ORIGINAL ARTICLE

Outcome of 235 Renal Transplant Recipients Followed Up at Ministry of Health Hospitals in the State of Johor

A Y K Chan, MRCP, L S Hooi, MRCP, W J Liu, MRCP, Department of Medicine and Haemodialysis Unit, Hospital Sultanah Aminah, Johor Bahru, Johore

Summary

Retrospective analysis was done on 235 recipients, 133 males and 102 females, who were transplanted between 25th September 1979 and 25th June 1999. 85.1% were Chinese, 7.7% were Indians and 7.2% Malays. 23% (54) were living related renal transplants (LRRT) all except 5 done at Hospital Kuala Lumpur. 60% (141) were living unrelated donor renal transplants (LURT) done in India. 17% (40) were cadaveric transplants (CADT) (all done in China except 2 at Hospital Kuala Lumpur and one in London). 97% (228) were first transplants. Primary renal disease was unknown in 69.4%, 17% (40) glomerulonephritis, 5.5% diabetic nephropathy and 8.1% 19 others. All were on prednisolone, 93.2% were on azathioprine and 96.6% were on cyclosporin A. The acute rejection rate was 23.4% (55 episodes). Patient survival was 88% at five years and patients alive with functioning graft was 84% at 5 years. LRRT had significantly better survival compared to LURT. 34 grafts were lost to chronic allograft nephropathy. 46 recipients died (33 died with functioning graft).

Key Words: Outcome, Renal transplant

Introduction

There is compelling evidence that renal transplantation is superior to dialysis in the treatment of end-stage renal disease. It is cost effective, allows better quality of life and improves survival[1]. The lack of renal grafts is a familiar predicament. CADT in Malaysia is still in its fledging stage after 25 years of its inception. Many patients have gone abroad for commercial renal transplantation. Recipients of commercial renal grafts are known to fare worse than LRRT recipients[2] e.g. due to transmission of blood borne diseases. There are calls for non-commercial LURT to be made acceptable especially from emotionally related donors. In this retrospective analysis the outcome of recipients of LRRT, LURT and CADT are compared and the factors contributing to graft and patient survival studied.

Materials and Methods

This is a retrospective analysis of all renal transplant recipients who were transplanted before 30th June 1999, and had been followed up at Ministry of Health hospitals in the state of Johor. The charts of patients were traced from the transplant registry. Recipients who have had more than one transplant were studied for their latest graft. Duration of follow up was calculated from the date of transplant

to the date of graft loss or death. Graft failure was defined as a need for long term dialysis. Date of graft failure was the date of return to long term dialysis. Death from any cause with a functioning graft was considered a transplant death. Patients who were alive with functioning graft are censored at the end of the study period. All patients who were transferred out were traced and their outcomes included. The end of the study was 31st December 1999. Acute rejection (AR) was diagnosed as an episode of declining urine output with rising serum creatinine in the absence of other causes of graft dysfunction and where anti-rejection therapy was instituted. Graft biopsy was done in some of the rejection episodes. Early rejection was defined as occurring within 3 months of transplant.

Kaplan Meier survival function was used to estimate patient and graft survival. Tests of differences between survival curves were done using log-rank test. Null hypotheses were rejected if $p < 0.05$. Statistical analyses were done using Medcalc ® for Windows.

Results

235 recipients who were transplanted between 25/9/79 and 25/6/99 were enrolled. 97% were primary grafts and 2.5% were second transplants. One patient was on his third graft. All except 5 of the LRRT were transplanted at Hospital Kuala Lumpur (3 from Singapore, 1 Tawakal Hospital Kuala Lumpur and 1 from India). All LURT were done in India. All CADT were commercial China transplants except 3 (2 from Hospital Kuala Lumpur and 1 from London). Commercial transplants made up 75.7% (178) of the total. The annual transplant frequency is shown in Figure 1.The demographic characteristics of the recipients are shown in Table I. The mean age at the time of transplant was significantly higher for LURT and CADT patients. The duration of follow up was longest in the LRRT recipients and shortest for CADT. There was no difference in the causes of primary renal disease among the three groups.

Of the 54 patients with LRRT 36 received a kidney with one haplotype match (HLA haplo-identical), 12 with two haplotype match (HLA identical), 6 unknown (HLA = human leucocyte antigen). 27 of the donors are siblings, 26 are parents and 1 is a maternal uncle. There were 29 male donors and 25 female. For commercial transplants information about donors are not available.

All recipients were on prednisolone, 93.2% had been on azathioprine and 96.6% had been on cyclosporin A. 186 patients had complete follow up records, 32 were transferred in from other centres and 17 were transferred out. All patients in the last category were traced and the survival data reported. There was no patient that could not be traced.

Figures 2, 3 and 4 show the survival functions of all recipients and between different donor types. Survival with functioning graft for all recipients at 5 and 10 years is 84% and 58.5% respectively. Survival with functioning graft for LRRT at 5 and 10 years is 93% and 72% respectively, 80% and 54% for LURT, and 91% at 5 years for CADT. Survival was significantly better among LRRT compared to LURT recipients. Comparison of survival between CADT with LRRT and LURT were not significant.

Table II shows the causes of graft loss and death among transplant recipients. 70 grafts were lost during the study period. Presumed chronic allograft nephropathy (CAN) accounted for almost half of all grafts lost. Only 2 out of 34 patients who lost their graft from CAN had a renal biopsy with this diagnosis. It is defined clinically as gradual increase in serum creatinine with increasing proteinuria and worsening hypertension. 46 recipients died. Death with functioning graft was a significant cause of graft loss (33 or 47.2%). Among the deaths with functioning graft 9 died of sepsis, 6 were due to cirrhosis (5 from hepatitis C virus), 6 from ischaemic heart disease, 4 Acquired Immunodeficiency Syndrome (AIDS), 3 each of malignancy and cerebrovascular accidents, 1 suicide with tuberculosis and 1 unknown cause at a private hospital.

47 recipients experienced one episode of acute rejection and 4 had 2 episodes. 17 of these episodes were proven by renal biopsy. 13 were LRRT recipients, 36 LURT and 2 were CADT recipients. As there were proportionately fewer acute rejections among CADT recipients (CADT vs LRRT, $p = 0.06$

Table I
Demographic characteristics of transplant recipients by donor type

	LRRT N = 54	LURT N = 141	CADT N = 40	p
Male recipients (%)	32 (59.3)	79 (56)	22 (55)	NS
Race (%)				
Malay	10 (18.5)	5 (3.5)	2 (5)	
Chinese	35 (64.8)	127 (90.1)	38 (95)	NS
Indian	9 (16.7)	9 (6.4)	0	
Age at transplant ± SD (years)	30.1 ± 9.3	40.7 ± 10.2	39.2 ± 11	*
Duration of follow up ± SD (years)	8.3 ± 4.6	6.8 ± 2.7	2.7 ± 1.5	< 0.05
Primary renal disease (%)				
Glomerulonephritis	17 (31.5)	18 (12.8)	6 (15)	NS
Diabetes mellitus	0	9 (6.4)	4 (10)	NS
Adult polycystic kidneys	0	2 (1.4)	2 (5)	NS
Obstruction and reflux	4 (7.4)	6 (4.3)	0	NS
Drug induced	0	3 (2.1)	0	NS
Trauma	0	1 (0.7)	0	NS
Unknown	33 (61.1)	102 (72.3)	28 (70)	NS

** Age at transplant:* *LRRT vs LURT p < 0.0000*
LRRT vs CADT p < 0.0000
LURT vs CADT p < 0.421

Table II
Cause of graft loss and death

Cause of graft loss (N = 70)	Frequency (%)	Cause of death (N = 46)	Frequency (%)
Chronic allograft nephropathy	34 (48.6)	Sepsis	13 (28.3)
Death with functioning graft	33 (47.2)	Sudden death / ischaemic heart disease	7 (15.2)
Renal vein thrombosis	1 (1.4)	Cirrhosis	6 (13)
Recurrence of primary disease	1 (1.4)	AIDS	4 (8.7)
Ureteric obstruction	1 (1.4)	Malignancy	3 (6.5)
		Cerebrovascular accident	3 (6.5)
		End-stage renal failure	3 (6.5)
		Heart failure	1 (2.2)
		Suicide	1 (2.2)
		Malnutrition	1 (2.2)
		Unknown	4 (8.7)

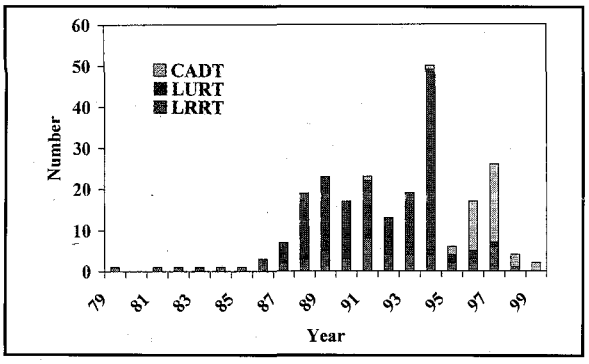

Fig 1: Number of new transplants by year.

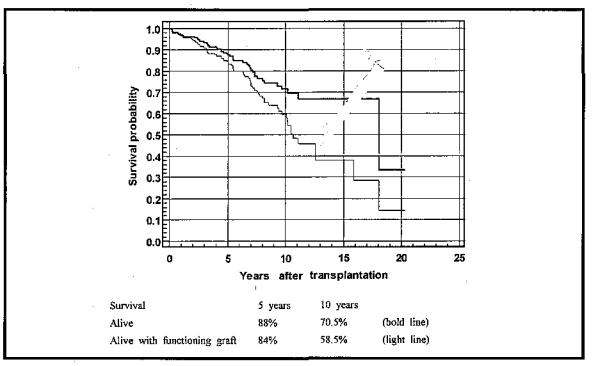

Fig 2: Kaplan Meier survival function of all transplant recipients, N=235.

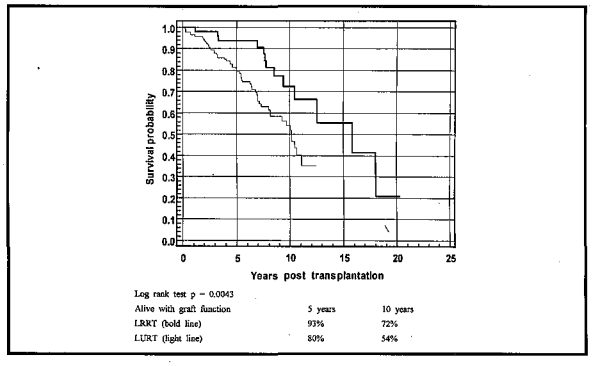

Fig 3: Kaplan Meier survival function of LRRT (N=54) and LURT (N= 141) (alive with functioning graft).

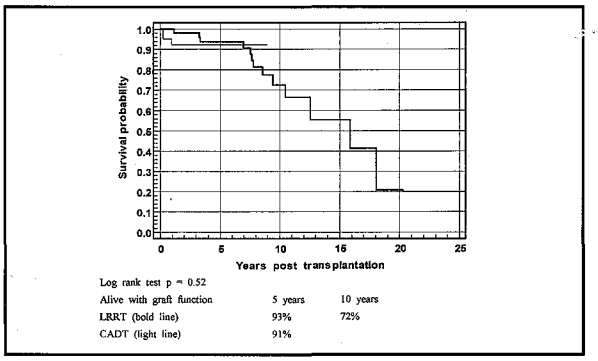

Fig 4: Kaplan Meier survival function of LRRT (N=54) and CADT (N= 140) recipients (alive with functioning graft).

and CADT vs LURT, p = 0.03), they were excluded in this analysis. Univariate analysis (non-immunological causes of graft loss uncensored) showed that a history of AR had a significant negative impact on graft survival (Figure 5). The significance level was higher when non-immunological causes of graft loss were censored (p < 0.000). However the time of onset of AR did not appear to affect long-term survival (Figure 6).

Discussion

Three quarters of the study population bought their grafts, as with 60 - 70% of the Malaysian renal transplant recipients[3]. Legislation facilitating and campaigns promoting CADT locally have met with limited success in meeting the demand for renal allografts in Malaysia. This is true elsewhere as evident from the increasing number of patients on transplant waiting lists[4]. There is a growing call for the use of living unrelated donors[5] as evidence shows that the results of LURT is comparable to one haplotype match LRRT and superior to CADT[4,6,7]. This study found a 80% graft survival at 5 years for LURT recipients which was significantly lower compared to LRRT. No comparison could be made between LURT and CADT as the latter number was small and follow up time short. All 4 of the LURT recipients with AIDS presumably caught HIV during their transplant[8,9]. Less than 5% of blood products are screened for HIV (human immunodeficiency virus) in India[2]. It would appear that LURT if conducted under a medically stringent setting is an option to be reconsidered. The Transplantation

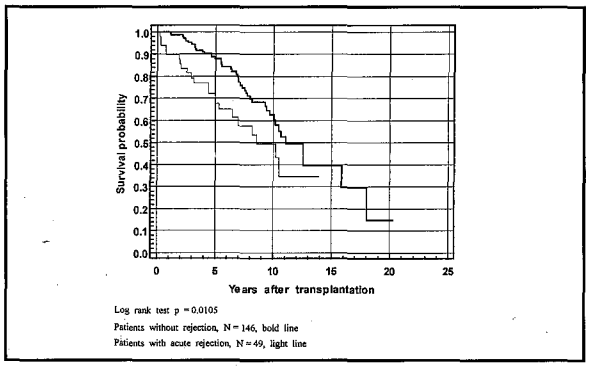

Fig 5: Kaplan Meier survival function (alive with functioning graft) of patients with and without history of acute rejection (LRRT and LURT, N=195), graft loss due to patient death uncensored.

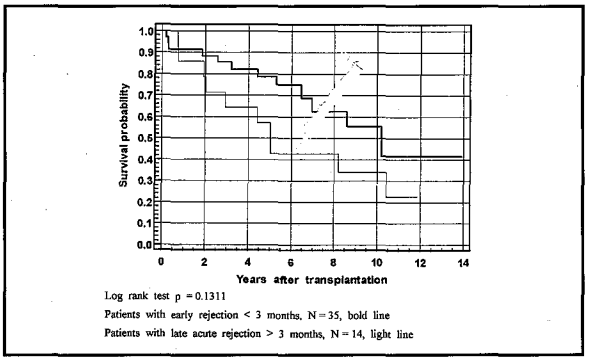

Fig 6: Kaplan Meier survival function (alive with functioning graft) of patients (LRRT and LURT) with early (N=35) and late (N=14) acute rejection.

Society supports altruistic LURT[10]. It is necessary to put in place safeguards in the forms of legislation and the setting up of ethical committees to monitor LURT.

It is estimated that 40% of grafts are lost to chronic allograft nephropathy 10 years post-transplant[11]. Acute rejection is one of the many causes of CAN. Ishikawa[12] found that AR lowered the 5 year graft survival by 30%. Humar[13] showed that there was still a 10 - 15% risk of CAN among recipients whose serum creatinine returned to baseline levels after treatment of AR. In our study, recipients who suffered at least one episode of AR had significantly lower graft survival. Timing of development of AR has also been linked to outcome. The definitions of early and late AR are arbitrary[14]. Some studies found late-onset AR have worse outcome,[12] while others have not[15]. This study did not find any difference between early and late AR, presumably due to the small number of patients. Late-onset AR is ominous as it often indicates non-compliance to immunosuppresants[16] and does not respond to anti-rejection therapy[13]. As HLA matching is often not done in LURT[9] there would be expectedly more episodes of AR or more severe episodes among LURT recipients. Although the proportion of AR was similar between LRRT and LURT recipients, this study did not look at the severity of the rejection episodes. Severity is known to be a strong predictor of outcome[17].

In this study excluded are patients who died or whose grafts failed before returning for follow up. Therefore it is possible survival figures are an overestimate. Many recipients returned without any clinical summary from their transplant centres abroad. Details of the immediate post-transplant period are often scanty. Nevertheless this study provides a fairly representative picture of transplant recipients.

Conclusion

This series reports a 84% 5 year graft survival for all recipients. 75.7% were commercial transplants. LRRT had better survival compared to LURT. Main causes of graft loss were chronic allograft nephropathy and patient death. Cautious approach towards the use of living unrelated donors to alleviate graft shortage could perhaps begin with emotionally related donors.

Acknowledgement

We would like to thank the Director General of Health of Malaysia for permission to publish this article. We would like to thank Dr. Gan Chiing Chiing, Dr. Sree Kumar Ravindran and paramedical staff of Haemodialysis Unit, Hospital Sultanah Aminah Johor Bahru for helping to collect the data.

References

1. Wolfe RA, Ashby VB, Milford EL et al. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. N Engl J Med 1999; 1725 - 30.
2. Salahudeen AK, Woods HF, Pingle A et al. High mortality among recipients of bought living unrelated donor kidneys. Lancet 1990; 336: 725 -28.
3. Lim TO, Lim YN (eds). 5th Report of the Malaysian Dialysis and Transplantation Registry, Ministry of Health Malaysia, 1997; 155.
4. Lowell JA, Brennan DC, Shenoy S et al. Living unrelated renal transplantation provides comparable results to living related renal transplantation: a 12 year single center experience. Surgery 1996: 119: 538 -43.
5. Foss A, Leivestad T, Brekke IB et al. Unrelated living donors in 141 kidney transplantations. a one-center study. Transplantation 1998; 66: 49-52.
6. D'Alessandro AM, Pirsch JD, Knetchtle SJ et al. Living unrelated renal donation: the University of Wisconsin experience. Surgery 1998; 124: 604 -11.
7. Said MR, Curtis JJ. Living unrelated renal transplantation: progress and potential J Am Soc Nephrol 1998; 9: 2148 -52.
8. Hooi LS. HIV infection in recipients of living unrelated donor renal transplants - a report of 4 cases. Med J Malaysia 1993; 48: 232 - 35.
9. The Living Non-Related Renal Transplant Study Group. Commercially motivated renal transplantation: results in 540 patients transplanted in India. Clin Transplant 1997; 11: 536 - 44.
10. The Council of the Transplantation Society. Commercialisation in transplantation: the problems and some guidelines for practice. Lancet 1985; 2: 715-16.
11. Paul LC. Chronic allograft nephropathy: an update. Kidney Int 1999; 56: 783-93.
12. Ishikawa A, Flechner SM, Goldfarb DA et al. Quantitative assessment of the first acute rejection as a predictor of renal transplantat outcome. Transplantation 1999; 68: 1318 -24.
13. Humar A, Kerr S, Gillingham KJ, Matas AJ. Features of acute rejection that increase risk for chronic rejection. Transplantation 1999; 68: 1200- 203.
14. Danovitch GM. Immunosuppressive medications and protocols for kidney transplantation. In: Danovitch GM (ed). Handbook of kidney transplantation. Boston/Toronto/London: Little, Brown and Company. 102.
15. Almond PS, Matas AJ, Gillingham KJ et al. Risk factors for chronic rejection in renal allograft recipients. Transplantation 1993: 55: 752 -57.
16. Pirsch JD, Ploeg RJ, Gange S et al. Determinants of graft survival after renal transplantation. Transplantation 1996; 61: 1581-86.
17. Pelletier RP, Cosio F, Henry ML et al. Acute rejection following renal transplantation. Evidence that severity is the best predictor of subsequent graft survival time. Clin Transplant 1998; 12: 543-52.