

## POSTTRANSPLANT LYMPHOPROLIFERATIVE DISORDERS IN ADULT AND PEDIATRIC RENAL TRANSPLANT PATIENTS RECEIVING TACROLIMUS-BASED IMMUNOSUPPRESSION<sup>1</sup>

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Between March 27, 1989 and December 31, 1997, 1316 kidney transplantations alone were performed under tacrolimus-based immunosuppression at our center. Posttransplant lymphoproliferative disorders (PTLD) developed in 25 (1.9%) cases; the incidence in adults was 1.2% (15/1217), whereas in pediatric patients it was 10.1% (10/99;  $P < .0001$ ). PTLD was diagnosed  $21.0 \pm 22.5$  months after transplantation,  $25.0 \pm 24.7$  months in adults and  $14.4 \pm 18.2$  months in pediatric patients. Of the 4 adult cases in whom both the donor and recipient Epstein Barr virus (EBV) serologies were known, 2 (50%) were seropositive donor  $\rightarrow$  seronegative recipient. Of 7 pediatric cases in whom both the donor and recipient EBV serologies were known, 6 (86%) were EBV seropositive donor  $\rightarrow$  seronegative recipient. Acute rejection was observed before the diagnosis of PTLD in 8 (53%) of 15 adults and 3 (30%) of 10 pediatric patients. Initial treatment of PTLD included a marked decrease or cessation of immunosuppression with concomitant ganciclovir therapy; two adults and two pediatric patients required chemotherapy. With a mean follow-up of  $24.9 \pm 30.1$  months after transplantation, the 1- and 5-year actuarial patient and graft survival rates in adults were 93% and 86%, and 80% and 60%, respectively. Two adults died, 3.7 and 46.2 months after transplantation, of complications related to PTLD, and 10 (including the 2 deaths) lost their allograft 3.7-84.7 months after transplantation. In children, the 1- and 5-year actuarial patient and graft survival rates were 100% and 100%, and 100% and 89%, respectively. No child died; one child lost his allograft 41.3 months after transplantation. One child had presumed recurrent PTLD that responded to discontinuation of tacrolimus and reinitiation of antiviral therapy. The mean serum creatinine level in adults was  $2.5 \pm 1.2$  mg/dl, and in children, it was  $1.3 \pm 0.6$  mg/dl. Under tacrolimus-based immunosuppression, PTLD is less common after renal transplantation in

adults than in children, but PTLD in children is associated with more favorable outcomes than in adults.

Among the many possible complications that can occur after renal transplantation, the development of posttransplant lymphoproliferative disorder (PTLD\*) is one of the most worrisome. As a manifestation of overimmunosuppression, it represents an important, if uncommon problem. It was first described as a complication of azathioprine-based therapy (1-5) and later with cyclosporine-based therapy (6-8), so that it is not surprising that it has also been seen with the new immunosuppressive agents that have become available over the past several years. Tacrolimus, one of these new agents, has been used extensively in our program. It has been associated with improved primary and secondary outcomes in both adult and pediatric kidney recipients (9-14). However, particularly in pediatric patients, there has been a significant (although declining) incidence of PTLD (13, 14). Given the relatively large number of patients receiving tacrolimus, we thought it would be worthwhile to review the incidence of PTLD in our adult and pediatric renal transplant recipients. The purpose of this analysis was to get a sense of how common or uncommon a problem PTLD has been, and to evaluate the outcomes associated with its occurrence.

### PATIENTS AND METHODS

Between March 27, 1989, and December 31, 1997, 1316 kidney transplantations alone were performed under tacrolimus-based immunosuppression at our center, 1217 in adults and 99 in children (Table 1). The details of immunosuppressive management with tacrolimus-based therapy have been previously described (9-14) and were not markedly different in the patients who did or did not develop PTLD. Very few patients (<5%) have received antibody induction in our program. The numbers of adults and children who developed PTLD were taken from an in-house computerized database that has recorded the cases of PTLD on an ongoing basis. The incidence, recipient age, transplant number, donor status, cold ischemia time, mean time to diagnosis, donor and recipient Epstein Barr virus (EBV) serologic status (where known), and the incidence of rejection before the development of PTLD were tabulated. In addition, the histopathology of the cases of PTLD, their treatment, the patient and graft survival rates, and the serum creatinine levels in the surviving patients with functioning allografts were analyzed.

\* Abbreviations: CMV, cytomegalovirus; EBV, Epstein Barr virus; PTLD, posttransplant lymphoproliferative disorder.

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TABLE 1. Patients and incidence

	Kidney transplantation	PTLD	
Total	1,316	25 (1.9%)	
Adult	1,217	15 (1.2%)	$> P < 0.001$
Pediatric	99	10 (10.1%)	
		3/89-12/92-7/29 (24.1%)	$> P < 0.003$
		1/93-12/97-3/70 (4.3%)	

## RESULTS

**Incidence and demographics.** There were 25 (1.9%) cases of PTLD in the entire group of 1316 patients undergoing kidney transplantation (Table 2). Of 1217 adults and 99 pediatric patients, 15 (1.2%) and 10 (10.1%), respectively, developed PTLD ( $P < .0001$ ). Although the adult incidence remained low and relatively constant over time, the pediatric incidence declined substantially. Five early (1 year or less after transplantation) and 2 late ( $> 3$  years) cases of PTLD were seen in the first 29 patients (24.1%) who underwent transplantation between March 1989 and December 1992, and 3 early cases of PTLD were seen in the 70 patients (4.3%) who underwent transplantation between January 1993 and December 1997 ( $P < .003$ ).

The mean adult recipient age was  $46.4 \pm 12.7$  years (range 29.2-76.6). Four (26.7%) were undergoing retransplantation, none had a panel-reactive antibody over 40%, and 1 (6.7%) received a kidney from a living donor (a 0 antigen-match sister). The mean cold ischemia time (for the cadaveric cases) was  $31.8 \pm 8.8$  hr (range 18.0-50.6) (Table 2).

The mean pediatric recipient age was  $9.0 \pm 4.5$  years (range 3.1-16.2). One (10%) child was undergoing retransplantation, none had a panel-reactive antibody over 40%, and 6 (60%) received kidneys from living donors (4 parents, 1 grandmother, and 1 adopted father). The mean cold ischemia time was  $24.8 \pm 8.6$  hr (range 17.2-35.9) (Table 2). The demographics of the adults and children who developed or did not develop PTLD were generally similar (9-14).

PTLD was diagnosed  $21.0 \pm 22.5$  months after transplantation,  $25.0 \pm 24.7$  months (range 2.7-78.5) in adults and  $14.4 \pm 18.2$  months (range 3.6-51.8) in children. In 4 adult cases, the donor and recipient EBV serologies were known; 2 (50%) were seropositive donor  $\rightarrow$  seronegative recipient. In 7 pediatric cases, 6 (86%) were seropositive donor  $\rightarrow$  seronegative recipient. Biopsy-proven acute rejection was documented in 8 (53%) of 15 adults and 3 (30%) of 10 children before the diagnosis of PTLD. Except where noted above, these numbers were too small to allow for meaningful statis-

TABLE 2. Demographics

	Adult	Pediatric
Recipient age (yr)	$46.4 \pm 12.7$	$9.0 \pm 4.5$
Range	29.2-76.6	3.1-16.2
Retransplantation	4 (26.9%)	1 (10%)
Panel-reactive antibody $> 40\%$	0	0
Cold ischemia time (hr)	$31.8 \pm 8.8$	$24.8 \pm 8.6$
Living donors	1 (6.7%)	6 (60%)
Time of diagnosis (months after transplantation)	$25.0 \pm 24.7$	$14.4 \pm 18.2$
EBV --- (where known)	2/4 (50%)	6/7 (86%)
Rejection (before diagnosis of PTLD)	8/15 (53%)	3/10 (30%)

tical comparison. The clinical presentation of PTLD was variable and ranged from asymptomatic cervical adenopathy to vague gastrointestinal complaints to fulminant multisystem organ failure.

**Histopathological examination of PTLD.** Surgical pathology reports were reviewed. PTLDs were categorized according to the classification recommended by the American Society of Hematopathology (15). Of the 25 patients, 15 had monomorphic PTLD, 5 had polymorphic PTLD, and in 2 cases the tumors had a plasmacytoma-like appearance. In the remaining three cases the lesions had features of infectious mononucleosis with areas of polymorphic PTLD. These were considered to represent low-grade tumors, which had evolved from EBV infection. Two of these low-grade PTLDs arose in pediatric patients, and the third was in an adult. Of the monomorphic tumors, seven were not further characterized due to necrosis, small sample size, or unavailability of slides. Five were of a diffuse large B-cell type and three were Burkitt-like.

Eight of the 15 PTLD cases in adults were monomorphic, 4 were polymorphic, 2 were plasmacytoma-like, and 1 was infectious mononucleosis/polymorphic. Seven of the 10 PTLD cases in children were monomorphic, 1 was polymorphic, and 2 were infectious mononucleosis/polymorphic.

The location of the PTLDs was predominantly the gastrointestinal tract in 11 cases (44%) or the lymph nodes in 6 cases (24%). There were also 2 (8%) cases each which presented in the liver or in the renal allograft, and 1 (4%) case each presenting in the lungs, salivary gland, skin, and multiple organs.

**Treatment of PTLD.** After the diagnosis of PTLD, all patients had either a complete cessation or a marked diminution of their tacrolimus and steroid dosages, and discontinuation of azathioprine or mycophenolate mofetil, if they were taking either of those agents. They were also treated empirically with either intravenous ganciclovir or, less commonly, acyclovir (a few pediatric patients also received cytomegalovirus [CMV] hyperimmune globulin). Maintenance immunosuppression was reintroduced at a low level after the disappearance of the PTLD. In several cases, the patients developed rejection before (or even after) immunosuppression was reintroduced.

In two adult and two pediatric patients, this conservative approach was inadequate, and chemotherapy was required (one adult received lymphokine-activated killer cell therapy (16), which failed, before starting chemotherapy). In one of the adults, chemotherapy was ultimately ineffective, and she died of PTLD; the other adult responded to chemotherapy but ultimately lost her kidney 69 months after transplantation, to acute rejection. Both of the pediatric patients receiving chemotherapy (these were the two late PTLDs occurring 47 and 52 months after transplantation) had complete eradication of their PTLD and are back on low-dose immunosuppression.

One pediatric patient has had presumed (not biopsy proven) recurrent PTLD that was treated successfully with ganciclovir and temporary discontinuation of immunosuppression.

**Patient and graft survival.** With a mean follow-up of  $24.9 \pm 30.1$  months after transplantation, the 1- and 5-year actuarial patient survival rates in the adults were 93% and 86% (Table 3). Two adults died, 3.7 and 46.2 months after

TABLE 3. Outcomes

	Adult	Pediatric
Actuarial patient survival		
1 year	93%	100%
5 year	86%	100%
Actuarial graft survival		
1 year	80%	100%
5 year	60%	89%
Serum creatinine level (mg/dl)	2.5±1.2	1.3±0.6

transplantation, of complications related to PTLD (one had received chemotherapy, as noted above). The 1- and 5-year actuarial graft survival rates in the adults were 80% and 60%. In addition to the two deaths, eight adults lost their allografts to acute and/or chronic rejection 3.7–84.7 months after transplantation (one underwent, before resuming dialysis, retransplantation with a kidney and a pancreas).

In the pediatric patients with PTLD, the 1- and 5-year actuarial patient survival rates were 100% and 100%. No child died. The 1- and 5-year actuarial graft survival rates were 100% and 89%. One child lost his kidney to chronic rejection 41.3 months after transplantation, 36 months after the diagnosis of PTLD.

**Renal function.** At most recent follow-up, the mean serum creatinine level in the five adults with functioning kidneys was 2.5±1.2 mg/dl; in the nine pediatric patients, it was 1.3±0.6 mg/dl (Table 3).

#### DISCUSSION

Our experience with PTLD in renal transplant patients receiving tacrolimus-based immunosuppression demonstrated a significantly higher incidence of PTLD in children than in adults. This was probably related to a higher proportion of EBV-seropositive donor/EBV-seronegative recipient cases in the pediatric patients (6 of the 7 cases in which both the donor and recipient EBV serology was known), although this point is not absolutely certain, given that both donor and recipient EBV serologies were known in only 4 of the 15 adult cases. The incidence of PTLD in the pediatric patients declined significantly over time, from 24.1% in the first 3.5 years to 4.3% in the subsequent 5 years. The reason for this decline probably reflects a conscious effort, beginning in 1993, to taper tacrolimus and steroid dosages aggressively beginning 6–8 weeks after transplantation, with the goal of maintaining chronic tacrolimus trough levels of 5–9 ng/ml, and discontinuing steroids within 6–12 months after transplantation. In addition, antiviral prophylaxis with ganciclovir and CMV immune globulin began to be used in the high-risk patients. Although the subsequent decline in the incidence of PTLD has been encouraging, it remains too high and is the focus of aggressive prophylaxis and monitoring (13, 14, 17). In EBV-seropositive donor/EBV-seronegative recipient cases, current management includes intravenous and oral ganciclovir and CMV immune globulin prophylaxis (18) (the former for up to 1 year and the latter for one or two doses in the hospital), and monthly quantitative EBV polymerase chain reaction (19) monitoring for the first year after transplantation and every 2–3 months thereafter. A conversion to a positive EBV polymerase chain reaction will prompt reinstitution of intravenous ganciclovir and a reduction in immunosuppression.

Although the incidence of PTLD in children has been relatively high, the outcomes have been generally favorable, with 1- and 5-year actuarial patient survival rates of 100%, and 1- and 5-year actuarial graft survival rates of 100% and 89%, respectively. The mean serum creatinine level has remained reasonable, at 1.3±0.6 mg/dl. Our overall experience with tacrolimus in pediatric renal transplantation has been comparable, with 1- and 4-year actuarial patient survival rates of 99% and 94%, and corresponding 1- and 4-year actuarial graft survival rates of 98% and 84% (14). The ability to discontinue steroids and antihypertensive medications in 66% and 86% of patients, respectively, and the relatively low cholesterol levels of 155±31 mg/dl, have been important additional advantages for our pediatric patients; many of them have had normal growth (14). In contrast, although the incidence of PTLD in adults has been low, the outcomes have been less favorable, with 1- and 5-year actuarial patient survival rates of 93% and 86%, and 1- and 5-year actuarial graft survival rates of 80% and 60%, respectively. In addition, the mean serum creatinine level of 2.5±1.2 mg/dl in the five patients with functioning allografts reflects somewhat impaired function. These outcomes are somewhat worse than our overall outcomes in adults (11, 12, 20).

Our best explanation for these somewhat disparate outcomes reflects at least partially the fact that most of the PTLD cases in children have behaved like EBV infections, rapidly disappearing with temporary discontinuation of immunosuppression and intravenous ganciclovir, with or without CMV hyperimmune globulin. Many of the adult cases, by contrast, were EBV negative and were perhaps less responsive to reduction of immunosuppression and antiviral therapy.

It should be noted that, although PTLD under tacrolimus-based therapy represented a significant morbidity for our patients and was associated with an increased rate of graft loss in our adult patients, it was associated with no mortality in our pediatric patients and a 14% mortality at 5 years in our adult patients. In contrast, single-center reports, registry data, and reviews have reported a mortality of 50% or greater with PTLD in cyclosporine-treated patients (21, 22, 23).

In summary, PTLD under tacrolimus-based immunosuppression in renal transplant recipients remains an uncommon complication in adults, but, when it occurs, is associated with relatively unfavorable outcomes. In pediatric patients, the incidence of PTLD has been higher, although it has declined significantly over time, and the outcomes have been relatively good. These long-term results have been somewhat reassuring but have not allowed us to become complacent. The goal remains to reduce further or hopefully even eliminate the problem of PTLD in pediatric patients by more aggressive prophylaxis and early monitoring.

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## REFERENCES

1. Penn I, Hammond W, Bretschneider L, Starzl TE. Malignant lymphomas in transplantation patients. *Transplant Proc* 1969; 1(1): 106.
2. Starzl TE, Penn I, Putnam CW, Groth CG, Halgrimson CG. Iatrogenic alterations of immunologic surveillance in man and their influence on malignancy. *Transplant Rev* 1971; 7: 112.
3. Frizzera G, Hanto DW, Gajl-Peczalska KJ, et al. Polymorphic diffuse B-cell hyperplasias and lymphomas in renal transplant recipients. *Cancer Res* 1981; 41: 4262.
4. Hanto DW, Frizzera G, Gajl-Peczalska KJ, et al. Epstein-Barr virus-induced B-cell lymphoma after renal transplantation: acyclovir therapy and transition from polyclonal to monoclonal B-cell proliferation. *N Engl J Med* 1982; 306: 913.
5. Hanto DW, Frizzera G, Gajl-Peczalska KJ, Simmons RL. Epstein-Barr virus, immunodeficiency, and B cell lymphoproliferation. *Transplantation* 1985; 39: 461.
6. Starzl TE, Porter KA, Iwatsuki S, et al. Reversibility of lymphomas and lymphoproliferative lesions developing under cyclosporine-steroid therapy. *Lancet* 1984; 1: 583.
7. Nalesnik MA, Jaffe R, Starzl TE, et al. The pathology of post-transplant lymphoproliferative disorders occurring in the setting of cyclosporine A-prednisone immunosuppression. *Am J Pathol* 1988; 133: 173.
8. Nalesnik MA, Makowka L, Starzl TE. The diagnosis and treatment of post-transplant lymphoproliferative disorders. *Curr Prob Surg* 1988; 25: 371.
9. Shapiro R, Jordan ML, Scantlebury V, et al. FK 506 in clinical kidney transplantation. *Transplant Proc* 1991; 23: 3065.
10. Shapiro R, Jordan ML, Scantlebury VP, et al. A prospective, randomized trial of FK506-based immunosuppression after renal transplantation. *Transplantation* 1995; 59(4): 485.
11. Shapiro R, Jordan ML, Scantlebury VP, et al. Tacrolimus in renal transplantation. *Transplant Proc* 1996; 28(4): 2117.
12. Shapiro R, Jordan ML, Scantlebury VP, et al. A prospective, randomized trial of tacrolimus/prednisone versus tacrolimus/prednisone/mycophenolate in renal transplant recipients. *Transplantation* 1999; 67(3): 411.
13. Shapiro R, Scantlebury VP, Jordan ML, et al. Tacrolimus in pediatric renal transplantation. *Transplantation* 1996; 62(12): 1752.
14. Shapiro R, Scantlebury VP, Jordan ML, et al. Pediatric renal transplantation under tacrolimus-based immunosuppression. *Transplantation* 1999; 67(2): 299.
15. Harris NJ, Ferry JA, Swerdlow SH. Posttransplant lymphoproliferative disorders: summary of Society for Hematopathology Workshop. *Semin Diagn Pathol* 1997; 14: 8.
16. Nalesnik MA, Rao AS, Furukawa H, et al. Autologous lymphokine-activated killer cell therapy of Epstein-Barr virus-positive and -negative lymphoproliferative disorders arising in organ transplant recipients. *Transplantation* 1997; 63(9): 1200.
17. Shapiro R. Tacrolimus in pediatric renal transplantation: a review. *Pediatr Transplant* 1998; 2: 270.
18. Proceedings of a Symposium on High-Risk Transplantation. Snyderman DR, ed. *Transplant Proc* 1994; 26(5, suppl 1): 45.
19. Green M, Reyes J, Todo R, Rowe DT. Use of quantitative competitive PCR (QC-PCR) to guide preemptive therapy (PT) against EBV associated post-transplant lymphoproliferative disorders (PTLD) after intestinal transplantation (ITx) in children. *Transplant Proc* 1996; 28: 2759.
20. Starzl TE, Eliasziw M, Gjertson D, et al. HLA and cross reactive antigen group matching for cadaver kidney allocation. *Transplantation* 1997; 64(7): 983.
21. Cockfield SM, Preiksaitis JK, Jewell LD, et al. Post-transplant lymphoproliferative disorder in renal allograft recipients: clinical experience and risk factor analysis in a single center. *Transplantation* 1993; 56(1): 88.
22. Hebert D, Sullivan EK. Malignancy and posttransplant lymphoproliferative disorder (PTLD) in pediatric renal transplant recipients: a report of the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS). *Pediatr Transplant* 1998; 2(suppl 1): 57.
23. Basgoz N, Preiksaitis JK. Post-transplant lymphoproliferative disorder. *Infect Dis Clin North Am* 1995; 9(4): 901.

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