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Kidney after Extrarenal Transplantation – The Impact of Alemtuzumab Induction

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In patients undergoing extrarenal 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 extrarenal 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 extrarenal 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 extrarenal 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 (or, for the most part, any other antibody induction); they routinely received additional induction and maintenance steroids, higher doses of CNIs, and the addition of an antiproliferative agent (usually MMF) if they had not been on one previously. 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. 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. 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 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 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 $\pm$ 0.7 mg/dl and 1.5 $\pm$ 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). The incidence of viral complications was not different between the two groups.

Discussion

Kidney after extrarenal 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 extrarenal transplants 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 has the further advantage of less rejection, less DGF and slightly better graft survival, without any increase in viral complications.

There are certain settings in kidney after extrarenal transplantation where alemtuzumab is not necessarily 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 extrarenal organ. In these situations, we have recently 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 seems anecdotally to be a satisfactory approach.

This experience has obvious limitations. It is retrospective, not randomized, and the no alemtuzumab group is something of an historical control. Unfortunately, kidney after extrarenal 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 represents a simple and effective regimen in patients undergoing kidney after extrarenal 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 Extrarenal 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
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

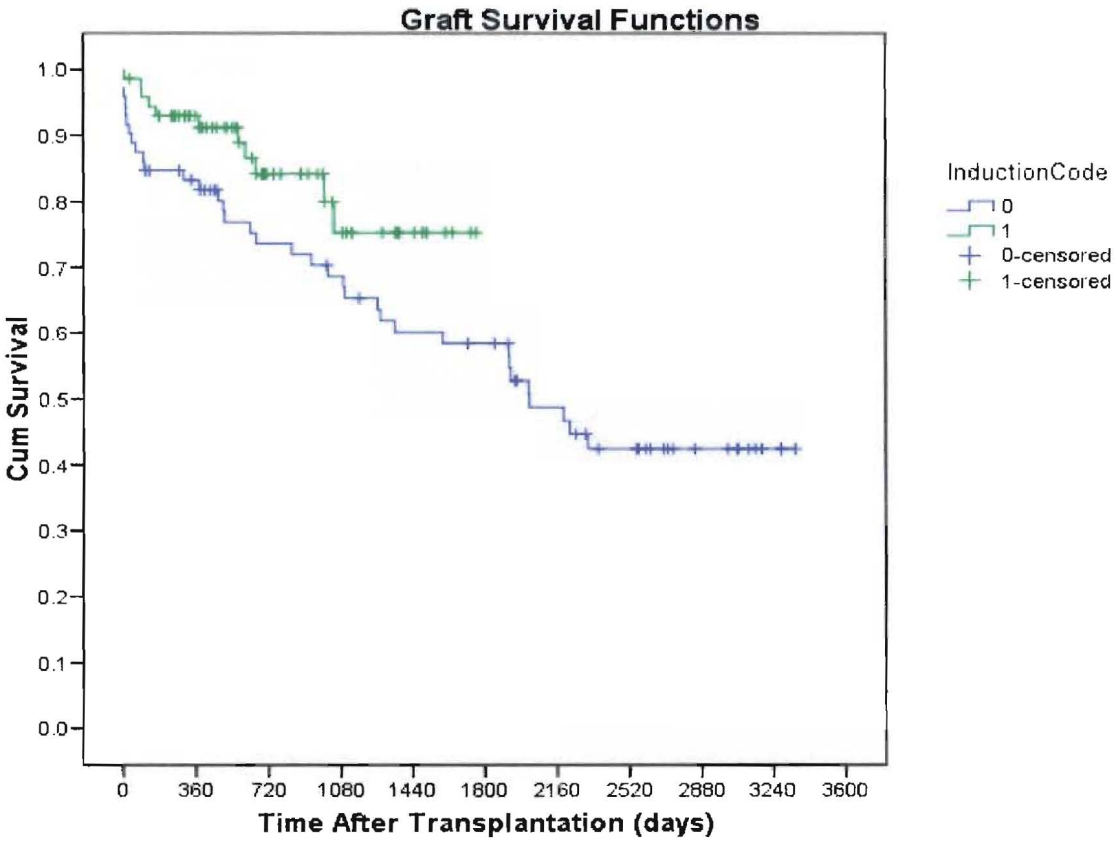
	Overall	Alemtuzumab Group	No Alemtuzumab Group
Patient			
1 year Survival %	91.5%	93.0%	90.0%
3 year Survival %	75.3%	78.9%	72.4%
Graft			
1 year Survival %	88.1%	93.0%	83.3%
3 year Survival %	71.4%	75.3%*	68.7%
Mean Serum Creatinine			
1 year	1.4 +- 0.7 mg/dl	1.3 +- 0.5 mg/dl	1.5 +- 0.8 mg/dl
3 year	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	28.5%	15.3%	41.7%**
Delayed Graft Function	17.4%	9.7%	25.0%***
CMV	0%	0%	0%
PTLD	0.7%	0%	1.4%
BK Virus	4.2%	4.2%	2.8%
			** p = 0.0001
			*** p = 0.003

Figure 1 - Graft Survival in Kidney after Extrarenal Transplantation

(alemtuzumab ; no alemtuzumab)



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