment of acute rejection was usually three consecutive daily 1,000-mg doses of intravenous methylprednisolone, whilst Orthoclone OKT3 (muromonab-CD3; 5 mg daily for 7–10 days) was reserved for cases of steroid-refractory or severe (usually vascular) rejection.

Histopathology

Biopsy specimens were fixed in formalin, embedded in paraffin and stained with haematoxylin and eosin and with Giemsa. All slides were reviewed by one pathologist (D.N.). Polymorphic PTLD was classified according to the criteria of Frizzera et al. [9], whilst the categorisation of monomorphic PTLD was based on the World Health Organization classification [16]. The presence of EBV-encoded RNA in tumour samples was determined by in situ hybridisation (EBER-ISH), according to the method described by Hummel et al. [19].

Treatment and response

Upon diagnosis of PTLD, the therapeutic approach varied, dependent on the extent of disease and the histological classification. Immunosuppression was reduced in all cases. This reduction generally involved the cessation of azathioprine or mycophenolate mofetil, reduction of calcineurin inhibitors by at least 50%, and the decreasing of prednisone dosage to 7 mg daily or below. Thereafter, patients with limited stage disease were generally treated with surgical resection or local radiotherapy, whilst patients with more extensive disease were treated with systemic therapies. The implication of EBV in the pathogenesis of PTLD prompted a trial of antiviral therapy for all newly diagnosed cases of PTLD in the late 1980s and early 1990s. Sub-optimal response to this treatment led to the introduction of a more aggressive combination of chemotherapy, including CHOP [26], modified HyperCVAD [21] or the Hoelzer regimen [18], with one patient additionally receiving rituximab as consolidation therapy.

A complete remission was defined as the disappearance of all known signs of disease, as determined by two observations at least 4 weeks apart [49]. Partial remission was defined as reduction in total tumour size by at least 50%. Patients with tumours that had decreased in size by $\leq 50\%$ or increased by $\leq 25\%$ were said to have stable disease. Patients were considered to have progressive disease if there was at least a 25% increase in the size of one or more measurable lesions or the appearance of new lesions.

Statistical analysis

Data distribution was assessed with the Kolmogorov–Smirnov test with Lilliefor's correction. Continuous variables were expressed as mean ($\pm$SEM) for normally distributed data or median (range) for non-parametric data. Categorical data were expressed as frequencies and percentages. Differences between groups were determined by either Student's *t*-test or the Mann–Whitney test (depending on data distribution) for continuous variables, and the chi-square test for discrete variables. Independent predictors of early (<2 years) onset of PTLD were determined by logistic regression. Survival curves and survival probabilities were generated in accordance with the Kaplan–Meier method. Survival was defined as the time from diagnosis of PTLD to either death or the end of the survey period, at which point data were censored. A multivariate Cox's proportional hazards model was also applied. It included age, gender, IPI score, polymorphic histology, EBER-ISH positivity and exposure to Orthoclone OKT3, cyclosporine, azathioprine and intravenous methylprednisolone as covariates. A backward elimination procedure was carried out with removal testing based on the probability of the Wald statistic until the most parsimonious model was identified. Adjusted survival curves were estimated with the Cox

Table 1 Causes of end-stage renal disease in PTLD patients and the remainder of the renal transplant population. Results are expressed as number (percentage) within each group. There were no significant differences between the two groups

Renal disease	PTLD group ($n=29$)	Other transplant patients ($n=2,030$)
Chronic glomerulonephritis	14 (48.3)	818 (40.3)
Reflux nephropathy	5 (17.2)	228 (11.2)
Polycystic kidney disease	3 (10.3)	197 (9.7)
Analgaesic nephropathy	2 (6.9)	261 (12.9)
Diabetes mellitus	3 (10.3)	93 (4.6)
Urolithiasis	0 (0)	10 (0.4)
Interstitial nephritis	1 (3.4)	19 (0.9)
Lead nephropathy	1 (3.4)	37 (1.8)
Renovascular nephrosclerosis	0 (0)	83 (4.0)
Other cystic renal disease	0 (0)	36 (1.8)
Other	0 (0)	248 (12.2)

average covariate method, which calculated predicted survival probabilities at the mean levels of the covariates. Data were analysed with the software program, SPSS for Windows release 10.0.5 (SPSS, North Sydney, Australia). P values less than 0.05 were considered to be statistically significant.

Results

Demographic data

From a total of 2,030 renal transplant recipients, 29 (1.4%) with PTLD were identified. Two PTLD patients had received a second graft. The risk of a patient's developing PTLD increased in proportion to the burden of immunosuppression received (dual therapy 1.1% versus triple therapy 1.7% versus OKT3 therapy 3.7%, $P<0.05$). The median age of cases at the time of transplantation was 39 years (range 19 to 65 years), which was similar to the median age of 44 years (range 2 to 73 years) for the overall population at the time of transplantation ($P=$ NS). The proportion of male patients in the PTLD group (69%) tended to be higher than in the remainder of the transplant population (58%, $P=$ NS). The distribution of causes of end-stage renal failure was similar between PTLD patients and the rest of the transplant population (Table 1). The median time from transplant to diagnosis of PTLD was 0.5 years (range 0.1 to 23 years) (Fig. 1). The median length of follow-up after the diagnosis of PTLD was 0.7 years (range 0.1 to 17 years).

Immunosuppression

The distributions of immunosuppressive therapy in the PTLD and source renal transplant populations are shown in Table 2. The influence of immunosuppression on PTLD clinical stage, histology, EBER-ISH positivity and therapeutic outcome are displayed in Table 3. Compared with the remainder of the transplant population, patients who developed PTLD were more likely to have received cyclosporine (76% versus 62%, $P<0.05$), tacrolimus (10% versus 2%, $P<0.05$) or Orthoclone OKT3 (28% versus 10%, $P<0.01$). As the burden of immunosuppression increased from dual therapy (prednisolone plus azathioprine) to triple therapy (cyclosporine/tacrolimus plus azathioprine/mycophenolate mofetil plus prednisolone) to dual/triple therapy plus OKT3, there were significant reductions in PTLD onset and survival together with significant increases in IPI scores and the frequencies of polymorphic histology and EBER-ISH positivity (Table 3, Fig. 1). Using logistic regression, we found that the only significant independent predictor of the development of PTLD within 2 years of transplantation was exposure to OKT3 (HR 22.8, 95% CI 2.1–245, $P=0.01$).

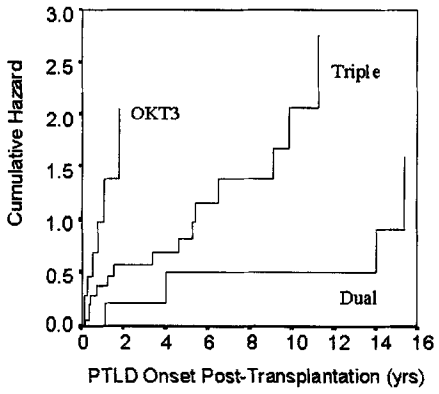

Fig. 1 Cumulative hazard plot of effect of immunosuppression burden on PTLD onset. *Dual* combination of azathioprine and prednisolone (no OKT3 exposure), *Triple* combination of a calcineurin inhibitor (cyclosporine or tacrolimus), DNA synthesis inhibitor (azathioprine or mycophenolate mofetil) and prednisolone (no OKT3 exposure). The differences between the groups were statistically significant (log rank score 11.2, $P<0.01$)

Table 2 Distribution of immunosuppressive therapy in PTLD patients and the remainder of the renal transplant population. Most patients received more than one agent. Results are expressed as number (percentage) within each group. *NA* not available, *NS* not significant

Agent	PTLD Group ($n=29$)	Other ($n=2,030$)	P
Cyclosporine	22 (75.9)	1,262 (61)	<0.05
Azathioprine	24 (82.8)	1,690 (83.6)	NS
Mycophenolate mofetil	5 (17.2)	293 (14.4)	NS
Sirolimus	0 (0)	41 (2.0)	NS
Tacrolimus	3 (10.3)	51 (2.5)	<0.05
Methylprednisolone	16 (55.2)	NA	NA
Anti-thymocyte globulin	3 (10.3)	212 (10.4)	NS
OKT3	8 (27.6)	208 (10.2)	<0.01

Table 3 Effect of prior exposure to immunosuppressive agents on PTLD characteristics ($n=29$). *Dual therapy* patients treated with the combination of azathioprine and prednisolone (no OKT3 exposure). *Triple therapy* patients treated with the combination of a calcineurin inhibitor (cyclosporine or tacrolimus), DNA synthesis inhibitor (azathioprine or mycophenolate mofetil) and prednisolone (no OKT3 exposure). *OKT3* any patient with PTLD who had previously received Orthoclone OKT3

Agent	*n*	Median onset (years)	Median IPI score	Stage-IV disease (%)	EBER-ISH positivity (%)	Polymorphic histology (%)	Complete remission (%)	Mean survival (years)
Dual therapy	5	14	0.5	40	0	0	80	11
Triple therapy	16	4.0	2	50	64	7	67	6.4
OKT3	8	0.5	3	88	75	50	25	0.1

Clinical presentation

Thirteen (45%) patients presented with an extra-nodal mass, whilst the remaining individuals presented with cytopenia (four, 14%), bowel obstruction (three, 10%), febrile illness (three, 10%), renal failure (three, 10%), lymphadenopathy (two, 7%) and respiratory failure (one, 3%). Fever was not a prominent early feature of PTLD and was evident in only seven (24%) patients. Four (17%) patients died before their disease could be adequately staged. In the remaining 25 patients, the majority presented with extensive disease (stage IV, 60%; stage III, 12%; stage-II disease, 4%, stage I, 24%). From binary logistic regression, it was found that the only independent predictor of stage-IV disease was OKT3 treatment (HR 10.5, 95% CI 1.02–109, $P<0.05$). There was no significant effect of age, gender, histology, EBER-ISH positivity or other immunosuppressive agents on clinical stage.

Histology

Histological specimens were reviewed for 27 patients. Of these, 22 (82%) had monomorphic PTLD and five (18%) had polymorphic PTLD. Eighty-one percent were of B-cell origin. The bulk of patients had diffuse large B-cell lymphoma (13, 48%), whilst the remainder had polymorphic PTLD (five, 17%), follicular non-Hodgkin's lymphoma G1 (two, 7%), T cell-rich B cell non-Hodgkin's lymphoma (one, 4%), and mucosa-associated lymphatic tissue lymphoma (one, 4%). Nineteen percent were of T-cell origin, including anaplastic large cell lymphoma (T cell, two, 7%), $\delta\gamma$-lymphoproliferation (one, 4%), peripheral T-cell lymphoma (one, 4%) and T cell cutaneous lymphoma (one, 4%). The only independent predictor of histology was prior OKT3 therapy, which was significantly associated with polymorphic PTLD (RR 20, 95% CI 1.7–229, $P<0.05$). EBER-ISH studies were positive in 15 (58%) of the 26 tumours that were evaluated.

Treatment

In all cases, immunosuppression was significantly reduced and did not result in either rejection or graft loss. Thereafter, the treatments for PTLD included high-dose acyclovir, local excision, combination chemotherapy and/or radiotherapy, dependent on the extent and type of PTLD (Table 4). Overall, 17 (59%) patients experienced complete remission, one (3%) had stable disease, four (14%) developed progressive disease culminating in death and seven (24%) died before therapy could be commenced. Patients who experienced complete remission to therapy were significantly more likely to be younger than the median age of 42 years (92% versus 38%, $P<0.05$), have an IPI score of 0 or 1 (100% versus 50%, $P<0.05$) and have no prior exposure to OKT3 (88% versus 50%, $P=0.05$). There were no significant differences between responders and non-responders in terms of gender, histology or prior treatment with cyclosporine or intravenous methylprednisolone. In the only patient who relapsed twice, the initial treatment consisted of reduced immunosuppression and involved field radiation. At first relapse, complete remission was attained with eight cycles of CHOP chemotherapy and further reduction in immunosuppression. After the second relapse, immunosuppression was ceased and further CHOP chemotherapy was administered.

Survival

A total of 13 patients (45.8%) who had been diagnosed with PTLD died. The cause of death was unrelated to PTLD in two patients (one myocardial infarction, one carcinoma of the stomach). The actuarial 5-year disease-free survival for patients who developed a PTLD was 53.7%. Survival was significantly worse in patients with previous OKT3 exposure (25.0% versus 76.2% at 2 years, $P<0.05$) (Fig. 2), early-onset (within 2 years) PTLD (40.0% versus 85.7% at 2 years, $P<0.05$), an IPI score greater than 1 (47.1% versus 100% at 2 years, $P=0.01$) and polymorphic histology (0% versus 75% at

Table 4 Summary of therapeutic interventions instituted for treatment following diagnosis of PTLD. Some patients received more than one therapeutic modality. The chemotherapy regimens included *CHOP* [26], Hyper-CVAD [21] and Hoelzer [18]. *NA* not available; *FNHL* follicular non-Hodgkin's lymphoma; *MALT* mucosa-associated lymphatic tissue lymphoma, *ALCL* anaplastic large cell lymphoma, *DLBCL* diffuse large B-cell lymphoma, *δγ*-LP *δγ*-lymphoproliferation, *XRT* radiotherapy

Age	Histology	Antiviral	Chemotherapy	XRT	Excision	Outcome
52	NA	–	–	–	–	Died before therapy
62	FNHL	–	–	–	–	Stable
47	MALT	–	–	–	–	Complete remission
27	Polymorphic	–	–	–	–	Died before therapy
37	ALCL	–	–	–	–	Died before therapy
34	DLBCL	–	–	–	–	Died before therapy
51	NA	–	–	–	–	Died before therapy
44	DLBCL	–	–	–	–	Died before therapy
33	Polymorphic	–	–	–	–	Died before therapy
60	T cell (skin)	–	–	✔	✔	Complete remission
49	DLBCL	–	CHOP ×6	–	–	Complete remission
36	*δγ*-LP	–	Hyper-CVAD	–	✔	Complete remission
49	BNHL	–	CHOP ×6	–	–	Complete remission
30	DLBCL	–	CHOP ×8	–	✔	Complete remission
42	DLBCL	–	CHOP ×6	–	–	Complete remission
27	Peripheral T	–	Hoelzer regimen	–	✔	Complete remission
24	ALCL	–	CHOP ×6	–	–	Complete remission
23	FNHL	–	CHOP ×6	–	✔	Complete remission
36	DLBCL	–	CHOP ×6	–	–	Complete remission
45	DLBCL	–	CHOP ×6	–	–	Complete remission
30	DLBCL	–	CHOP ×6	–	–	Complete remission
51	DLBCL	–	CHOP ×8 then CHOP ×6	✔	✔	Complete remission
35	DLBCL	–	CHOP ×6 + rituximab ×4	✔	✔	Complete remission
39	DLBCL	–	CHOP ×6	✔	✔	Complete remission
65	DLBCL	✔	–	–	–	Progressive disease
22	Polymorphic	✔	–	–	✔	Progressive disease
43	Polymorphic	✔	–	–	–	Progressive disease
42	Polymorphic	✔	–	–	–	Progressive disease
19	DLBCL	✔	CHOP ×6	–	–	Complete remission

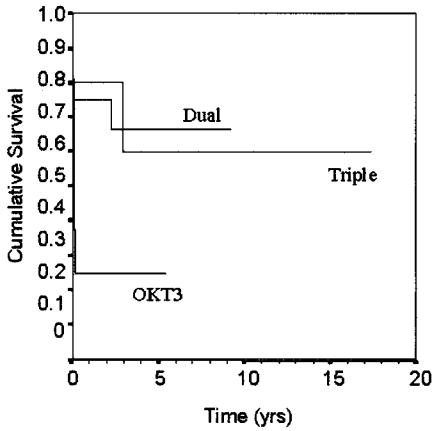

Fig. 2 Kaplan–Meier survival curve for PTLD patients previously treated with dual, triple or OKT3 immunosuppression. Patients with PTLDs in the setting of prior OKT3 exposure fared significantly worse than the other patients (log rank score 4.6, $P<0.05$)

2 years, $P<0.001$). Using a multivariate Cox's proportional hazards model, we found that the only significant independent predictors of mortality were IPI score (adjusted hazard ratio 2.7, 95% confidence limits 1.1 to 6.8, $P<0.05$) and polymorphic histology (adjusted hazard ratio 7.4, 95% CI 1.5–37, $P<0.05$). If we excluded those seven patients who died before treatment could be commenced, we found that treatment with combination chemotherapy was associated with a significantly better survival (100% versus 17.6% at 2 years, $P=0.0001$).

Discussion

The present report represents the largest series to date of PTLDs that complicated renal transplantation. The overall prevalence of PTLD was 1.4%, which is similar to that reported in the literature [22, 30, 33, 39]. The risk of PTLD increased substantially as the burden of immunosuppression increased from dual to triple to OKT3 therapy. More intense immunosuppressive regimens were also significantly more likely to be associated with earlier onset, EBV-associated PTLD with high mortality rates. In spite of this, the actuarial 5-year disease-free survival rate of PTLD at our hospital was excellent (53.7%).

This observed survival rate is appreciably higher than those reported by other centres. In a retrospective review of 24 PTLDs that had complicated 1,385 solid-organ transplants, Leblond et al. [22] described a median survival of only 5 months. Similarly, Morrison and associates [28] found a median survival of 14 months in 26 solid-organ (mostly renal) transplant recipients with PTLD. Their reported survival, however, was an overestimate, since they excluded 12 patients with PTLDs

who were either diagnosed at post-mortem or who died shortly after diagnosis. Other groups have observed mean survival rates of 18.7 ± 0.6 months [36] and 1 year [32, 34]. The lower survival rates in these studies than those of the present investigation may reflect the reliance on more intensive immunosuppression in the former, since most of these studies used higher dosages of cyclosporine in their initial anti-rejection therapy, and many routinely employed prophylactic OKT3 or anti-thymocyte globulin induction protocols.

As with other studies, we found that the use of calcineurin inhibitors and/or OKT3 were associated with a greatly increased risk of early onset, extensive-stage and fatal PTLD [22, 39, 43, 47, 48]. Penn [37, 39] reported that the mean lag times between solid-organ transplantation and PTLD diagnosis were 7 months in the OKT3 group, 15 months in the cyclosporine group and 48 months in the azathioprine/cyclophosphamide group. In cardiac transplant recipients, Swinnen et al. [47] noted a ninefold increase in the incidence, and a much earlier occurrence of B-cell PTLDs following OKT3 therapy. However, other investigators [3] have not been able to confirm a high incidence and early onset of PTLDs in OKT3-treated transplant recipients. Moreover, Mihalov et al. [27] did not observe a significant effect of the withdrawal of prophylactic OKT3 from the immunosuppression regimen of heart transplant recipients on the subsequent incidence of PTLD. Similarly, although several authors [39, 43, 48] have noted an increase in the frequency and a reduction in the time interval to onset of PTLD in cyclosporine-treated patients, these observations have been refuted by other studies [10]. The negative findings of these studies may be explained by a combination of organ transplant heterogeneity, small numbers, short follow-up times and high background immunosuppression.

The association that is demonstrated in the present study, between the total burden of immunosuppression and the frequency, latency, stage, EBER-ISH positivity and mortality of PTLD, fits in well with the identified pathogenetic role of EBV [6, 11,12, 13, 14, 15, 17, 24, 25, 40, 42]. In our study, 58% of tumours demonstrated EBV-encoded RNAs (EBER-1 and EBER-2) on in situ hybridisation. These results are markedly similar to those reported by Leblond and associates [23] who found that in 59% of their patients with PTLD, the disorder was EBV-associated. Most (76%) of the EBV-positive tumours occurred early (within 2 years of transplantation), which again is in concordance with our findings (60%). In contrast, other in situ hybridisation studies have demonstrated that over 90% of all PTLDs have detectable EBV genomes within the transformed B cells [11, 12, 40]. The potential reasons for the disparity in our observations may relate to smaller patient numbers, the pooling of solid-organ transplant PTLDs, and selective inclusion of only early-onset PTLD in the latter studies.

The implication of EBV in most PTLDs has prompted the use of antiviral therapy, such as high-dose acyclovir. Although there is some anecdotal support for this strategy [13, 28, 36, 44, 45, 46], acyclovir was associated with disappointing outcomes in both our study and in those of other investigators [14, 22, 31]. This may be due to the fact that antiviral drugs only inhibit viral replication in productive cells and do not affect episomal EBV in non-productive, transformed lymphocytes [22]. Such limitations may be more effectively addressed by emerging therapies, which include recombinant interferon-alpha plus immunoglobulin [31, 41], interleukin-2 [2, 20], anti-CD20 monoclonal antibodies [4, 8, 22, 46], infusions of donor leukocytes [35] and immunotherapy with autologous lymphokine-activated killer cells [29].

The impetus to trial newer anti-viral treatments has been provided by early reports in the literature, which indicated that conventional combination chemotherapy and/or radiotherapy were ineffective in the setting of PTLD. For example, Morrison et al. [28] reported a complete remission rate of only 31% in PTLDs treated by surgery or radiotherapy and 11% in PTLDs treated with chemotherapy. Leblond and associates [22] observed a cure rate of 20% in PTLD patients treated with chemotherapy. Similarly, Cohen [7] described survival rates of 23% for cytotoxic chemotherapy and 20% for radiotherapy in the setting of PTLD. These findings contrast markedly with those of the present study, where chemotherapy and/or radiotherapy was associated with complete remission in 100% of cases, with no recorded fatalities due to PTLD to date. The discrepancy may be accounted for by the fact that the other studies generally resorted to chemo-radiotherapy only after a failed response to immunosuppression reduction and antiviral therapy. Thus, timely initiation of standard lymphoma treatment may have been crucial to our achieving the excellent survival rates in our series.

In conclusion, PTLDs complicated 1.4% of renal transplants performed at our centre over a 30-year period. The risk of PTLD was increased nearly threefold in patients who were exposed to Orthoclone OKT3. As the burden of immunosuppression increased from low (dual therapy) to intermediate (triple therapy) to high levels (OKT3), the risks of early onset, extensive-stage, polymorphic, EBV-associated and fatal PTLD progressively increased. Although various treatment methods were employed, the highest complete remission rate was attained with reduced immunosuppression and combination chemotherapy. The early institution of such treatment appeared to be critical to our achieving long-term successful outcome. Nevertheless, there is a pressing need for the development of more effective therapeutic strategies for dealing with OKT3-associated, early-onset, polymorphic PTLD, which continues to have a bleak prognosis.

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