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Kidney after Non-renal Transplantation – The Impact of Alemtuzumab Induction

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In patients undergoing non-renal transplantation, the favorable outcomes associated with calcineurin inhibitors (CNI) have been tempered by the negative impact of CNI nephrotoxicity (1). This well described phenomenon has led to the development of end stage renal disease (ESRD) as an important complication of non-renal transplantation, and some of these patients have gone on to kidney transplantation. A number of centers have reported on the efficacy of alemtuzumab induction or preconditioning in patients undergoing kidney transplantation alone (2 – 10). However, there are no publications describing the utility of alemtuzumab in patients undergoing kidney after non-renal transplantation. In this report, we discuss our single center, retrospective experience with alemtuzumab induction, and compare it to a previous cohort not receiving alemtuzumab.

Patients and Methods

Between May 18, 1998 and October 8, 2007, 144 patients underwent kidney after non-renal transplantation (Table 1). 72 patients received alemtuzumab induction (1 dose of 30 mg IV or 0.4 - 0.5 mg/kg in pediatric patients), with 2 perioperative doses of steroids, and simple resumption of the pre-kidney transplantation immunosuppressive regimen. 72 patients did not receive alemtuzumab; they routinely received additional induction and maintenance steroids, higher doses of CNIs, and the addition of an antiproliferative agent (MMF) if they had not been on one previously; in addition 3 patients received thymoglobulin and 10 received daclizumab induction. There were 133 (92.4%) adults and 11 (7.6%) children. 35 (24.3%) had undergone previous heart, 16 (11.1%) lung, 87 (60.4%) liver, and 6 (4.2%) multivisceral transplantation. There were 100 (69.4%) deceased donor transplants, with a mean CIT of 24.7 $\pm$ 7.9 hours, and 44 (30.6%) living donor cases; although there was a slightly higher percentage of living donors in the alemtuzumab group compared to the no alemtuzumab group, this was not statistically different. Alemtuzumab began to be used in our institution in late 2002, so that the follow-up for the alemtuzumab patients was shorter, 23.3 $\pm$ 15.0 months, than for the no alemtuzumab patients, 48.1 $\pm$ 36.9 months. Once alemtuzumab began to be utilized, almost all patients undergoing kidney after non-renal transplantation received it, except for 1 patient who received thymoglobulin and 6 patients who received daclizumab. The overall mean follow-up was 35.7 $\pm$ 30.7 months.

Statistics

Continuous variables were compared using the t-test with Levene's test employed for verifying the assumption of equality of variance. The chi-square test was used to compare categorical variables.

Institutional Oversight

The data analysis was performed on de-identified data by one of the honest brokers in our division, Joseph Donaldson, under the guidelines of the IRB protocol number 0505123. (11)

Results (Table 2)

Overall 1 and 3 year actuarial patient survival was 91.5% and 75.3%, and was 93.0% and 78.9% in the alemtuzumab group and 90.0% and 72.4% in the no alemtuzumab group, respectively (p = ns). Overall 1 and 3 year actuarial graft survival was 88.1% and 71.4%, and was 93.0% and 75.3% in the alemtuzumab group and 83.3% and 68.7% in the no alemtuzumab group, respectively ($p = 0.051$ – Figure 1). The overall mean serum creatinine levels at 1 and 3 years were 1.4 ± 0.7 mg/dl and 1.5 ± 0.9 mg/dl, respectively, and were not statistically different between the two groups. The incidence of acute rejection was lower in the alemtuzumab group, 15.3%, than in the no alemtuzumab group, 41.7% ($p = 0.0001$ – Table 3). The incidence of delayed graft function, defined as the need for dialysis during the first week after transplantation, was lower in the alemtuzumab group, 9.7%, than in the no alemtuzumab group, 25.0% ($p = 0.003$ – Table 3). This difference persisted when only the deceased donor cases were considered: The incidence of DGF in the alemtuzumab group was 15.6%, and in the no alemtuzumab group, it was 32.7% ($p < 0.05$). The incidence of viral complications was not different between the two groups. We performed several subgroup analyses, looking for any other significant factors, including living donation, hepatitis C, diabetes, and the use of extended criteria donor kidneys, which might have explained the differences, but none was associated with any outcome differences (data not shown).

There were 19 HCV+ patients undergoing kidney after non-renal transplantation; 7 (4 liver, 2 heart & 1 lung) received alemtuzumab and 12 (all liver) did not; 10 received no induction, and 2 received daclizumab. The alemtuzumab cases were transplanted prior to the publication of the paper that showed problematic outcomes associated with alemtuzumab and HCV in liver transplantation (12). The numbers of cases were in any event too small to analyze.

The alemtuzumab/no alemtuzumab differences were observed in all non-renal transplant subgroups (i.e. heart, lung, liver, multivisceral – data not shown), although statistical significance was noted only when the groups were combined.

Discussion

Kidney after non-renal transplantation is an uncommon subject for discussion, and the approach to immunosuppression is not well defined. In our center, it has accounted for 7.1% of the kidney transplantations that have been performed, with 144/2034 cases in less than 10 years. As the kidney is a third party antigen, and as the level of immunosuppression in non-renal transplant recipients tends to be relatively low by the time a kidney transplantation needs to be performed, some additional immunosuppression needs to be administered to prevent rejection of the kidney. The advantage of alemtuzumab induction in this context is that the baseline immunosuppression does not need to be changed. This simplifies patient management after transplantation and may have the further advantage of being associated with less rejection, less DGF, and slightly better graft survival, without any increase in viral complications. It is important to remember, however, that the no alemtuzumab group was not randomized and was more of an historic control, so that these differences have to be interpreted with caution.

There are certain settings in kidney after non-renal transplantation where alemtuzumab may not necessarily be a good idea. These would include patients who are hepatitis C (HCV) positive and have had a previous liver transplant (12), or recently transplanted patients who have received heavy immunosuppression for the non-renal organ. In these situations, accounting for 6 cases in our series, we utilized daclizumab induction 1mg/kg at the time of transplantation and every 2 weeks for 4 additional doses, with standard tacrolimus/MMF-based immunosuppression, without additional maintenance steroids. This seemed anecdotally to be a satisfactory approach in these 6 patients.

This experience has important and obvious limitations. It is retrospective, and, as mentioned above, not randomized, and the no alemtuzumab group is mostly an historical control. Unfortunately, kidney after non-renal transplantation is not performed very often, and a randomized trial, either single center or multicenter, while desirable, will not be straightforward to perform. In the absence of such a trial, the experience reported here suggests that alemtuzumab induction with resumption of pre-kidney transplantation immunosuppression may possibly represent a simple and effective regimen in patients undergoing kidney after non-renal transplantation.

Table 1

	Overall	Alemtuzumab Group	No Alemtuzumab Group
Time	5/18/1998 - 10/8/2007	1/15/2003 - 10/8/2007	5/18/1998 - 7/21/2007
N	144	72	72
Recipient Age (yrs.)	52.1 +- 16.6	54.1 +- 15.5	50.1 +- 17.5
Donor Age (yrs.)	38.4 +- 16.5	38.0 +- 15.5	38.9 +- 17.6
Time after Non-renal Tx (yrs.)	8.1 +- 4.7	8.3 +- 5.1	8.0 +- 4.4
Adult	133 (92.4%)	68 (94.4%)	65 (90.3%)
Child	11 (7.6%)	4 (5.6%)	7 (9.7%)
Previous			
Heart	35 (24.3%)	26 (36.1%)	9 (12.5%)
Lung	16 (11.1%)	7 (9.7%)	9 (12.5%)
Liver	87 (60.4%)	37 (51.4%)	50 (69.4%)
Multivisceral	6 (4.2%)	2 (2.8%)	4 (5.6%)
Deceased Donor	100 (69.4%)	45 (62.5%)	55 (76.4%)
Cold Ischemia Time	24.7 +- 7.9 hrs	24.2 +- 7.5 hrs	25.1 +- 8.4 hrs
HCV+	19 (13%)	7 (10%)	12 (17%)
Living Donor	44 (30.6%)	27 (37.5%)	17 (23.6%)
PRA	3.3 +- 9.6	2.6 +- 9.7	4.0 +- 9.4

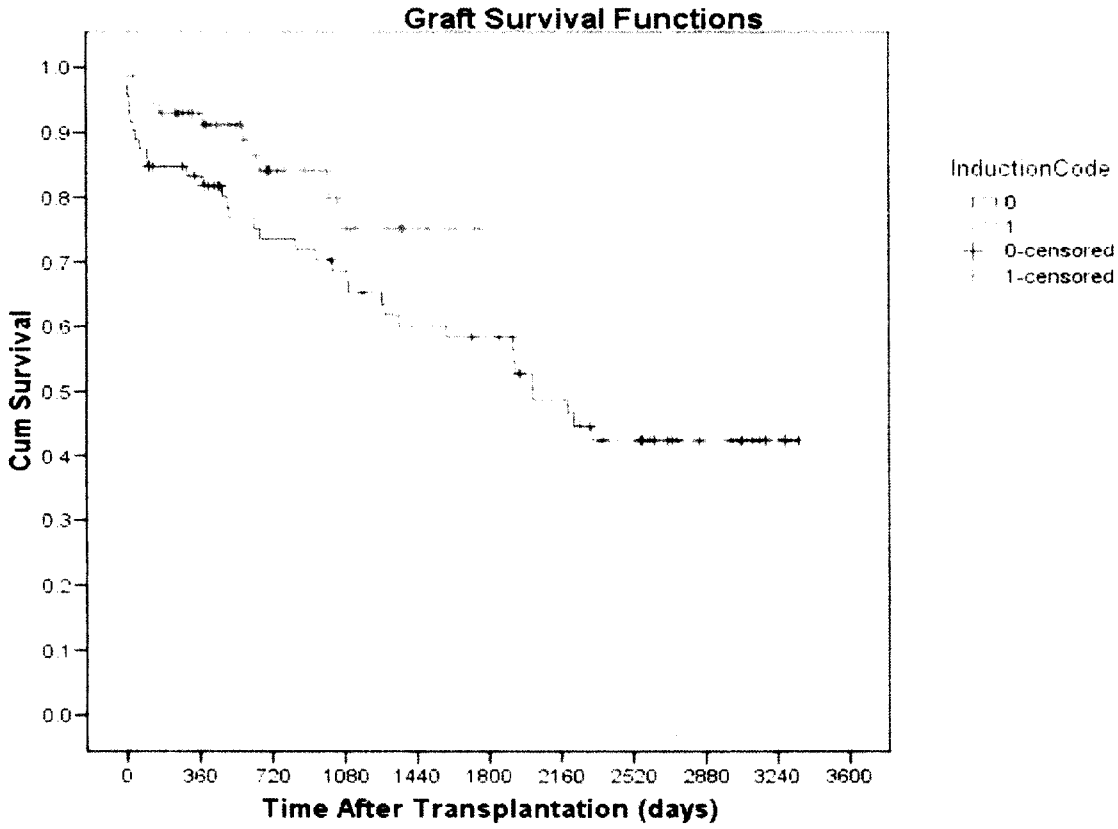
Table 2

	Overall	Alemtuzumab Group	No Alemtuzumab Group
Patient			
1 year Survival %	91.5%	93.0%	90.0%
3 year Survival %	75.3%	78.9%	72.4%
Graft			
1 year Survival %	88.1%	93.0%	83.3%
3 year Survival %	71.4%	75.3%*	68.7%
Mean Serum Creatinine			
1 year	1.4 +- 0.7 mg/dl	1.3 +- 0.5 mg/dl	1.5 +- 0.8 mg/dl
3 year	1.5 +- 0.9 mg/dl	1.3 +- 0.7 mg/dl	1.6 +- 1.0 mg/dl
		* p = 0.051	

Table 3

	Overall	Alemtuzumab Group	No Alemtuzumab Group
Complications			
Acute Rejection			
6 Month	16%	2.8%	29.2%**
1 Year	20.8%	8.3%	33.3%***
Total	28.5%	15.3%	41.7%**
Delayed Graft Function	17.4%	9.7%	25.0%***
Living Donor	0%	0%	0%
Deceased Donor	25%	15.6%	32.7%****
CMV	0%	0%	0%
PTLD	0.7%	0%	1.4%
BK Virus	4.2%	4.2%	2.8%
			** $p = 0.0001$
			*** $p = 0.003$
			**** $p < 0.05$

Figure 1 - Graft Survival in Kidney after Non-renal Transplantation
(alemtuzumab [redacted] ; no alemtuzumab [redacted])



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References

1. Ojo AO, Held PJ, Port FK, Wolfe RA, Leichtman AB, Young EW, Arndorfer J, Christensen L, Merion RM. Chronic Renal Failure after Transplantation of a Nonrenal Organ. N Engl J Med 2003; 349(10):331-40.

2. Waldmann H. A personal history of the CAMPATH-1H antibody. Med Oncol 2002; 19(suppl):3.

3. Calne R, Friend P, Moffatt S, et al. Prope tolerance, perioperative Campath 1H, and low-dose cyclosporine Monotherapy in renal allograft recipients. Lancet 1998; 351:1701.

4. Stuart FP, Leventhal JR, Kaufman DB. Alemtuzumab facilitates prednisone free immunosuppression in kidney transplant recipients with no early rejection. Am J Transplant 2002; 2(suppl):397.

5. Knechtle SJ, Pirsch JD, H Fechner J Jr, et al. Campath-1H induction plus rapamycin monotherapy for renal transplantation results of a pilot study. Am j Transplant 2003; 3:722.

6. Kirk AD, Hale DA, Mannon RB, et al. Results from a human renal allograft tolerance trial evaluating the humanized CD52-specific monoclonal antibody alemtuzumab (CAMPATH-1H). Transplantation 2003; 76:120.

7. Shapiro R, Basu A, Tan HP, et al. Kidney transplantation under minimal immunosuppression after pretransplant lymphoid depletion with thymoglobulin or Campath. J Am Coll Surg 2005; 200:505.

8. Shapiro R, Ellis D, Tan HP, et al. Antilymphoid antibody preconditioning and tacrolimus monotherapy for pediatric kidney transplantation. J Pediatr 2006; 148:813.

9. Tan HP, Kaczorowski DJ, Basu A, et al. Living donor renal transplantation using alemtuzumab induction and tacrolimus monotherapy. Am J Transpl 2006; 6:2409.

10. Shapiro R, Zeevi A, Basu A, Tan HP, Kayler L, Blisard D, Thai N, Girnita A, Randhawa P, Gray E, Marcos A, Starzl TE. Alemtuzumab preconditioning with tacrolimus monotherapy-the impact of serial monitoring for donor-specific antibody. Transplantation 2008; 85(8):1125-1132.

11. University of Pittsburgh Institutional Review Board (homepage on the internet) Pittsburgh: University of Pittsburgh;2006 (updated 2006 January 17; cited 2006 February 10). Jurisdiction, Structure, and Responsibilities of the Institutional Review Board. Reference Manual for the Use of Human Subjects in Research. Available online at http://www.irb.pitt.edu/manual/preface.pdf

12. Eghtesad B, Fung JJ, Demetris, AJ, Murase N, Ness R, Bass DC, Gray EA, Shakil O, Flynn B, Marcos A, and Starzl TE, Immunosuppression for Liver Transplantation in HCV-Infected Patients: Mechanism-Based Principles. Liver Transplantation 2005; 11(11):1343-52.