An Extended Abstract For the 3rd Saudi international conference 2009

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Introduction:

End stage chronic kidney disease (CKD) is a condition requiring specialist care. It is treated with either dialysis or renal transplantation both of which are very expensive. The number of patients receiving renal transplant therapy in United Kingdom is rising and is unlikely to reach steady state for another 25 years, costing more than 2% of the total NHS budget.

Chronic kidney disease usually develops in months and even years. The use of immunosuppressive agents, in renal transplantation has greatly reduced the incidence and severity of acute renal allograft rejection. One-year patient survival rate can be easily achieved with the use of optimal immunosuppressive regimens. Cyclosporin has been used in organ transplantation since the early 1980s, and has been shown to largely reduce the rate and severity of graft rejection and to increase success in survival of patients (1).

The therapeutic range of drug concentration for desired therapeutic effect and its acceptable tolerability is very limited. Levels less than the therapeutic range are associated with a high risk of organ rejection, whereas levels above the therapeutic range correlate with side effects, such as nephrotoxicity and tumor (2).

The objective of the study was to investigate the relationship between cyclosporin doses, blood level and graft function, as a function of blood creatinine level, on patient survival.

Data were extracted from computerized clinical records of 811 renal transplants from cadaveric donors, in calendar years 1994 to 2007 at Western Infirmary Hospital. Patients with incomplete data (n: 229) were identified and removed. All patients who did not receive cyclosporin as a base of their immunosuppressive regimen at the time of transplantation (n: 85) were excluded from the analysis. A total of 497 transplant patients were included in the final analysis in four eras (1994-1996, 1997-1999, 2000-2003 and 2003-2007). Including active patients (n:401), who completed follow up without any events (death or lost follow up). Graft lost patients (n:27), that includes patients with graft lost after transplantation and died patients (n:69). For patients survival the event of interest is death. Data were extracted on treated acute rejection episodes, date of transplant, date of birth, date of death if patient is died. In addition, the immunosuppressive treatment (daily dose, plasma level,creatinine level were collected from clinical visit as immediately after transplantation, 3months, 6months, 9months and 12months following transplantation.

The data set is largely descriptive and presented as mean ± SD or median (range) for analysis, categorical variables were analyzed with the chi-square test. Comparison of time to death (survival) was performed using the Kaplan-Meier procedure with log-rank testing $P \leq 0.05$ was considered statistically significant. Calculations were performed using SPSS (version 16) statistics package. A Cox proportional hazards model with adjustment for cyclosporin dose, cyclosporin blood level and creatinine blood level were used to assess the prognostic value of these factors on long term patient survival.

Cyclosporin dose used at the end of first transplant year fell within time, from 4.68mg/kg per day to 3.41 mg/kg per day. Patient using cyclosporin in lower dose had a chance of longer term patient survival. The achieved trough levels of cyclosporin also fell within time and serum creatinine levels at 1-year remained relatively constant. Effect of the extent in change of these two parameters on long term patient survival was insignificant.

Table1: Demographic and clinical parameters of allograft recipient patient by time interval.

parameter	1994-1996	1997-1999	2000-2003	2004-2007	P-value
CSA(mg/kg/day)	4.68±1.08	4.45±0.86	4.15±1.14	3.41±0.80	0.144
CSA(mg/L)	159±63	162±78	175±168	141±93	0.0001
Ct(mmol/L)	291±103	284±73	255±72	254±68	0.0001

CSA/kg,cyclosporin dose in mg/kg/day; CSA,cyclosporin serum level(mg/L); Ct,serum creatinine level(mmol/L).All these parameters were recorded at 1year post transplant(P-value representing the level of significance between the four groups of time era.

Mean cyclosporin dose (CSA dose) in mg/kg/d was obtained from 489 stable kidney recipients (range: 00-11.49). Doses used were divided into three frequencies equal groups.Group1 for patient consuming cyclosporin in dose of ≤ 3.53mg /kg/day N=163, group2 using the medication in dose range of 3.53-4.57 mg/kg/day, N=163 and group 3 were patients using cyclosporin in dose ≥ 4.57 mg/kg/day=204. Although group 1 receiving lowest dose has a chance of higher patient survival than other groups, the study indicated that difference in survival between the three groups was insignificant (P=0.459) (Figure 1). Using Cox-proportional hazards analysis, each additional mg/kg in cyclosporin dose was found to be associated with 10% increase in hazard of death (P=0.273), table2.

Table 2. Cox regression analysis for patient survival using cyclosporin dose, blood level and creatinine blood level.

parameters	mean±SEM	cofficient	Hazard Ratio	P-value
Cyclosporin dose mg/kg/Day)	4.252± 0.91	0.99	1.104	0.273
Cyclosporin blood level (mg/L)	159.933±.002	-0.001	0.999	0.653
Creatinine blood level (mmol/L)	268.447±.002	.000	1.000	0.791

Patient survival: Hazard ratios (95% confidence interval) were adjusted, cyclosporin dose, cyclosporin blood level, creatinin blood level. Results are based on 497patient. (P value representing the level of significance between the different groups)

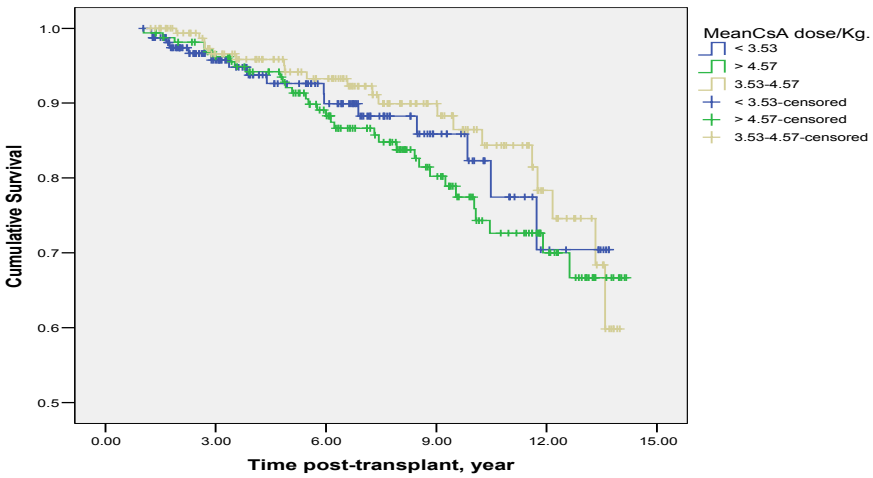

Fig .1. Kaplan Meier estimates for patient survival as a function of the three Frequency group of Cyclosporine dose (CsA dose/kgl). Log rank test, P = 0.459.

Mean cyclosporin level (CSA level) were obtained from 480 stable kidney recipients (range 26-1097mg/L) and were divided into three frequancies equal groups of mean cyclosporine level range. Group1 with level of ≤122 mg/l,N=160,group2 with cyclosporin level in the range of 122-154 mg/l,N=160, and group3 with cyclosporin level of ≥ 154 mg/l,N=160. Actuarial patient survival did not differ significantly between the three groups. There is a decrease of hazard of death by 0.1% associated with each additional mg/l in cyclosporine level (P= 0.653) as indicated by Cox-regression analysis for patient survival table 2.

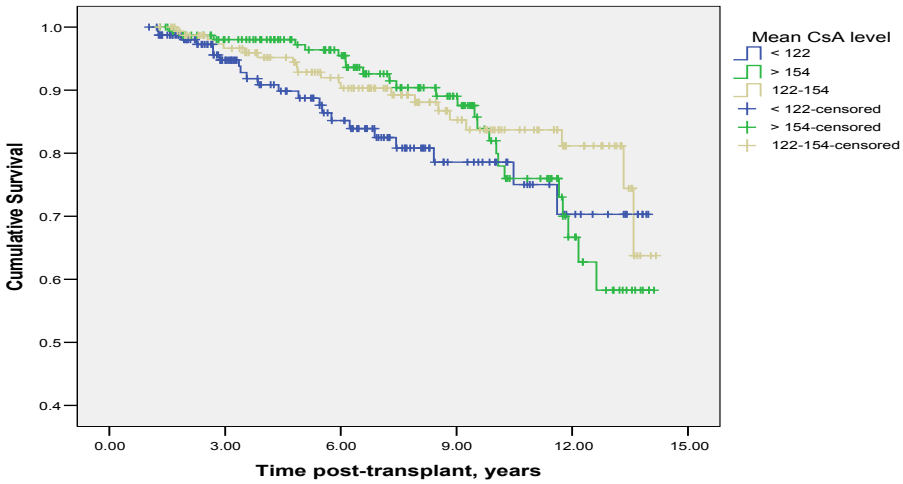

Fig. 2. Kaplan Meier estimates for patient survival as a function of the three frequency group of Cyclosporin blood Level (CsA level). Log rank test, P = 0.302.

To show the effect of graft function, based on the serum creatinine value,on long term patient survival, the mean serum creatinine level in mmol/l was obtained from 497 stable kidney recipients (range: 56-2129 mmol/l). Patients were divided into three frequencies equal groups of mean creatinine level. Group1, patients with serum creatinine level of ≤ 232.7 mmol/l,N: 166, group2 having serum creatinine level in the range of 232.7 to 300mmol/l,N:166 and group3 patients having serum creatinine level ≥ 300mmol/l, N:165. The difference in the extent of change in the serum creatinine concentration and patient survival among the three groups was insignificant (P=0.345) Fig3. The cox-proportional hazards survival regression proved that the change in serum creatinine does not have any effect on survival curve (P= 0.791) (Table 2)

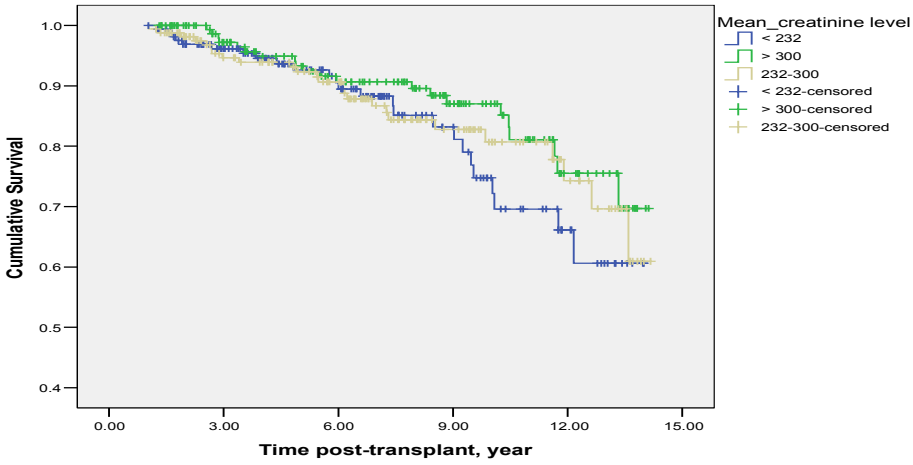

Fig. 3. Kaplan Meier estimates for patient survival as a function of the three frequency group of mean creatinine level(µmol/Liter). Log rank test, p=0.34

Cyclosporin dose and the achieved blood concentration both fell within time. This effect corresponds with progressive improvement in patient survival. Although statistically insignificant, the result of this study suggested that patients receiving lower doses of cyclosporin had a higher chance of survival than other groups. The advantage of low dose of cyclosporin found in this study could be related to decreased side effects of this medication especially on kidney function. Reduction in cyclosporin dose proved to be effective in obtaining long-term survival and improved renal function so avoiding chronic renal failure. Cyclosporin dose is conventionally based on its trough blood levels, which is known to correlate poorly with acute rejection and cyclosporin nephrotoxicity after renal transplant.

In this study,no significant differences were noticed in the survival of patients a amongst the 3 groups of patients with different mean blood levels of creatinine.The result could suggest that cyclosporin does not necessarily expose patients to progressive renal damage.

Conclusion

In this retrospective analysis, low cyclosporin level appear to give optimal calcineurin inhibition and may lead to improvement in patient survival as well as decreasing the drug side effects. Low serum creatinine levels, were much more likely to be a achieved with low doses of cyclosporin. Therefore, low doses and concentrations would appear to have no adverse effects on patient survival or creatinine levels. This is a reassuring result given the worry that lower cyclosporin doses could result in allograft rejection.

References

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