American Journal of Transplantation 2004; 4: 87–93
Blackwell Munksgaard

doi: 10.1046/j.1600-6135.2003.00274.x

Immunosuppression and the Risk of Post-Transplant Malignancy Among Cadaveric First Kidney Transplant Recipients

Rami T. Bustami[a,*], Akinlolu O. Ojo[a,b,c], Robert A. Wolfe[b,d], Robert M. Merion[a,e], William M. Bennett[f], Suzanne V. McDiarmid[g], Alan B. Leichtman[a,c], Philip J. Held[a] and Friedrich K. Port[a]

[a] *Scientific Registry of Transplant Recipients/University Renal Research and Education Association, Ann Arbor, MI*
[b] *Scientific Registry of Transplant Recipients/University of Michigan Kidney Epidemiology and Cost Center, Ann Arbor, MI*
[c] *Department of Veterans Affairs Medical Center, Division of Nephrology, University of Michigan, Ann Arbor, MI*
[d] *Department of Biostatistics, University of Michigan School of Public Health, Ann Arbor, MI*
[e] *Division of Transplantation, Department of Surgery, University of Michigan Health System, Ann Arbor, MI*
[f] *Solid Organ and Cellular Transplantation, Legacy Good Samaritan Hospital, and Northwest Renal Clinic, Portland, OR*
[g] *Pediatric Liver Transplantation, Department of Pediatrics and Surgery, UCLA Medical Center, Los Angeles, CA*
**Corresponding author: Rami T. Bustami, RBustami@urrea.org*

The success of renal transplantation may be counterbalanced by serious adverse medical events. The effect of immunosuppression on the incidence of *de novo* neoplasms among kidney recipients should be monitored continuously. Using data from the Scientific Registry of Transplant Recipients, we studied the association of induction therapy by immunosuppression with antilymphocyte antibodies, with the development of *de novo* neoplasms. The study population included more than 41 000 recipients who received a cadaveric first kidney transplant after December 31, 1995, and were followed through February 28, 2002.

Using Cox regression models, we estimated time to development of two types of malignancy: *de novo* solid tumors and post-transplant lymphoproliferative disorder (PTLD). We made adjustments for several patient demographic factors and comorbidities.

Induction therapy was significantly associated with a higher relative risk (RR) of PTLD (RR = 1.78, p < 0.001), but not with a greater likelihood of *de novo* tumors (RR = 1.07, p = 0.42). Treatment with maintenance tacrolimus vs. cyclosporine showed a significantly different RR of developing *de novo* tumors for recipients with induction than for those not receiving induction (p = 0.024). These new estimates of the magnitude of malignancy risk associated with induction therapy may be useful for clinical practice.

Key words: Antilymphocyte antibodies, cadaveric kidney transplantation, *de novo* tumors, immunosuppression, induction therapy, PTLD, risk factors

Received 7 May 2003, revised 22 July 2003 and accepted for publication 1 August 2003

Introduction

The incidence of malignancy is significantly higher for organ transplant recipients than for the general population that has not undergone transplantation. For instance, the incidence of post-transplant lymphoproliferative disorder (PTLD) among kidney transplant recipients is approximately 1%, which confers a risk of lymphoma approximately 20-fold greater than that seen in the general population (1). Several cross-sectional studies (2–6) suggest a close relationship between immunosuppression and incidence rates of *de novo* solid tumors and PTLD among recipients of kidneys and other solid organ transplants.

As a consequence of immunosuppressive therapy to prevent transplant rejection, a transplant recipient's immune surveillance mechanism for tumor cells is likely to be compromised. In fact, recipients of organ transplants are slightly more vulnerable to the development of uncommon tumors and also have a higher incidence of some more common tumors, such as skin cancer (2%) (6,7). Skin cancer (basal and squamous cell types) is the most common tumor in both the transplant and normal population, but transplant recipients are threefold more likely to develop it (8).

Most PTLD is thought to be caused by transformations of lymphoid tissue frequently resulting from uncontrolled Epstein-Barr virus (EBV) infection or reactivation of latent EBV infection. It afflicts many recipients of solid organ transplants (9–11). Previous studies have shown that transplant recipients at increased risk for PTLD include children

with primary EBV infection (12) and recipients who have been heavily immunosuppressed (11,13,14). It has been shown that kidney recipients who receive less immunosuppression have a lower risk of developing PTLD (15). Such patients include recipients of a living-related donor kidney, as well as cadaveric kidney transplant recipients who have never had a rejection episode and thus have not been exposed to the most intensive post-transplant immunosuppression therapy.

Patients with post-transplant malignancies have higher rates of mortality. Among all US patients with functioning kidney transplants received between 1994 and 1996, the total death rate was approximately 25.8 per 1000 patient years. Moreover, the death rate from malignant diseases was 1.9 per 1000 patient years, which represents approximately 7% (1.9/25.8) of the total death rate (16).

Most of the above-cited studies investigated the amount and duration of administered immunosuppression and rates of post-transplant malignancy. In this study we examine the incidence of *de novo* tumors and PTLD in kidney recipients exposed to specific immunosuppressive agents. We focus specifically on the use of antilymphocyte preparations as induction therapy at time of transplantation, as the use of these agents has been associated with an increase in the severity and frequency of infection compared with noninduction immunosuppressive regimens (17,18).

Data and Methods

The database of the Scientific Registry of Transplant Recipients (SRTR) includes extensive data for all solid organ transplant recipients in the US (19). Major components of the SRTR data are collected by the Organ Procurement and Transplantation Network (OPTN); the database also includes information from other national sources (20). Transplant centers report known post-transplant malignancies to the OPTN at 6 months and at each anniversary following transplantation.

On the OPTN data collection forms, and therefore in the SRTR database, *de novo* tumors are classified by site: bladder; breast; colorectal; liver; prostate; renal carcinoma; skin; lung; stomach; vulva, perineum or penis, and scrotum; other cancer; and primary unknown. Post-transplant lymphoproliferative disorder is classified as polymorphic hyperplasia, monomorphic or polymorphic PTLD (lymphoma), multiple myeloma, plasmacytoma, or Hodgkin's disease.

For this study, we defined induction therapy as immunosuppression during the initial transplant hospitalization with one of the following agents: equine antithymocyte globulin (ATGAM®, or ATG, Pharmacia and Upjohn Inc., Kalamazoo, MI), rabbit antithymocyte globulin (Thymoglobulin®, Sang-Stat Medical Corp., Fremont, CA), muromonab-CD3 (Orthoclone OKT3®, Ortho Pharmaceutical Corporation, Biotech Division, Raritan, NJ), daclimuzab (Zenapax®, Protein Design Laboratories, Fremont, CA), basiliximab (Simulect®, Novartis Pharmaceuticals Corporation, East Hanover, NJ), NRATG/NRATS (Nashville rabbit antithymocyte globulin/Nashville rabbit antithymocyte serum), or T10B9 (Medimmune, Medimmune Inc., Gaithersburg, MD). Treatment by any other immunosuppressive agent at the time of transplantation was not classified as induction therapy. Several patient risk factors were also studied, including age, gender, race (White, Asian, Black, other), ethnicity (non-Hispanic, Hispanic), body weight, Hepatitis C antibody screen (positive, negative, unknown), Hepatitis B core antibody (positive, negative, unknown), time since first dialysis, presence of diabetes, and year of transplantation. Information on EBV infection, a risk factor for developing PTLD, is not complete in the SRTR database, and thus this factor was not examined in the analyses.

The study population includes all cadaveric first kidney transplant recipients who received a transplant between January 1, 1996, and February 28, 2002. These patients were followed through February 2002. For both *de novo* tumor and PTLD analyses, recipients with pre-existing malignancies were excluded. For *de novo* tumor analyses, we also excluded recipients who had less than 6 months of follow up after transplantation and recipients with a first tumor diagnosis in the first 6 months following transplantation (total of 8%), as such tumors were likely unrelated to induction therapy. These two exclusions resulted in a study group of 38 191 recipients for *de novo* tumor analyses. We did not make these last two exclusions for the PTLD analyses, as PTLD can develop early after transplantation. The early development of PTLD following renal transplantation has been reported in a number of studies (11,21). The study group for the PTLD analyses included 41 686 recipients.

A logistic regression model, including all the above-listed patient factors, was used to identify groups of patients with higher likelihood of receiving induction therapy. Multivariate Cox proportional hazards regression models, also adjusted for all the above-listed patient factors, were used to analyze rates of *de novo* tumors and PTLD. The two Cox models are based on time from transplant to the first reported *de novo* tumor or PTLD, censored at death or the end of the study (February 2002). All models were fitted using SAS 8.2 (SAS Institute, Inc., Cary, NC).

Additional analyses were performed including separate categories for equine antithymocyte globulin (ATG), rabbit antithymocyte globulin, muromonab-CD3, daclimuzab, and basiliximab in the model. The remaining medications for induction therapy, T10B9 (Medimmune) (<0.1%) and NRATG/NRATS (0.6%), were grouped together in a separate category.

Further analyses were also performed to investigate the effect of different maintenance therapies on the risk of *de novo* tumors and PTLD, for patients with and without induction therapy. Two calcineurin inhibitors were chosen for comparison: tacrolimus and cyclosporine. Other comparisons were also made between two antimetabolites: azathioprine and mycophenolate mofetil (MMF). Both comparisons were adjusted for all the patient factors included in the main model as well as for the effects of both antimetabolites and calcineurine inhibitors.

Results

Our data showed that 45% of patients received induction therapy at the time of transplantation. Results from a logistic model for identifying groups of patients more likely to receive induction therapy showed that pediatric (<18 years of age) recipients were more likely to receive induction therapy than recipients older than 50 years of age (odds ratio = 1.42, $p < 0.001$); all other age groups had a likelihood similar to that of patients older than 50 years. Increased odds of receiving induction therapy were also observed for females compared with males and for a more recent year of transplantation, while decreased odds were observed for Whites and Asians compared with Blacks, and for recipients with positive Hepatitis B core antibody.

Table 1: Counts of first cadaveric kidney transplant recipients and percentages with *de novo* solid tumors and post-transplant lymphoproliferative disorder, by year of transplantation

De novo solid tumors			Post-transplant lymphoproliferative disorder		
Transplantation (year)	Transplants (n)	With tumor (%)	Transplantation (year)	Transplants (n)	With tumor (%)
1996	6585	2.34	1996	6587	0.62
1997	6607	2.15	1997	6608	0.61
1998	6829	2.23	1998	6836	0.51
1999	6835	1.40	1999	6841	0.41
2000	6766	0.80	2000	6772	0.25
2001[1]	4569	0.39	2001	6912	0.29
			2002[2]	1130	0.00
All	38 191	1.61	All	41 686	0.49

[1] Includes January through August 2001 only.
[2] Includes January through February 2002 only.

Table 2: Average length of follow up (in years) in cross-tabulation of induction therapy, by *de novo* solid tumors and post-transplant lymphoproliferative disorder

	De novo solid tumors		Post-transplant lymphoproliferative disorder	
	Yes	No	Yes	No
With induction therapy	2.83	3.42	1.77	3.12
Without induction therapy	3.25	4.05	2.18	3.86

Table 3: Baseline factors and relative risk (Cox) of developing a *de novo* solid tumor (n = 38 191, *de novo* solid tumors = 616)

Factor	Mean or %	RR	95% CI	p-value
Induction therapy (yes vs. no)	44.6%	1.07	(0.91, 1.26)	0.42
Age (per 10 years older)	47.52	1.80	(1.68, 1.93)	< 0.0001
Gender (male vs. female)	60.3%	1.33	(1.12, 1.59)	0.002
Race (white vs. Black)	64.1%	1.98	(1.58, 2.50)	< 0.0001
Race (Asian vs. Black)	4.3%	0.90	(0.51, 1.60)	0.72
Race (other vs. Black)	2.5%	0.36	(0.11, 1.15)	0.085
Ethnicity (non-Hispanic vs. Hispanic)	85.4%	3.33	(2.18, 5.07)	< 0.0001
Weight (per 10 kg heavier)	76.49	1.03	(0.97, 1.09)	0.34
Hepatitis C antibody screen (positive vs. negative)	5.4%	0.66	(0.40, 1.10)	0.11
Hepatitis C antibody screen (unknown vs. negative)	10.9%	1.07	(0.81, 1.41)	0.62
Hepatitis B core antibody (positive vs. negative)	7.0%	1.12	(0.80, 1.57)	0.50
Hepatitis B core antibody (unknown vs. negative)	28.0%	0.93	(0.76, 1.13)	0.46
Time since first dialysis (per additional year)	3.04	1.01	(0.98, 1.04)	0.43
Year of transplantation (per additional year after 1996)	1998	1.31	(1.22, 1.41)	< 0.0001
Diabetes (absent vs. present)	67.0%	1.59	(1.30, 1.95)	< 0.0001

Results for missing categories are not shown. The following variables had missing values in the database (percentage missing shown in parentheses): weight (25%), Hepatitis C antibody screen (1%), Hepatitis B core antibody (1%), time since first dialysis (12.7%), and diabetes (7.3%).

Of the 38 191 cadaveric first kidney transplant recipients who had at least 6 months of follow up after transplantation, 616 (1.61%) developed *de novo* tumors. Of the 41 686 recipients without the above follow-up time restriction, 181 (0.43%) developed PTLD.

Table 1 summarizes descriptive statistics including counts of patients and percentages with *de novo* tumors and PTLD by year of transplantation. Table 2 shows the average length of follow up (in years) in a cross-tabulation of induction therapy by *de novo* tumors and PTLD. Although the follow-up period for patients with *de novo* tumors was 6 months longer in our analysis, the markedly shorter average length of follow up for patients with PTLD compared with that for patients with *de novo* tumors, as seen in Table 2, indicates earlier incidence of PTLD. Mean or percent values of the factors examined in the analyses are shown in the second column of Tables 3 and 4.

Figures 1 and 2 show the estimated percentages, obtained from the unadjusted Kaplan-Meier survival curves, of patients with *de novo* tumors and PTLD, respectively, stratified by whether or not the patient received induction therapy. The curves for *de novo* tumors (Figure 1) show similar

Table 4: Baseline factors and relative risk (Cox) of developing post-transplant lymphoproliferative disorder (n = 41 686, PTLD = 181)

Factor	Mean or %	RR	95% CI	p-value
Induction therapy (yes vs. no)	45.8%	1.78	(1.31, 2.40)	0.0002
Age (per 10 years older)	47.67	0.86	(0.77, 0.95)	0.003
Gender (male vs. female)	60.2%	1.43	(1.04, 1.96)	0.028
Race (White vs. Black)	64.0%	1.45	(1.00, 2.12)	0.052
Race (Asian vs. Black)	4.3%	1.90	(0.98, 3.69)	0.057
Race (other vs. Black)	2.5%	0.88	(0.27, 2.86)	0.83
Ethnicity (non-Hispanic vs. Hispanic)	85.4%	1.79	(1.04, 3.07)	0.037
Weight (per 10 kg heavier)	76.63	0.89	(0.82, 0.97)	0.012
Hepatitis C antibody screen (positive vs. negative)	5.3%	0.70	(0.30, 1.61)	0.40
Hepatitis C antibody screen (unknown vs. negative)	10.7%	0.52	(0.28, 0.98)	0.042
Hepatitis B core antibody (positive vs. negative)	7.0%	1.15	(0.64, 2.07)	0.65
Hepatitis B core antibody (unknown vs. negative)	27.4%	1.22	(0.86, 1.73)	0.26
Time since first dialysis (per additional year)	3.07	0.97	(0.89, 1.04)	0.36
Year of transplantation (per additional year after 1996)	1999	1.10	(0.99, 1.23)	0.087
Diabetes (absent vs. present)	67.3%	1.35	(0.90, 2.02)	0.15

Results for missing categories are not shown. The following variables had missing values in the database (percentage missing shown in parentheses): weight (23.8%), Hepatitis C antibody screen (1.4%), Hepatitis B core antibody (1.4%), time since first dialysis (13.2%), and diabetes (6.9%).

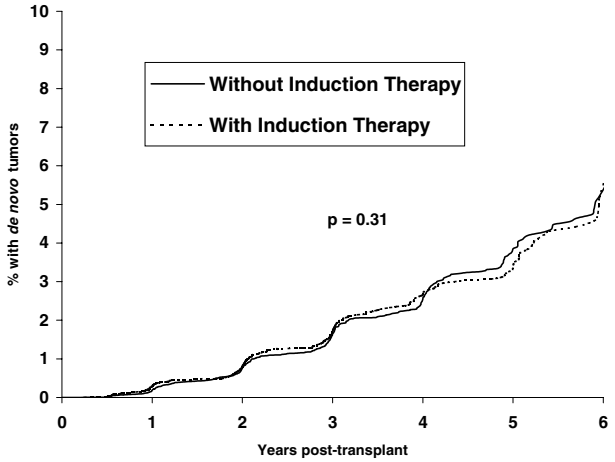

Figure 1: Rates of developing *de novo* solid tumors, with and without induction therapy.

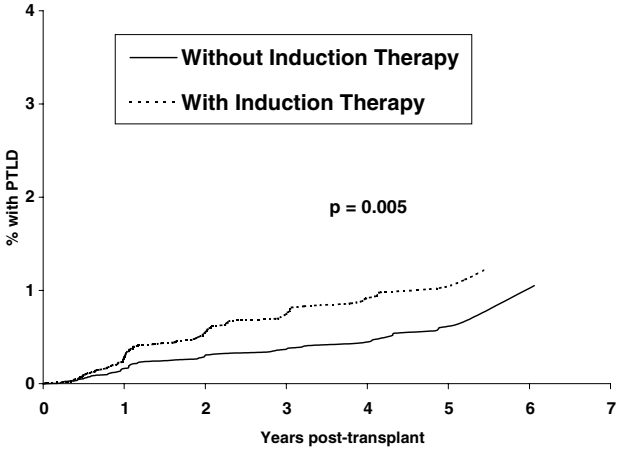

Figure 2: Rates of developing post-transplant lymphoproliferative disorder, with and without induction therapy.

percentages of patients developing tumors with and without induction therapy. These percentages were compared using a log-rank test that resulted in a p-value of 0.31. In contrast, the percentage of patients with PTLD (Figure 2) was significantly higher for those with induction therapy ($p = 0.005$). During the first 6 months following transplant, the difference between the two groups' rates was small. The apparent increase suggested by the undulating patterns in Figures 1 and 2 at each anniversary is likely a reflection of imprecise reporting of the date of first malignancy diagnosis during each annual follow-up visit.

The results of fitting the two multivariate Cox models to the data are shown in Tables 3 and 4. Table 3 provides results of a model for time to the development of *de novo* tumors (starting at 6 months post-transplant), and Table 4 provides analogous model results for PTLD (starting at time of transplantation). The tables show the relative risk (RR) of malignancy according to induction therapy and several patient factors, together with 95% confidence intervals and p-values for testing the hypothesis that the corresponding model parameter = 0.

Induction therapy was significantly associated with higher risk (RR = 1.78, $p < 0.001$) of developing PTLD (Table 4), but not of developing *de novo* tumors (RR = 1.07, $p = 0.42$) (Table 3). The RR of PTLD indicates that the risk of developing PTLD is approximately 1.8-fold higher among recipients of induction therapy. Greater risk of PTLD was also significantly associated with younger recipient age (RR = 0.86 per 10 years older), males compared with females (RR = 1.43), non-Hispanic ethnicity compared

Table 5: Relative risk of developing *de novo* solid tumors, by specific medications for induction therapy (n = 38 191, *de novo* solid tumors = 616)

Factor[1]	%	RR	95% CI	p-value
Induction: ATG	9.6	1.24	(0.97, 1.58)	0.084
Induction: rabbit antithymocyte globulin	4.6	1.53	(0.92, 2.56)	0.10
Induction: muromonab-CD3	10.9	0.85	(0.65, 1.11)	0.22
Induction: daclimuzab	7.6	1.06	(0.73, 1.54)	0.77
Induction: basiliximab	11.2	1.12	(0.79, 1.59)	0.54
Induction: No	55.4	1.00	Ref	

[1]Model adjusted for age, gender, race, ethnicity, weight, Hepatitis C antibody screen, Hepatitis B core antibody, time since first dialysis, year of transplantation, and diabetes.
Induction with T10B9 (Medimmune) (<0.1%) and NRATG/NRATS (0.6%) are not shown in the table.
P-value for testing differences between the specific medications for induction therapy in the model: 0.18.

with Hispanic (RR = 1.79), and recipients with lower body weight (RR = 0.89 per 10 kg heavier). Greater risk of *de novo* tumors was significantly associated with older recipient age (RR = 1.80 per 10 years older), males compared with females (RR = 1.33), White race compared with Black (RR = 1.98), non-Hispanic ethnicity compared with Hispanic (RR = 3.33), absence of diabetes (RR = 1.59), and a more recent year of transplantation (RR = 1.31). Table 1 shows that the percentage of patients with *de novo* tumors or PTLD decreased for a more recent year of transplantation. This decrease is likely the result of the relatively short length of follow up for more recently transplanted patients.

The effect of including indicators for the specific medications for induction therapy in the model for *de novo* tumors was not significant (p = 0.19). However, Table 5 shows a trend (RR = 1.24) of borderline significance (p = 0.08) towards a higher risk of *de novo* tumors for recipients receiving induction therapy with ATG compared with those who received no antilymphocyte induction. No significant differences were found among the specific medications for induction therapy in the model for *de novo* tumors (p = 0.18).

The effect of including indicators for the specific medications for induction therapy in the model for PTLD was highly significant (p = 0.010). Table 6 shows that, except for ATG (RR = 1.50, p = 0.10), the risk of developing PTLD was significantly higher for recipients that received any of the antilymphocyte induction regimens compared with those who received no antilymphocyte induction. As for the model for *de novo* tumors, no significant differences were found among the specific medications for induction therapy in the model for developing PTLD (p = 0.34).

The effect of receiving maintenance with tacrolimus compared with that of maintenance with cyclosporine on the risk of *de novo* tumors and PTLD was analyzed, and comparisons between these effects were made for recipients with and without induction therapy. Of all kidney recipients who received induction therapy (45%), 55.7% were reported to have received maintenance with cyclosporine, 34.3% received maintenance with tacrolimus, and 6.6% received maintenance with neither drug. Of all kidney recipients not receiving induction therapy (55%), 55.7% received maintenance with cyclosporine, 27.2% received maintenance with tacrolimus, and 11.0% received maintenance with neither drug. For the purpose of making reliable comparisons, the remaining 3.4% of patients with induction and 6.1% of patients without induction who were reported to have received maintenance with both cyclosporine and tacrolimus during the same observation period were not included in these additional analyses.

The results for these analyses by maintenance therapy showed that among kidney recipients who received induction therapy, the risk of developing *de novo* tumors

Table 6: Relative risk of developing post-transplant lymphoproliferative disorder, by specific medications for induction therapy (n = 41 686, post-transplant lymphoproliferative disorder = 181)

Factor[1]	%	RR	95% CI	p-value
Induction: ATG	9.0	1.50	(0.93, 2.43)	0.10
Induction: rabbit antithymocyte globulin	5.7	3.00	(1.53, 5.89)	0.001
Induction: muromonab-CD3	10.1	1.71	(1.12, 2.63)	0.014
Induction: daclimuzab	8.1	1.92	(1.08, 3.41)	0.027
Induction: basiliximab	12.4	1.83	(1.05, 3.18)	0.032
Induction: no.	54.2	1.00	Ref	

[1]Model adjusted for age, gender, race, ethnicity, weight, Hepatitis C antibody screen, Hepatitis B core antibody, time since first dialysis, year of transplantation, and diabetes.
Induction with T10B9 (Medimmune) (<0.1%) and NRATG/NRATS (0.6%) are not shown in the table.
P-value for testing differences between the specific medications for induction therapy in the model: 0.34.

was nonsignificantly higher for those who received maintenance tacrolimus vs. cyclosporine (RR = 1.16, p = 0.38). However, among recipients not receiving induction, the risk of developing *de novo* tumors was significantly lower (RR = 0.70, p = 0.020) for those who received maintenance tacrolimus compared with those receiving maintenance cyclosporine. This observation for maintenance tacrolimus vs. cyclosporine was significantly different for those receiving induction than for those not receiving induction (p = 0.024).

Similar comparisons showed that among recipients who received induction therapy, the risk of developing PTLD was nonsignificantly higher (RR = 1.12, p = 0.64) for those who received maintenance tacrolimus vs. cyclosporine. Among recipients not receiving induction, the risk of developing PTLD was significantly higher for those who received maintenance tacrolimus vs. cyclosporine (RR = 2.03, p = 0.008). This difference in PTLD risk for recipients with and without induction was of borderline significance only (p = 0.091).

Comparisons were also made between the effects of receiving maintenance with azathioprine and maintenance with MMF on the risk of developing *de novo* tumors and PTLD. Of all kidney recipients who received induction therapy, 71.8% received maintenance with MMF, 13.2% received maintenance with azathioprine, and 10.3% received maintenance with neither drug. Of all kidney recipients not receiving induction therapy, 60.6% received maintenance with MMF, 12.0% received maintenance with azathioprine, and 23.1% received maintenance with neither drug. The remaining 4.7% of patients with induction and 4.3% of patients without induction that were reported to have received maintenance with both azathioprine and MMF during the same observation period were excluded from these analyses.

The risk of developing *de novo* tumors and that for PTLD were not significantly modified by maintenance azathioprine vs. MMF whether or not the patient received induction therapy.

Discussion

Post-transplant malignancies are receiving increased attention as important complications following transplantation. By studying a large cohort of cadaveric first kidney transplant recipients, we found that induction therapy was associated with an increased risk of PTLD but not of *de novo* tumors. The negative finding for *de novo* tumors may be the result of the relatively short length of follow up for more recently transplanted patients, as antilymphocyte antibody induction therapy has been found to be associated with higher risk for late malignancy-related death (18).

In seeking to study the effects of specific immunosuppressants on the incidence of *de novo* tumors and PTLD, the use of the SRTR database offered a number of advantages. The database is large, comprehensive, and includes national data. In addition, patients were followed for an average time of approximately 4 years after transplantation, allowing a sufficient amount of time to detect malignancy cases. It should be emphasized, however, that there might be underreporting of malignancy cases in these data. Thus, ascertainment of malignancy might not be complete during follow up. The SRTR is in the process of conducting linkage studies using several sources of information in order to validate the data captured in the SRTR database (20). Preliminary data suggest underreporting of malignancies; the results of the present study assume that such underreporting does not bias our findings. More recent years in the present study appear to show an improved ascertainment, as suggested by the increased relative risk by year of transplantation (Tables 3 and 4). With more complete ascertainment, additional factors may be identified as significantly associated with PTLD or *de novo* solid tumors.

Several prior studies have focused on the relationship between post-transplant malignancy and the administered dose or duration of immunosuppressive therapy, factors that may contribute to the risk of post-transplant malignancy (6,7,22). Information on dose and duration of therapy is not complete in the SRTR database. Instead, we investigated the relationship between post-transplant malignancy and a list of selected immunosuppressive agents used for induction therapy, comparing malignancy rates to those observed in the absence of antilymphocyte induction treatment. Our analyses showed statistical evidence that the risk of developing PTLD (RR = 1.78) among cadaveric first kidney transplant recipients is significantly associated with induction therapy ($p < 0.001$). There was also a nonsignificant trend (p = 0.42) toward a greater risk of developing *de novo* tumors (RR = 1.07) among recipients who were treated with induction agents. Our analyses also showed that in the presence of induction therapy, the choice of maintenance tacrolimus vs. cyclosporine does not significantly modify the risk of either *de novo* tumors or PTLD. However, in the absence of induction therapy, the choice of tacrolimus vs. cyclosporine appeared to modify the risk of *de novo* tumors and PTLD. The nonsignificant difference in post-transplant malignancy risk by tacrolimus vs. cyclosporine for patients receiving induction therapy may suggest that the strong immunosuppressive effect of induction may override differences by maintenance drugs that are observed without induction therapy. Although certain groups of patients (e.g. pediatric age group) had higher likelihood of receiving induction therapy, our analyses are not influenced by these differences, as the multivariate Cox models use adjusted comparisons for patients with the same characteristics.

In good agreement with previous studies (22–24), we detected significant associations of increased recipient age with an elevated risk of post-transplant *de novo* tumors, and younger recipient age with higher risk of PTLD.

Moreover, our study showed that other demographic factors, such as male gender, White race, and non-Hispanic ethnicity, were also associated with post-transplant malignancies. The presence of diabetes appeared to reduce the tendency to develop *de novo* tumors. The reason for this finding is unknown.

Future SRTR studies will assess the risk of specific malignancy sites and associations with other immunosuppressive agents. Other informative studies will investigate the risk of post-transplant malignancies among transplant recipients of other organs. For instance, we plan to use the SRTR database to investigate the association between the above-mentioned immunosuppressive therapies and post-transplant malignancies among liver transplant recipients. Previous studies have suggested that recipients of an organ containing a large number of lymphocytic lineage cells that may be infected with EBV may be at greatest risk for developing PTLD (12,25). The SRTR database provides an excellent source to reinvestigate these issues to better estimate risks and modifiable factors with the goal of decreasing the number of malignancies among solid organ transplant recipients.

Acknowledgments

The authors acknowledge the helpful suggestions from Drs M. Kauffman, M. McBride, and J. Whiting of the Post-Transplant Tumor Registry Technical Advisory Committee, which serves the SRTR's Scientific Advisory Committee. The authors also thank Dr Steven K. Takemoto for his comments on a revised version of the manuscript and Miles P. Finley for his editorial assistance.

This work was supported by the Scientific Registry of Transplant Recipients (SRTR, contract number 231-00-0116), which is funded by the Department of Health and Human Services, Health Resources and Services Administration, Office of Special Programs, Division of Transplantation. The data and analyses were supplied by the SRTR through its contractor: University Renal Research and Education Association. The authors alone are responsible for the interpretation offered here.

References

1. Kew CE 2nd, Lopez-Ben R, Smith JK et al. Posttransplant lymphoproliferative disorder localized near the allograft in renal transplantation. Transplantation 2000; 69: 809–814.
2. Winkelhorst JT, Brokelman WJ, Tiggeler RG, Wobbes T. Incidence and clinical course of de-novo malignancies in renal allograft recipients. Eur J Surg Oncol 2001; 27: 409–413.
3. Ondrus D, Pribylincova V, Breza J et al. The incidence of tumours in renal transplant recipients with long-term immunosuppressive therapy. Int Urol Nephrol 1999; 31: 417–422.
4. Jain AB, Yee LD, Nalesnik MA et al. Comparative incidence of *de novo* nonlymphoid malignancies after liver transplantation under tacrolimus using surveillance epidemiologic end result data. Transplantation 1998; 66: 1193–1200.
5. Penn I. Posttransplantation *de novo* tumors in liver allograft recipients. Liver Transpl Surg 1996; 2: 52–59.
6. Mihalov ML, Gattuso P, Abraham K et al. Incidence of post-transplant malignancy among 674 solid-organ-transplant recipients at a single center. Clin Transplant 1996; 10: 248–255.
7. Barrett WL, First MR, Aron BS, Penn I. Clinical course of malignancies in renal transplant recipients. Cancer 1993; 72: 2186–2189.
8. National Kidney Federation. Cancer after kidney transplantation. Available at: http://www.kidney.org.uk/MedicalInfo/transplant/txcancer.html. Accessed May 7, 2003.
9. Libertiny G, Watson CJ, Gray DW et al. Rising incidence of post-transplant lymphoproliferative disease in kidney transplant recipients. Br J Surg 2001; 88: 1330–1334.
10. Angel LF, Cai TH, Sako EY, Levine SM. Posttransplant lymphoproliferative disorders in lung transplant recipients: clinical experience at a single center. Ann Transplant 2000; 5: 26–30.
11. Opelz G, Henderson R. Incidence of non-Hodgkin lymphoma in kidney and heart transplant recipients. Lancet 1993; 342: 1514–1516.
12. Holmes RD, Sokol RJ. Epstein-Barr virus and post-transplant lymphoproliferative disease. Pediatr Transplant 2002; 6: 456–464.
13. Winter P, Schoeneich G, Miersch WD, Klehr HU. Tumour induction as a consequence of immunosuppression after renal transplantation. Int Urol Nephrol 1997; 29: 701–709.
14. Younes BS, McDiarmid SV, Martin MG et al. The effect of immunosuppression on posttransplant lymphoproliferative disease in pediatric liver transplant patients. Transplantation 2000; 70: 94–99.
15. Jamil B, Nicholls K, Becker GJ, Walker RG. Impact of acute rejection therapy on infections and malignancies in renal transplant recipients. Transplantation 1999; 68: 1597–1603.
16. U.S. Renal Data System. USRDS 1998 Annual Data Report. Bethesda, MD: National Institutes of Health. National Institute of Diabetes and Digestive and Kidney Diseases, 1998.
17. Melosky B, Karim M, Chui A et al. Lymphoproliferative disorders after renal transplantation in patients receiving triple or quadruple immunosuppression. J Am Soc Nephrol 1992; 2: S290–S294.
18. Meier-Kriesche HU, Arndorfer JA, Kaplan B. Association of antibody induction with short- and long-term cause-specific mortality in renal transplant recipients. J Am Soc Nephrol 2002; 13: 769–772.
19. 2002 OPTN/SRTR Annual Report 1991–2001. HHS/HRSA/OSP/DOT; UNOS; URREA.
20. Dickinson DM, Ellison MD, Webb RL. SRTR Report on the State of Transplantation: data sources and structure. Am J Transplant 2003; 3: 13–28.
21. Bates WD, Gray DW, Dada MA et al. Lymphoproliferative disorders in Oxford renal transplant recipients. J Clin Pathol 2003; 56: 439–446.
22. Dharnidharka VR, Sullivan EK, Stablein DM et al. North American Pediatric Renal Transplant Cooperative Study: Risk factors for posttransplant lymphoproliferative disorder (PTLD) in pediatric kidney transplantation: a report of the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS). Transplantation 2001; 71: 1065–1068.
23. Cockfield SM. Identifying the patient at risk for post-transplant lymphoproliferative disorder. Transpl Infect Dis 2001; 3: 70–78.
24. Montagnino G, Lorca E, Tarantino A et al. Cancer incidence in 854 kidney transplant recipients from a single institution: comparison with normal population and with patients under dialytic treatment. Clin Transplant 1996; 10: 461–469.
25. Holmes RD, Orban-Eller K, Karrer FR et al. Response of elevated Epstein-Barr virus DNA levels to therapeutic changes in pediatric liver transplant patients: 56-month follow up and outcome. Transplantation 2002; 74: 367–372.