The risk of cancer in kidney transplant recipients may be reduced in those maintained on everolimus and reduced cyclosporine

Wai H. Lim[1,2], Graeme R. Russ[3], Germaine Wong[4,5], Helen Pilmore[6,7], John Kanellis[8] and Steven J. Chadban[9,10]

[1]Department of Renal Medicine, Sir Charles Gairdner Hospital, Perth, Australia; [2]University of Western Australia, Perth, Australia; [3]Central and Northern Adelaide Renal and Transplantation Services, South Australia, Australia; [4]Centre for Transplant and Renal Research, Westmead Hospital, New South Wales, Australia; [5]Centre for Kidney Research, The Children's Hospital at Westmead, New South Wales, Australia; [6]Renal Unit, Auckland Hospital, Auckland, New Zealand; [7]Department of Medicine, Auckland University, Auckland, New Zealand; [8]Department of Nephrology and Transplant Services, Monash Medical Centre, Melbourne, Australia; [9]Department of Renal Medicine, Royal Prince Alfred Hospital, Sydney, Australia; and [10]Kidney Node, Charles Perkins Centre, University of Sydney, Australia

Kidney transplant recipients are at a high risk of developing cancers after transplantation. Switching from calcineurin inhibitors to sirolimus has been shown to prevent secondary nonmelanoma skin cancer but whether everolimus with reduced exposure to calcineurin inhibitors has similar anti-cancer effects remains unknown. Therefore, we compared the risk of incident cancer over seven years of follow-up among kidney transplant recipients randomized to everolimus plus reduced exposure cyclosporine versus mycophenolate sodium and standard exposure cyclosporine. Using the Australian and New Zealand Dialysis and Transplant Registry (ANZDATA), we assessed the seven-year risk of incident cancer and other graft outcomes among a subgroup of recipients who had participated in the A2309 study using adjusted Cox proportional hazard models. Of 95 recipients, 66 were randomized to everolimus (1.5 mg or 3 mg) with reduced cyclosporine and 29 received mycophenolate sodium and standard exposure cyclosporine. Compared to mycophenolate sodium and standard exposure cyclosporine, everolimus treatment was associated with unadjusted hazard ratios of 0.28 (95% confidence interval 0.11-0.74), 0.39 (0.16-0.98) and 0.41 (0.23-0.71), respectively for nonmelanoma skin cancer, non-skin cancers and any cancers. Interestingly, the adjusted hazard ratios were 0.34 (0.13-0.91), 0.35 (0.09-1.25) and 0.32 (0.15-0.71), respectively. There was no association between treatment groups and rejection, graft loss or death. Compared to standard-exposure cyclosporine, everolimus with reduced exposure to cyclosporine may be associated with a reduced risk of cancer, particularly for non-melanoma skin cancer. Thus, if confirmed in larger patient cohorts, *de novo* use of everolimus with reduced exposure to calcineurin inhibitors may enable a reduction in cancer burden after transplantation.

Correspondence: *Steven Chadban, Transplantation, Level 9, Royal Prince Alfred Hospital, Missenden Road, Camperdown, NSW Australia 2050. E-mail: steve.chadban@sswahs.nsw.gov.au*

Received 13 September 2016; revised 31 October 2016; accepted 10 November 2016

Kidney International (2017) ■, ■–■; http://dx.doi.org/10.1016/j.kint.2016.11.008

KEYWORDS: A2309 trial; ANZDATA; cancer; cyclosporine; epidemiology; everolimus

Calcineurin inhibitors (CNIs) revolutionized clinical practice in transplantation by enabling recipients to achieve excellent short-term patient and kidney survival. However, CNIs have done little to prevent graft and patient attrition beyond the first year, both of which continue to accrue at 2% per annum according to most reports.[1,2] Long-term CNI therapy has been associated with the development of chronic allograft dysfunction/interstitial fibrosis and tubular atrophy and increased risks of cardiovascular disease and cancer in kidney transplant recipients.[3–5]

Mammalian target of rapamycin (mTOR) inhibitors are alternative immunosuppressive agents with antiproliferative and immunosuppressive effects.[6] A recent meta-analysis of 27 randomized controlled trials (RCTs) showed that elimination of CNI after switching to an mTOR inhibitor after kidney transplantation may lead to improved graft function and lower risks of skin cancer and viral infections, while maintaining comparable rates of acute rejection compared with continuing CNI therapy.[7] Trials of *de novo* mTOR inhibition and trials of a combination of mTOR inhibitor and CNI were not included.

Trials of *de novo* use of mTOR inhibitors without CNI have demonstrated an excess of acute rejection as compared with CNI, mycophenolate, and steroids.[8,9] However, *de novo* mTOR inhibition in combination with CNI, at either usual or reduced exposure, has been reported to achieve rates of acute rejection and graft loss similar to those achieved with CNI, mycophenolate, and steroid controls across several studies.[9–11]

Most RCTs related to transplantation are limited by a relatively short duration of follow-up, thereby limiting capacity to compare the incidence of important long-term outcomes including cancer, graft failure, and death. Linkage

of clinical trials to registries may allow the provision of data concerning long-term outcomes, thereby greatly improving power to detect a difference between treatment groups.[12,13]

The A2309 Study was a global, multicenter, *de novo*, RCT in which graft and patient outcomes at 2 years were compared between kidney transplant recipients who received everolimus with reduced exposure cyclosporine and those who received standard dose cyclosporine and mycophenolate sodium, both in combination with basiliximab and maintenance steroids.[10] In this study, by linkage to the Australia and New Zealand Dialysis and Transplant (ANZDATA) Registry, we aimed to compare the longer-term graft and patient outcomes, including incidence of cancer, of those randomly assigned to the 2 treatment groups using intention-to-treat analysis.

RESULTS

Study population

Table 1 shows the baseline characteristics of the study population stratified by treatment type. Of the 95 living and deceased donor kidney transplant recipients who were followed up for a median of 7.3 years (interquartile range 6.7 to 7.6 years) resulting in 658 person-years, 35 (34.7%), 31 (40.5%), and 29 (24.8%) were randomized to receive everolimus 1.5 mg, everolimus 3 mg, and standard exposure cyclosporine with mycophenolate sodium and corticosteroids (MPA), respectively. A total of 26 (27.4%) recipients experienced acute rejection, 23 (24.2%) experienced graft loss, 17 (17.9%) developed nonmelanoma skin cancer (NMSC), 10 (10.5%) developed non-skin cancers, and 14 (14.7%) died. Donor and recipient age, immunologic profile, and burden of comorbidities were similar for the 3 treatment groups. The majority of the kidney transplantations were completed between 2006 and 2007, and more than 50% of kidneys were from living donors.

There were no significant differences in the incidence of delayed graft function, any rejection, type of rejection, graft loss, or death among groups. The majority of acute rejection episodes occurred in the first 12 months after transplantation, and treatment for acute rejection was administered to 6 patients in each group (17%–21%), including pulsed methylprednisolone in the majority and lymphocyte-depleting antibodies in only 2 cases (1 each in the everolimus 1.5 and MPA groups).

Table 1 | Baseline characteristics of A2309 study participants in Australia and Zealand (n = 95)

	1.5 mg Everolimus (n = 35)	3 mg Everolimus (n = 31)	MPA (n = 29)	*P* value
Demographics				
Age, yr (mean ± SD)	46.9 ± 12.6	45.4 ± 12.8	50.7 ± 11.6	0.230
Male (n, %)	24 (68.6)	22 (71.0)	20 (69.0)	0.976
Caucasian (n, %)	34 (97.1)	26 (83.9)	26 (89.7)	0.463
Diabetes (n, %)	8 (22.9)	4 (12.9)	7 (24.1)	0.468
Coronary artery disease (n, %)	6 (17.1)	7 (22.6)	13 (44.8)	0.109
Body mass index, kg/m^2, (mean ± SD)	25.0 ± 4.8	25.3 ± 3.8	26.3 ± 3.9	0.468
Waiting time, yr (mean ± SD)	2.5 ± 2.2	2.0 ± 1.9	2.5 ± 2.9	0.653
Hypertension (n, %)	5 (14.3)	6 (19.4)	4 (13.8)	0.801
Peripheral vascular disease (n, %)	4 (11.4)	0 (0.0)	7 (24.1)	0.063
Cerebrovascular disease (n, %)	0 (0.0)	1 (3.2)	0 (0.0)	0.153
Smoker (n, %)				0.930
Nonsmoker	18 (51.4)	16 (51.6)	14 (48.3)	
Former smoker	4 (11.4)	3 (9.7)	10 (34.5)	
Current smoker	13 (37.2)	12 (38.7)	5 (17.2)	
Cause of ESRD (n, %)				0.625
Glomerulonephritis	15 (42.9)	14 (45.2)	16 (55.2)	
Diabetes	3 (8.6)	4 (12.9)	1 (3.4)	
Cystic	7 (20.0)	7 (22.6)	4 (13.8)	
Vascular/hypertension	0 (0.0)	2 (6.5)	1 (3.2)	
Other	10 (28.5)	4 (12.8)	7 (24.4)	
Donor characteristics				
Age, yr (mean ± SD)	45.6 ± 15.5	43.9 ± 14.9	46.7 ± 14.7	0.765
Male (n, %)	18 (51.4)	9 (29.0)	14 (48.3)	0.149
Deceased donors (n, %)	17 (48.6)	15 (48.4)	14 (48.3)	0.342
Preemptive (n, %)	1 (2.9)	5 (16.1)	4 (13.8)	0.170
Immunology/Transplant				
HLA-ABDR mismatches (mean ± SD)	3.4 ± 1.6	3.3 ± 1.6	3.7 ± 1.7	0.543
Ischemic time, h (mean ± SD)	7.2 ± 6.1	7.0 ± 6.1	6.8 ± 5.2	0.962
Peak PRA >25% (n, %)	3 (8.6)	2 (6.5)	3 (10.3)	0.411
Induction (n, %)	32 (91.4)	29 (93.5)	27 (93.1)	0.941
Transplant era (n, %)				0.596
2005	1 (2.9)	0 (0.0)	1 (3.4)	
2006	25 (71.4)	26 (83.9)	24 (82.8)	
2007	9 (25.7)	5 (16.1)	4 (13.8)	

Data are expressed as number (proportion), median (interquartile range [IQR]), or mean ± SD.
ESRD, end-stage renal disease; HLA, human leukocyte antigen; MPA, mycophenolic acid sodium; PRA, panel-reactive antibody.