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Length of time on dialysis prior to renal transplantation is a critical factor affecting patient survival after allografting

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Abstract. Within the past year at our transplant center we have had the experience of performing renal allografts in two patients older than 65 years, each of whom had been on hemodialysis more than 10 years. Both resulted in patient mortality within 90 days of transplant (one due to myocardial infarction, the other due to visceral ischemia with infarction). This prompted us to review retrospectively our own data ($n = 204$) and the national (UNOS) data ($n = 10\,971$) regarding transplant outcome, patient age, and length of time on dialysis prior to renal transplantation. This review revealed that patient mortality after transplant increased with the length of end-stage renal disease (dialysis, regardless of type) independent of age, the greatest mortality occurring within the first 6 months of transplant (and not thereafter); graft survival was similar for all age cohorts analyzed. Our review of the literature reveals a paucity of articles pertaining to post-transplant mortality and length of time on dialysis prior to transplant. Our results indicate the following possible conclusions. (1) The length of time of end-stage renal disease therapy prior to renal transplantation is a significant and independent risk factor for post-transplant mortality. (2) Higher priority should be given to this factor when formulating strategies for allocation of scarce resources. (3) Patients on dialysis for extended periods of time who are elderly may be at particularly high risk. (4) Patients being considered for renal transplant should be informed of their individual risk factors for mortality post-transplant based on length of ESRD therapy. (5) Renal transplantation should be considered as early as possible in patients with ESRD (or imminent ESRD).

Key words: Renal transplantation – Dialysis – End-stage renal disease

Within the past year, we have experienced several deaths of renal transplant recipients, each of whom had been on hemodialysis for extended periods of time prior to transplantation. This prompted us to review retrospectively our own data ($n = 204$) and the UNOS data ($n = 10\,971$) regarding the effect of length of end-stage renal disease (ESRD) prior to transplantation on patient survival following allografting.

Many factors have been suggested to affect survival following renal transplantation, including recipient age, donor source (cadaver, LRD unrelated) and age, HLA matching, immunosuppressive regimen, and various other pretransplant conditions (e.g. cardiac status, presence or absence of diabetes mellitus, PRA, prior transplant, etc.). To our knowledge, length of time of ESRD prior to transplantation and its impact on patient survival have neither been previously emphasized nor systematically examined.

Materials and methods

Medical records of all adult recipients (> 17-years-old) of cadaver renal transplants performed at our center between 21 April 1981 (inception of program) and 1 September 1990 were reviewed ($n = 204$), revealing the following patient characteristics (see Table 1):

Before 1 February 1984, the standard immunosuppression protocol consisted of azathioprine and prednisolone. After this date all patients were treated with cyclosporine and prednisolone (and frequently triple-drug therapy adding azathioprine). Use of anti-thymocyte globulin (ATG) and OKT3 monoclonal antibody were

Table 1. Patient characteristics ($n = 204$)

Age (years)	
Mean	41.49
SEM	0.89
Range	17.0–70.4
Length of ESRD (months)	
Mean	32.48
SEM	2.4
Range	0–182.9
Immunosuppressive ERA (number of patients)	
Pre-cyclosporin	38
Post-cyclosporin	166

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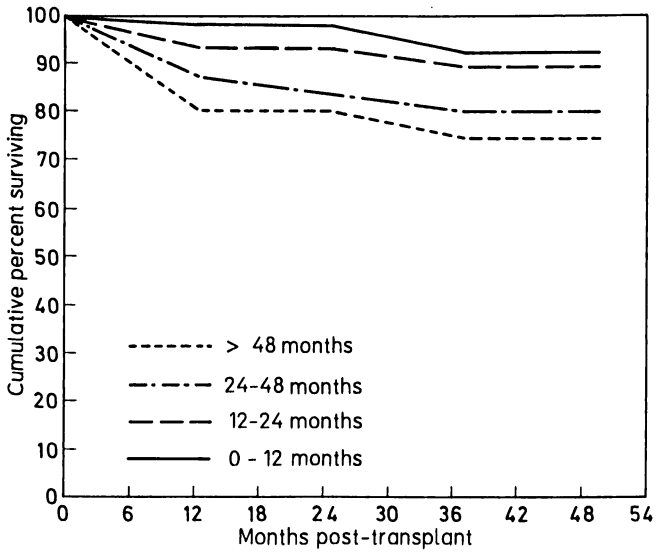

Fig. 1. Patient survival by length of ESRD prior to transplantation

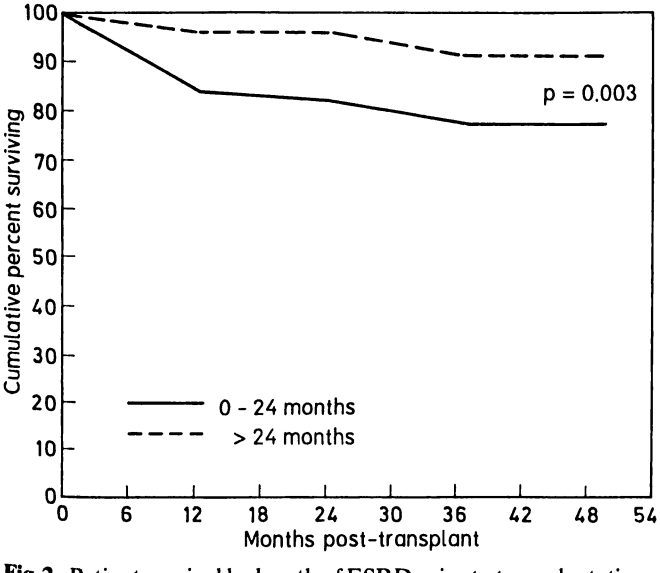

Fig. 2. Patient survival by length of ESRD prior to transplantation

generally reserved for treatment of steroid-resistant or recurrent rejection episodes (and occasionally for induction therapy in the high immunologic risk patient – retransplants, PRA > 75%, etc.).

Also abstracted from the records of each patient were the following: date of transplantation, date of first ESRD treatment (determined as the date of first maintenance dialysis, or date of transplantation if transplanted first without prior dialysis), date of death for those dying with a functioning graft or within 3 months of graft failure and return to dialysis, date of graft failure as defined by date of return to permanent dialysis, date of birth, history of prior transplantation, number of HLA-A,B and HLA-DR loci matches, presence of diabetic nephropathy, immunosuppressive era (see above), and cause of death.

Survival analyses were performed using the Kaplan-Meier product limit method. For purposes of calculating patient survival, any death occurring in a patient with a functioning allograft or within 3 months of return to dialysis following graft failure was considered a graft failure. Patients who returned to dialysis and survived 3 months were censored as to the date of return to dialysis. Patients alive with functioning grafts were censored as of 1 September 1990. No patients were lost to follow-up. Except as noted below, for the purposes of calculating graft survival, return to dialysis and death with a functioning graft were both considered graft losses.

Comparisons of survival between groups were performed with the Gehan's generalized Wilcoxon test. An extension of this test is used for comparing survival in multiple samples. Univariate analysis of the effects of variables on survival was performed using the Wilcoxon rank sum test. The relative contribution of variables to survival was tested with a forward stepwise sequence of chi-squares. The Cox proportional hazards model was also utilized to evaluate the effects of multiple variables on survival. Calculations were performed using CSS.STATISTICA (Stat Soft, Tulsa, Oklahoma) and SAS (SAS Institute, Cary, North Carolina) software on an IBM PS/2.

The United Network of Organ Sharing (UNOS) kindly performed preliminary analysis of their data on adult patients (> 17 years of age) in receipt of cadaver kidney transplants performed between 1 October 1987 and 31 December 1989 ($n = 10\,971$). Patient survival at one year was analyzed by a logistic regression model with consideration of the following variables: age at transplant (> 60-years-old versus < 60-years-old), race, PRA at transplant, status at transplant (home-bound or hospitalized), and length of time on dialysis prior to transplant (> 24 months versus < 24 months).

Results

When patients were assigned to groups based on increasing lengths of ESRD therapy prior to transplantation, a progressive increase in mortality was noted (Fig. 1). Reviewing only those cohorts of patients < 24 months versus > 24 months therapy for ESRD prior to transplantation, the patient survival in the former group post-transplant was significantly better ($P < 0.003$) (Fig. 2, Table 2). Similarly, graft survival was proportionately worse with increasing length of prior ESRD therapy. However, when death as a cause of graft failure was removed from the analysis (e.g. censored) there was no difference in graft survival between the two groups (i.e. the difference in graft survival was completely accounted for by the difference in death rates).

The effects of length of prior ESRD treatment, age, number of prior transplants, and number of HLA-A,B and HLA-DR matches on patient survival were first analyzed by univariate techniques and subsequently by Cox proportionate hazard regression. Only increasing length of prior ESRD treatment and increasing age were independently associated with poorer post-transplant patient survival ($P < 0.003$ and $P < 0.03$, respectively). Age and length of prior ESRD treatment did not correlate with each other. The other variables tested did not significantly influence patient or graft survival.

Table 2. Patient survival (%) by length of prior ESRD ($n = 204$)

Length of prior ESRD (months)	n	Time post-transplant (months)				
		12	24	36	48	60
0–24	115	96.2	96.2	91.4	91.4	91.4
> 24	89	83.3	81.5	77.1	77.1	73.4

Table 3. Relative risk of death at 1 year (n = 10 971)

Variable	Relative risk	n	Percent of total	95% confidence intervals
Age > 60 years	2.15	1052	9.6	1.77 to 2.61
Black	0.8	2462	22.4	0.67 to 0.96
Homebound	1.44	3146	28.7	1.23 to 1.68
Hospitalized	1.86	777	7.1	1.45 to 2.37
Dialysis > 24 months	1.42	3419	31.2	1.22 to 1.64

Σn 10 971 because these are not mutually-exclusive groups
Σ % of total $\neq$ 100% for the same reason

In order to corroborate our results and to avoid errors inherent in small, single-center analysis, the Scientific Advisory Committee of UNOS agreed to perform a retrospective analysis of their large database. The clinical relationship of length of time of ESRD prior to renal transplantation and its negative effect on patient survival was again confirmed. The effects on 1-year patient survival of age, status at time of transplant, race, PRA, and length of prior ESRD therapy were analyzed. Age > 60 years, status of patients pretransplant (home-bound versus hospitalized), and > 2 years of prior ESRD treatment significantly worsened 1-year patient survival (Table 3).

Cardiovascular disease and infection were the leading causes of death in our patients. There was no difference in the proportion of deaths attributable to cardiovascular disease or to infection in patients with < 24 or > 24 months of prior ESRD therapy.

In summary, increasing the time between institution of ESRD treatment and subsequent transplantation significantly increased the post-transplant mortality in 204 adult cadaveric renal transplant recipients in one center. Preliminary retrospective analysis of a very large database (UNOS) appeared to confirm the significant independent effect of length of prior ESRD treatment on patient survival post-transplant. This effect was independent of age, which was also a significant risk factor for mortality post-transplant. The degree of HLA-A,B and HLA-DR matching and the number of prior transplants did not affect patient survival. The length of prior ESRD treatment worsened graft survival, but only to the extent that it increased mortality.

Discussion

Because of the rapid successes of organ replacement therapy for end-stage organ disease, complex ethical questions have been raised and answers provided regarding equitable allocation of these scarce resources. In the US, the allocation of cadaveric kidneys is based upon a mandatory point system [2], recipients being awarded points based on: (1) time of waiting; (2) quality of antigen match; and (3) panel reactive antibody (PRA). The 'time of waiting' begins with being activated on the UNOS computer, one point being awarded to the candidate awaiting transplantation for the longest period and fractions of points to those waiting for shorter periods. Additionally, for each year after 1 year of waiting time, 0.5 points are awarded. However, 'time of waiting' is not equivalent to length of time on dialysis – an important distinction. Based upon our results showing that the length of prior ESRD treatment is a significant and independent risk factor for post-transplant mortality, it would seem imperative that strategies for allocating kidneys need to give more weight to this factor rather than the time-honored 'time of waiting'.

Conclusions

Strategies for allocating kidneys need to give more weight to the length of ESRD treatment prior to transplant as this has been shown to be a significant and independent risk factor for post-transplant mortality. Patients on dialysis for extended periods who are elderly may be at particularly high risk. Patients being considered for renal transplantation should be informed of their individual risk of mortality post-transplant based on age and length of ESRD therapy. Finally, renal transplantation should be considered as early as possible in patients with ESRD (or imminent ESRD).

Speculation

Most studies suggest that renal transplantation improves short- and long-term mortality (and rehabilitation) compared with dialysis in similar populations. The present data raises questions as to whether this is true for that subgroup of patients who have survived on dialysis > 2 years. It might be that renal transplantation does not confer a survival advantage to this subgroup and, indeed, may even be associated with a higher mortality rate (at least in the short term). Further studies are necessary to address this question.

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