Transplant International

LETTER TO THE EDITOR

Effect of alemtuzumab or basiliximab induction therapy on graft function and survival of kidneys from donors after cardiac death

doi:10.1111/j.1432-2277.2009.00910.x

We read with interest the manuscript entitled 'Alemtuzumab induction and triple maintenance immunotherapy in kidney transplantation from donors after cardiac death' recently published in Transplant International [1]. The authors compared the effect of three induction therapies and triple maintenance therapy on kidney transplants from DCD. In this report, there was a trend towards inferior graft survival and significantly higher incidence of CMV infections in the alemtuzumab group compared with those of anti-thymocyte globulin and basiliximab groups. The authors concluded that 'induction with alemtuzumab does not confer any advantage over traditional induction agents'. Interestingly, our experience with alemtuzumab as induction therapy in DCD kidney transplantation is different.

Recent reports suggest that early lymphocyte infiltration into the graft contributes to the pathogenesis of delayed graft function (DGF) secondary to ischaemia-reperfusion injury (IRI) [2,3], highlighting the potential role of lymphocyte-depleting agents in reducing the incidence of DGF in human DCD kidney transplants. With the aim of investigating whether induction with a lymphocyte-depleting agent such alemtuzumab is more effective in reducing the incidence of DGF in recipients of DCD kidneys than basiliximab, a nondepleting antibody, we compared the outcome of 15 consecutive recipients of

Table 1. Donor and recipient characteristics and pre-implantation data of kidneys from DCD according their induction therapy regime: alemtuzumab or basiliximab.

	Alemtuzumab, *n* = 15 (%)	Basiliximab, *n* = 15 (%)	*P*-value*
Donor data			
Age (years)†	41 ± 4.5 [17–61]	43 ± 3.8 [17–59]	NS
Female:Male‡	6:9 (40:60)	13:7 (65:35)	NS
Cerebrovascular accident‡	4 (27)	7 (47)	NS
History of Hypertension‡	1 (7)	0 (0)	NS
Creatinine Clearance (ml/min)§	104 [80–113]	106 [94–119]	NS
Recipient data‡			
Age (years)†	46.3 ± 3.7 [20–67]	48 ± 3 [30–69]	NS
Female:Male‡	3:12 (20:80)	8:7 (54:46)	0.06
Days waiting§	365 [280–500]	1030[491–2700]	0.02*
Re-transplant‡	3 (20)	2 (13)	NS
Pre-transplant HLA antibodies‡	3 (20)	4 (26)	NS
High sensitization (>85% PRA) ‡	2 (13)	1 (7)	NS
Number of HLA mismatches‡			
0	0 1 (7)	0 (0)	NS
1–2	5 (33)	5 (33)	NS
3–4	9 (60)	10 (67)	NS
5–6	0 (0)	1 (7)	NS
Pre-implantation data			
Pulsatile perfusion‡	15 (100)	15 (100)	NS
Warm ischemia time (m)§	18 [16–20]	17.8 [14–22]	NS
Cold ischemia time (m)§	1100 [870–1318]	1160 [950–1475]	NS
Implantation time (m)§	58 [51–72]	45 [38–58]	NS

†Values are Mean/[Range]; ‡Values are number (percentage); §Values are Median/[InterQuartile Range]; PRA, panel reactive HLA antibodies; *Fisher exact test: $P < 0.05$.

Table 2. Post-transplant clinical outcome of kidneys from DCD according to their induction therapy regime: alemtuzumab or basiliximab.

	Alemtuzumab *n* = 15 (%)	Basiliximab *n* = 15 (%)	*P*-value*
Clinical follow-up (days)†	1370 ± 47 [184]	1019 ± 103 [400]	0.005*
Maintenance therapy‡			
TAC/Sir+MMF	15 (100)	15 (100)	NS
Prednisolone	0 (0)	15 (100)	<0.000*
Recipient white cell count			
Total¶:PMN/Lymphocytes(%)§			
Day 0	7.6[3.8]/62[5]/25[4.5]	8.0[4.2]/65[8.5]/27[6]	NS
Day 1	11.8[6.8]/98[0.5]/0.8[0.7]	12.4[7.2]/71[8]/25[5.5]	<0.0000
Day 3	8.6[4.7]/96[2]/1.3[1.5]	9.7[5.5]/70[5]/28[4.5]	<0.0000
Day 5	4.1[1.5]/96[1]/1.5[0.4]	7.9[3.2]/75[6]/23[2.5]	<0.0000
Day 7	4.5[1.7]/96[1]/3[2]	6.8[3.1]/68[4]/28[2]	<0.0000
Early clinical outcome‡			
Primary nonfunction	0 (0)	0 (0)	NS
Immediate graft function	9 (60)	6 (40)	0.07
Delayed graft function	6 (40)	9 (60)	0.07
Acute rejection	0 (0)	1 (7)	NS
Hospitalization ± (days)	10 [7–16]	11 [6–25]	NS
Postoperative Complications‡			
Severe neutropenia	0 (0)	0 (0)	NS
Pneumonia	0 (0)	1 (7)	NS
Urosepsis	1 (7)	1 (7)	NS
Ureteral obstruction	1 (7)	0 (0)	NS
Retroperitoneal bleeding	1 (7)	0 (0)	NS
Medium-term complications‡			
Trigeminal Zoster	1 (7)	0 (0)	NS
EBV infection	1 (7)	0(0)	NS
CMV infection	1 (7)	0 (0)	NS
HVC infection	0 (0)	1 (7)	NS
BKV	3 (21)	2 (14)	NS
PTLD	2 (14)	1(7)	NS
Skin malignancies	1(7)	1 (7)	NS
Breast cancer	1 (7)	0 (0)	NS
Serum creatinine (mmol/dL)†			
1 year	155 ± 13 [51]	158 ± 18 [67]	NS
2 years	162 ± 14 [76]	140 ± 12 [41]	NS
3 years	165 ± 22 [82]	141 ± 10 [36]	NS
4 years	152 ± 22 [77]	147 ± 5 [8]	NS
Graft survival‡			
1 year	15 (100)	13 (86)	0.03**
4 years	15 (100)	12 (80)	0.004**
Patient survival‡			
1 year	15 (100)	13 (86)	0.03**
4 years	15 (100)	13 (86)	0.03**

†Values are mean ± S.E (S.D), ‡Values are number (percentage), §Values are Median/[S.D], ¶Total count in thousands.
*Fisher exact test: $P < 0.05$, **Log rank (Mantel-Cox): $P < 0.05$.

DCD kidney transplants treated with alemtuzumab with that of 15 consecutive recipients of DCD kidneys treated with basiliximab. All DCD were Maastrich category III [4] and their kidneys were retrieved and preserved by following our local DCD protocol [5]. From November 2004 to June 2005, 15 recipients of DCD kidneys were treated with two doses of 30 mg of alemtuzumab (Campath®, Berlex, Montville, NJ, USA) while from July 2005 to March 2006, 15 recipients were treated with two doses of 40 mg of basiliximab (Simulect®, Novartis Pharma, Numberg, Switzerland). Maintenance therapy in the basiliximab group was based on tacrolimus (TAC), mycophenolate of mophetil (MMF) and prednisolone (PDN). In contrast, all patients in the alemtuzumab group received only TAC and MMF, remaining steroid-free after transplantation.

Donor and recipient demographics and post-transplant outcome were retrospectively obtained from our prospective transplant database and confirmed by review of the clinical files. Primary end-points were the incidence of immediate graft function (IGF), primary nonfunction (PNF) and delayed graft function (DGF); levels of serum creatinine, and graft and patient survival. DGF was defined as the need for dialysis during the first week after transplantation, excluding episodes of dialysis secondary to fluid overload or hyperkalaemia during the first 24 h post-transplantation. Secondary end-points were the incidence of biopsy-proven episodes of acute rejection (AR), length of hospitalization, surgical complications, occurrence of viral infections, lymphoproliferative disease (PTLD) and solid malignancies. Fisher's exact test and Mann–Whitney *U*-test were used as appropriate, and two-tailed *P*-values <0.05 were considered to indicate statistical significance.

Donor and recipient characteristics were similar between both groups (Table 1). All kidneys in both groups were machine perfused, and there was no difference in warm and cold ischaemic and implantation time. Patients in the basiliximab group were transplanted after the first 15 consecutive cases and were on the waiting list longer than those in the alemtuzumab group. Administration of alemtuzumab produced rapid and profound lymphocyte depletion while basiliximab did not have a significant impact on the lymphocyte count (Table 2). The incidence of DGF in the alemtuzumab group was 40%, while that in the basiliximab group was 60%. Similarly, the levels of serum creatinine at day 7 were lower in the alemtuzumab group than that in the basiliximab group. However, these differences did not reach statistical significance (Table 2). The length of hospitalization, the incidence of biopsy-proven AR and the levels of serum creatinine at 1, 2, 3 and 4 years were similar between both groups. Similarly, there was no difference in the incidence of CMV active disease, BK virus infection, post-transplant lymphoproliferative disease (PTLD) and solid malignancies between both groups after 4 years of follow-up (Table 2). One patient in the alemtuzumab group developed B-cell lymphoma and was treated with immunosuppression withdrawal and administration of rituximab. After treatment, the lymphoma disappeared and the patient has remained immunosuppression-free, with normal renal function and no evidence of acute rejection episodes. Graft survival was significantly higher in the alemtuzumab group at 1 and 4 years (100%) compared to that of the basiliximab group (87% and 80%) (Fig. 1). Two recipients died, both with nonfunctioning grafts (cardiac failure and multi-organ failure), and one recipient underwent allograft nephrectomy after 900 days post-transplant as a result of CAN.

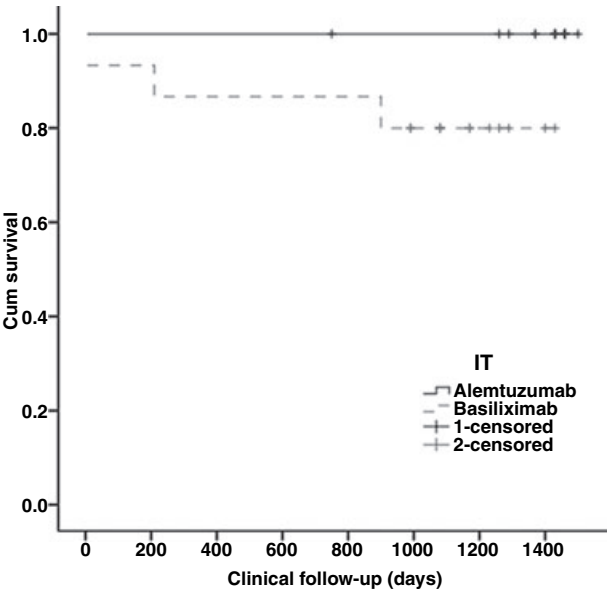

Figure 1 Graft survival of kidneys from DCD after induction therapy with alemtuzumab or basiliximab.

Studies with T, B and NKT cells knockout mice, which are genetically protected from IRI, showed that transfer of wild-type T, B and NKT cells reconstitutes the tissue injury observed in wild-type mice after reperfusion, emphasizing the potential role of these cells in the development of injury after transplantation [2,3]. Similarly, analyses of human samples have shown that induction with alemtuzumab causes a rapid and significant depletion of T and B lymphocytes, monocytes, dendritic cells and natural killer cells of transplant recipients, and that the degree of lymphocyte depletion correlated with a decrease in proliferative and effector T cell responses, acute rejection and probably the amount of cell injury after reperfusion [6,7]. These properties of alemtuzumab might be associated with the 20% reduction in the incidence of DGF observed in the alemtuzumab group compared with that of the basiliximab group in our clinical pilot study. In this short-term analysis, the trend towards lower DGF and significantly higher 1 and 4 year graft survival in the alemtuzumab group were not associated with a significant increase in the incidence of viral infections, as shown by Schadde *et al.* [1]. Additionally, the occurrence of PTLD, skin and solid malignancies in our study was similar in both groups and these results are consistent with recent evidence suggesting that alemtuzumab might have a protective effect against the development of PTLD in kidney transplantation [8]. We agree that results from randomized studies or the analysis of larger series is needed to clarify the role of alemtuzumab as induction therapy in DCD kidney transplantation. However, these

results will provide the readers of Transplant International the opportunity of contrasting two different experiences from alemtuzumab as induction agent in recipients of kidney transplants from DCD.

Juan J. Plata-Munoz,[1,2] Anil Vaidya,[2]
Susan V. Fuggle[1,2] and Peter J. Friend[1,2]
1 Nuffield Department of Surgery of the University of Oxford, Oxford, UK
2 Oxford Transplant Centre of the University of Oxford, Oxford, UK

References

1. Schadde E, D'Alessandro AM, Knechtle SJ, *et al.* Alemtuzumab induction and triple maintenance immunotherapy in kidney transplantation from donors after cardiac death. *Transpl Int* 2008; **21**: 625.
2. Burne MJ, Daniels F, El Ghandour A, *et al.* Identification of the $CD4^+$ T cell as a major pathogenic factor in ischemic acute renal failure. *J Clin Invest* 2001; **108**: 1283.
3. Gandolfo MT, Rabb H. Very early alloantigen-independent trafficking of lymphocytes during ischemic acute kidney injury. *Kidney Int* 2007; **71**: 1193.
4. Kootstra G, Daemen JH, Oomen AP. Categories of non-heart-beating donors. *Transplant Proc* 1995; **27**: 2893.
5. Plata-Munoz JJ, Muthusamy A, Quiroga I, *et al.* Impact of pulsatile perfusion on postoperative outcome of kidneys from controlled donors after cardiac death. *Transpl Int*, 2008; **21**: 899.
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-H1). *Transplantation* 2003; **76**: 120.
7. Trzonkowski P, Zilvetti M, Friend P, Wood KJ. Recipient memory-like lymphocytes remain unresponsive to graft antigens after CAMPATH-H1 induction with reduced maintenance immunosuppression. *Transplantation*, 2006; **82**: 1342.
8. Kirk AD, Cherikh WS, Ring M, *et al.* Dissociation of depletional induction and posttransplant lymphoproliferative disease in kidney recipients treated with alemtuzumab. *Am J Transplant* 2007; **7**: 2619.

