Master of Medicine

Comparison of clinical outcomes between preemptive and transplant after a short period of dialysis in living donor kidney transplantation : A propensity score-based analysis.

The Graduate School of
the University of Ulsan

Department of Medicine
Hyeyeon Kim

Comparison of clinical outcomes between preemptive and transplant after a short period of dialysis in living donor kidney transplantation : A propensity score-based analysis.

Supervisor : 신 성

A Dissertation

Submitted to
the Graduate School of the University of Ulsan
In partial Fulfillment of the Requirements
for the Degree of

Master of science of Medicine

by

Hyeyeon Kim

Department of Medicine
Ulsan, Korea
Febuary 2020

Comparison of clinical outcomes between preemptive and transplant after a short period of dialysis in living donor kidney transplantation : A propensity score-based analysis.

This certifies that the dissertation of Hyeyeon Kim is approved.

Committee Chair Ph.D 남궁정만

Committee Member Ph.D 김효상

Committee Member Ph.D 신 성

Department of Medicine
Ulsan, Korea
Febuary 2020

국문 요약

선제 신장 이식 (Preemptive kidney transplantation)은 이식 전 투석 없이 시행하는 신장 이식으로, 이러한 선제 신장 이식의 장점은 충분히 연구된 상태이다. 그러나 아시아에서는 이식 전 대기 시간이 비교적 긴 상태로, 많은 환자들은 신장 기증자를 찾지 못한 상태로 투석을 시작할 수밖에 없는 상황이다. 이식 전 투석 기간은 수술 후 환자 및 이식편 생존률에 영향을 미치는 아주 중요하고 독립적인 위험인자 중 하나이며 투석 기간이 길어질수록 환자의 임상 경과는 악화된다는 연구 결과도 있다. 이러한 내용을 바탕으로 비교적 짧은 기간 동안 투석을 시행한 후 신장 이식을 받는 사람들의 경우 임상 결과가 선제 신장 이식과 비슷할 수 있을 것으로 생각되나, 이에 대하여 충분히 연구된 부분이 없어 연구를 시작하게 되었다.

본 연구에서는 선제 신장 이식 환자군과 비교적 짧은 기간의 이식 전 투석 환자군의 이식 후 환자 생존률 및 이식편 생존률과 함께 수술 후 합병증 위험도를 분석하여 결과에 유의한 차이가 있는지, 유의한 차이가 없다면 이식 전 투석의 기간은 어느 정도까지 허용 가능한지를 판가름하고자 하였다.
2005년 1월부터 2016년 9월까지 서울아산병원에서 신장 이식 수술을 받은 환자들을 대상으로 하였으며, 이 중 뇌사자 신장 이식을 받은 경우, 다장기 이식을 받은 경우와 CDC 양성 환자를 제외한 생체 신장 이식을 받은 환자들에 대해서만 연구하였다.
또한 수혜자와 기증자 둘 다에 대해 고혈압, 당뇨, 이상지질혈증, 관상동맥질환, 뇌혈관질환, 암 발생 여부 등을 함께 조사하며 나이, 성별, 체질량 지수 등과 수혜자의 면역억제제에 대해 조사하였다. 조사 방법은 서울아산병원 의무기록에 저장된 각 환자의 임상 자료를 취득하여 후향적 분석을 시행하였다.

상기 환자들을 이식 전 투석기간에 따라 세 군으로 나누어 연구를 진행하였으며, 선제 신장 이식(이식 전 투석을 시행하지 않은 경우), 신장 이식 전 단기간의 투석을 시행한 경우, 그리고 비교적 장기간의 투석을 시행한 경우로 분류하였다. 기간의 분류는 c-statics를 이용하여 기준점을 확보하였으며 그 기준은 19개월이었다.
세 군에 대해 Kaplan-Meier curve를 이용하여 각각 생존률 및 이식편 생존률, 사망 중도절단 이식편 생존률을 비교하였으며 그 결과 선제 신장 이식군과 단기간의 투석 후 이식군은 장기간의 투석 후 이식군에 비해 생존률(p=0.024) 및 이식편 생존률(p<0.001), 사망 중도절단 이식편 생존률(p=0.001) 모두가 통계적으로 유의하게 높게 나타났다.
또한 생존률에 영향을 미칠 수 있는 인자들을 univariate와 multivariate 회귀분석을 이용하여 분석한 후, propensity score matching을 이용하여 상기 인자들을 통제하였다. Matching된 환자들을 위와 같이 세 군으로 나누어 다시 한 번 비교하였으며, 생존률(p=0.095) 및 이식편 생존률(p=0.006), 사망 중도절단 이식편 생존률(p=0.037) 모두에서 선제 신장 이식군과 단기간의 투석 후 이식군의 결과가 유사하였으며 장기간의 투석 후 이식군에 비해 높게 나타났다.

본 연구에서는 생체 신장 이식을 받은 환자 중 단기간의 투석 후 이식을 받은 군이 장기간의 투석을 받은 군에 비해 선제 신장 이식을 받은 군과 생존률 및 이식편 생존률에 있어 유사한 결과를 보인다는 것을 밝히고자 하였다.

또한 이식 전 대기 시간이 사망 및 이식편 기능부전에 영향을 미치는 중요 위험인자임이 널리 알려져 있지만, 환자들이 그러한 위험을 최소화하기 위해서 이식 전 어느 정도까지 투석을 받으며 대기할 수 있는지에 대하여는 잘 알려진 바가 없다. 본 연구에서는 그 기준을 19개월로 제시하였으며, 19개월 미만의 투석을 받은 경우 선제 신장 이식을 받은 환자들과 임상 결과가 유사함을 보였다.

본 연구의 한계점은 단일 기관에서 진행된 후향적 연구라는 점이다. 비록 교란변수를 통제하기 위해 propensity score matching 기법을 사용하였으나, 추후 더 큰 단위의 다기관 연구가 필요할 것으로 생각된다. 두 번째로는 본 센터의 이식 전 DSA의 측정이 2009년 1월부터 가능하여 이식 전 투석기간과 이식 전 DSA 유무와의 관계를 명확하게 밝히기가 어렵다는 점이다. 세 번째로는 약 16%에서 혈액형 부적합 이식을 시행하였는데 desensitization이 임상 결과에 어떤 영향을 미치는 지에 대해 확실히 알 수 없다는 점을 들 수 있다.

결론적으로 이식 전 19개월 이상 투석을 진행한 군에 비하여 이식 전 19개월 미만의 투석을 진행한 경우에 임상 결과가 우수하며 이는 선제 신장 이식군과 비슷한 정도의 결과이다. 추후 장기 생존률과 이식편 생존률과 관련된 이식 전 허용되는 투석 기간의 정확한 분석을 위하여 국가 전체 또는 국제적인 데이터 분석을 통한 추가적인 연구가 필요할 것으로 생각된다.

차 례

Introduction

Preemptive kidney transplantation (PKT) is defined as kidney transplantation (KT) before the initiation of chronic maintenance dialysis. PKT offers a significant improvement in clinical outcomes compared with KT after a period of maintenance dialysis therapy. So far, it has been reported that PKT has better outcomes compared with non-PKT in living-donor kidney transplantation (LDKT) as well as deceased donor kidney transplantation (1-6). Despite several advantages of PKT, not everyone can be matched with a proper living donor in time. Therefore, pre-transplant dialysis is inevitable for not a few patients.

In Asia, the mean waiting time for deceased donor KT (DDKT) is rather longer compared with those in Western countries (7). It is evident that prolonged waiting periods for DDKT may cause physical, psychological and economic problems and can lead to poor clinical outcomes (8).

Dialysis duration before KT is one of the strong, independent risk factors for patient and graft survival after KT. Recent studies have suggested that the duration of dialysis before KT is an important element in determining the clinical outcomes, with each additional year of dialysis treatment associated with an increase in the risk of death of approximately 6 percent (9-11). Our hypothesis is, however, that a short-term dialysis before KT may be permissible in terms of patient survival and graft survival as much as PKT.

The purpose of this study is to validate the cut-off value of pre-transplant dialysis duration to differentiate clinical outcomes and to analyze whether those with longer duration of pre-transplant dialysis had worse clinical outcomes.

Materials and Methods

Study design and population

We conducted a retrospective cohort study with recipients who underwent KT at our center between January 2005 and September 2016. This study was performed after receiving approval from the institutional review board of our center (S2017-2390-0001). Variables associated with recipients and donors were extensively reviewed.

Immunosuppressants

The main immunosuppressive regimen consists of basiliximab as an induction, and maintenance immunosuppressants consist of a combination of a calcineurin inhibitor (CNI; tacrolimus or cyclosporine), mycophenolic acid (MPA), and

prednisolone. As another option, recipients (n = 112) with immunologic risk factors (highly sensitized patients or re-transplantation) and those with complications owing to long-term use of steroids had rabbit anti-thymocyte globulin (Thymoglobulin®;Genzyme,Cambridge,MA,USA) as an induction regimen and maintenance immunosuppressant including tacrolimus., MPA, and early steroid -withdrawal in a week. In a case of ABO-incompatible KT, rituximab was used for desensitization two weeks before transplantation. The maintenance immunosuppression was not different from those in ABO-compatible KT.

Outcome Measures

We hypothesized that a short period of dialysis before KT will show the similar results with PKT. Primary endpoint is to discriminate the differences in patient and graft survival according to the duration of dialysis before transplantation; preemptive group, short-term dialysis group, and relatively long-term dialysis group. Secondary endpoint is biopsy-proven acute rejection (BPAR).

Statistical Analysis

All of the data were presented as percentages, means with standard deviation (SD) or medians with interquartile ranges (25%-75%). The differences in continuous variables between the two groups were compared by student *t* test or Mann-Whitney test according to the distribution of the variables.

The Kaplan-Meier method was used to estimate the survival distributions, and the differences between the two groups were compared using the log-rank test. The global c-index was computed, which represents the discrimination ability regarding patient survival and graft survival to determine a cut-off value of pre-transplant dialysis duration.

Propensity score matching was performed to eliminate the biases that might affect the results. Propensity scores for the estimated probability of each individual who underwent PKT were calculated using a multiple logistic regression model. Matching procedure was performed with the caliper of 0.1 score, and the model had c-statics of 0.68.

All statistical analyses were performed using SPSS version 19.0 for Windows (SPSS Inc., Chicago, IL) and R software version 2.13 (R Foundation for Statistical Computing, Vienna, Austria). *P* values <0.05 were considered statistically significant.

Results

A cut-off value of pre-transplant dialysis duration for discrimination of patient survival and graft survival

A total of 2,898 patients who underwent KT between January 2005 and September 2016 were included in this study. Among them, 1,984 patients were analyzed after 914 patients were excluded due to DDKT (n=667), multi-organ transplantation (n=207), and HLA-incompatible transplant including complement-dependent cytotoxicity (CDC)-positive or flow cytometry positive cases (n=40) (Figure 1).

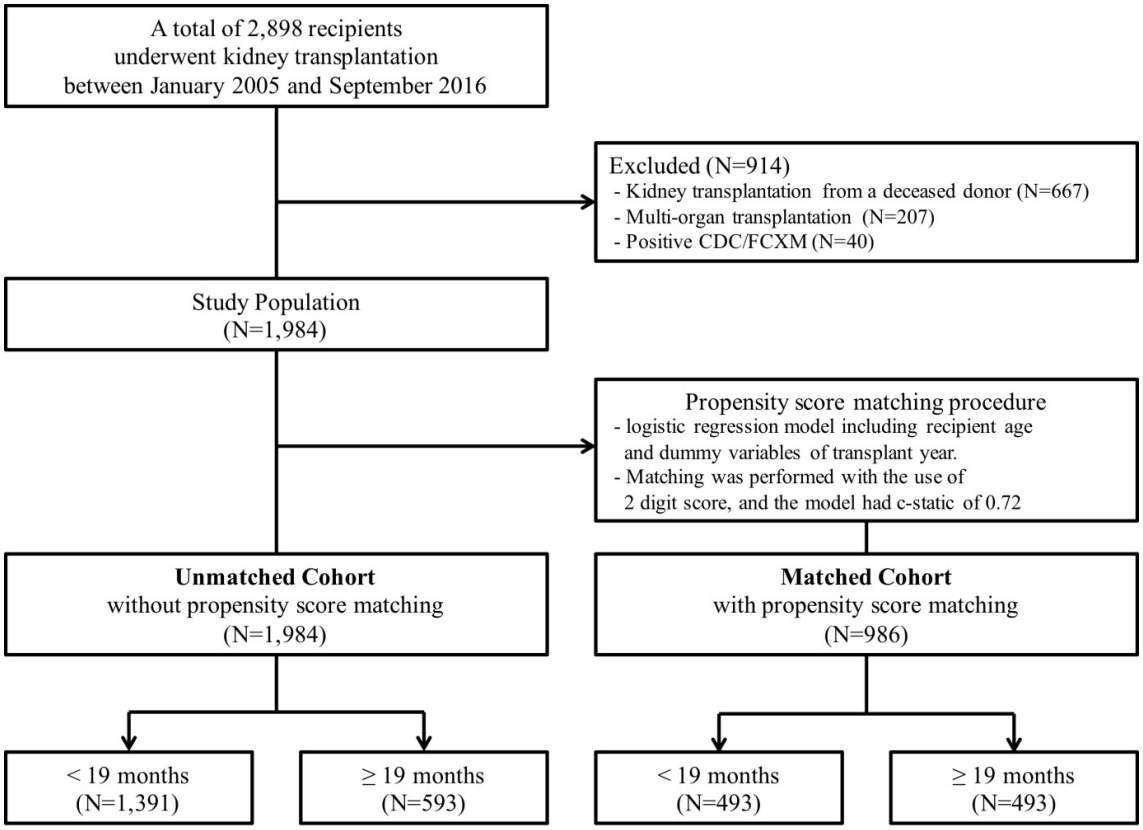

Figure 1. Flow diagram of the study. CDC, complement-dependent cytotoxicity; FCXM, flow cytometry crossmatch.

As we described above, we computed the global c-index which represents the discrimination ability regarding patient survival and graft survival to determine a cut-off value of pre-transplant dialysis duration. The most appropriate cut-off value of pre-transplant dialysis duration to differentiate clinical outcomes was 19 months. The receiver-operating-characteristic (ROC) curve showed that this cut-off

value yielded an area under the curve (AUC) of 0.617 (95% confidence interval [CI], 0.508 to 0.726; p<0.001) (Figure 2). This cut-off value of 19 months has 57.6% sensitivity and 70.6% specificity to discriminate clinical outcomes. There were 429 preemptive recipients who underwent KT before the initiation of dialysis, 962 patients had pre-transplant dialysis for less than 19 months, and 593 patients had pre-transplant dialysis for more than 19 months. In matched cohort, a total of 986 patients were included; 493 patients were assigned to a group with pre-transplant dialysis duration less than 19 months including PKT recipients (*a short pre-transplant dialysis group*) whereas the other 493 to another group with pre-transplant dialysis duration equal to and longer than 19 months (*a long pre-transplant dialysis group*).

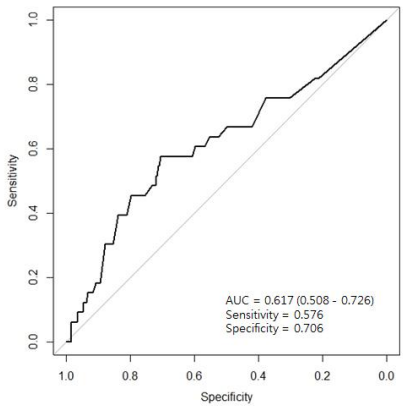

Figure 2. Receiver operating characteristic curve of pre-transplant dialysis duration, predicting patient survival and graft survival. AUC, area under curve.

Demographics and baseline characteristics

Table 1 shows the clinical characteristics of patients enrolled in this study. In unmatched cohort, the mean age of the recipients was 45 ± 12 years, and 754 recipients (38%) were female. ABO incompatible KT was performed in 319 recipients (16.1%). The mean follow-up period was 68.9 ± 40.3 months. The mean age of the donors was 42 ± 11 years, and 1,023 donors (51.6%) were female. A total of 1,269 recipients (64%) received a kidney from a related donor. In the unmatched cohort, those in the short pre-transplant dialysis group were less likely to have a history of malignancy, tuberculosis, chronic hepatitis, and congestive heart failure (CHF). In addition, anticoagulants and anti-platelet agents were more frequently used in the short pre-transplant dialysis group.

Meanwhile, in the matched cohort, the two groups are well balanced with respect to all potential relevant clinical confounders (Table 1).

Table 1. Characteristics of the study population before and after matching

Variables	Unmatched cohort		*P* value	Matched cohort		*P* value
	<19 months (n = 1391)	≥19 months (n = 593)		<19 months (n = 493)	≥19 months (n = 493)	
Recipient						
Duration of dialysis (mo)						
Median[interquartile range]	2.0 [3–48]	48.0 [19–288]		3.0 [0–18]	48.0 [19–288]	
Mean (SD)	4.2 (4.9)	61.3 (42.4)	<0.001	4.4 (4.90)	59.6 (40.44)	
Mean age, y (SD)	45.3 (12.2)	44.9 (12.1)	0.570	46.0 (12.2)	45.2 (11.9)	0.327
Female sex, n (%)	544 (39.1)	210 (35.4)		170 (34.5)	179 (36.3)	
Body mass index, kg/m^2 (SD)	24.7 (69.9)	23.1 (8.2)	0.408	22.8 (3.4)	23.3 (8.8)	0.246
Primary cause of ESRD, n (%)			<0.001			0.969
Glomerulonephritis	217 (15.6)	86 (14.5)		65 (13.2)	73 (14.8)	
IgA nephropathy	169 (12.1)	36 (6.1)		30 (6.1)	32 (6.5)	
Diabetes	283 (20.4)	115 (19.4)		109 (22.1)	98 (19.9)	
Hypertension	163 (11.7)	95 (16.0)		78 (15.8)	76 (15.4)	
FSGS	32 (2.3)	11 (1.9)		9 (1.8)	8 (1.6)	
Polycystic kidney disease	45 (3.2)	24 (4.0)		17 (3.4)	18 (3.7)	
Other/unknown	482 (34.6)	226 (38.1)		185 (37.5)	188 (38.1)	
Hypertension, n (%)	1201 (86.3)	502 (84.7)	0.360	426 (86.4)	416 (84.4)	0.417
Diabetes mellitus, n (%)	309 (22.2)	120 (20.2)	0.357	109 (22.1)	101 (20.5)	0.586
Chronic hepatitis, n (%)	63 (4.5)	52 (8.8)	0.021	35 (7.1)	34 (6.9)	1.000
History of tuberculosis, n (%)	50 (3.6)	41 (6.9)	0.002	26 (5.3)	30 (6.1)	0.680
History of malignancy, n (%)	31 (2.2)	24 (4.0)	0.035	16 (3.2)	16 (3.2)	1.000
Cerebrovascular accident, n (%)	34 (2.4)	12 (2.0)	0.682	8 (1.6)	9 (1.8)	1.000
Congestive heart failure, n (%)	4 (0.4)	15 (2.5)	<0.001	4 (0.8)	3 (0.6)	1.000
Coronary artery disease, n (%)	72 (5.2)	34 (5.7)	0.692	30 (6.1)	32 (6.5)	0.896
Arrhythmias, n (%)	15 (1.1)	14 (2.4)	0.048	8 (1.6)	8 (1.6)	1.000
Anticoagulant use, n (%)			<0.001			0.999
Antiplatelet	144 (10.3)	108 (18.2)		79 (16.0)	81 (16.4)	
Warfarin	5 (0.4)	9 (1.5)		5 (1.0)	5 (1.0)	
None	1242 (89.3)	476 (80.3)		409 (83.0)	407 (82.6)	
Number of HLA mismatch (ABDR), (SD)	3.1 (1.6)	3.1 (1.6)	0.948	3.1 (1.6)	3.1 (1.5)	0.617

Number of HLA mismatch (DR), (SD)	1.1 (0.6)	1.1 (0.7)	0.912	1.1 (0.7)	1.0 (0.7)	0.769
PRA>20%,n(%)	246 (17.7)	110 (18.5)	0.646	79 (16.0)	94 (19.1)	0.209
Pre-DSA, n (%)	80 (8.5)	32 (9.2)	0.683	83 (16.8)	78 (15.8)	0.667
ABO incompatible, n (%)	218 (15.8)	101 (17.1)	0.482	83 (16.8)	78 (15.8)	0.730
Induction, n (%)			0.586			0.888
Basiliximab	1137 (81.7)	490 (82.6)		404 (81.9)	404 (81.9)	
Thymoglobulin	76 (5.5)	36 (6.1)		26 (5.3)	29 (5.9)	
None	178 (12.8)	67 (11.3)		63 (12.8)	60 (12.2)	
Calcineurin inhibitor, n (%)			0.499			0.821
Cyclosporine	505 (37.8)	205 (35.8)		177 (35.9)	184 (37.3)	
Tacrolimus	832 (62.3)	365 (63.8)		314 (64.4)	309 (62.7)	
Antimetabolite, n (%)			0.118			0.897
Mycophenolate mofetil	679 (50.8)	284 (49.7)		250 (50.7)	243 (49.3)	
Myfortic acid	389 (29.1)	157 (27.4)		146 (29.6)	144 (29.2)	
Azathioprine	125 (9.3)	67 (11.7)		48 (9.7)	58 (11.8)	
CYT	67 (5.0)	40 (7.0)		28 (5.7)	28 (5.7)	
None	77 (5.8)	24 (4.2)		21 (4.3)	20 (4.1)	
Steroid, n (%)			0.876			1.000
Maintenance	1279 (95.5)	548 (95.8)		472 (95.7)	473 (95.9)	
Steroid withdrawal	60 (4.5)	24 (4.2)		21 (4.3)	20 (4.1)	
Delayed graft function, n (%)	21 (1.5)	17 (2.9)	0.066	12 (2.4)	12. (2.4)	1.000
Donor						
Mean age, y (SD)	42.5 (11.1)	41.8 (11.4)	0.217	41.6 (11.3)	41.8 (11.3)	0.817
Female sex, n (%)	721 (51.8)	302 (50.9)		249 (49.5)	247 (50.1)	
Body mass index, kg/m^2 (SD)	24.4 (3.3)	24.2 (3.2)	0.451	24.3 (3.2)	24.2 (3.3)	0.778
Current smoker, n (%)	472 (33.9)	180 (30.4)	0.133	148 (30.0)	156 (31.6)	0.629
Hypertension, n (%)	58 (4.2)	23 (3.9)	0.860	24 (4.9)	18 (3.7)	0.430
Diabetes mellitus, n (%)	9 (0.6)	1 (0.2)	0.302	1 (0.2)	1 (0.2)	1.000
Chronic hepatitis, n (%)	8 (0.6)	6 (1.0)	0.326	3 (0.6)	5 (1.0)	0.723
History of tuberculosis, n (%)	28 (2.8)	13 (2.2)	0.589	8 (1.6)	10 (2.0)	0.812
History of malignancy, n (%)	10 (0.7)	4 (0.7)	1.000	1 (0.2)	4 (0.8)	0.370
Relationship with recipient			0.011			1.000
Related, n (%)	915 (65.8)	354 (59.7)		299 (60.6)	300 (60.9)	

Unrelated, n (%)	476 (34.2)	239 (40.3)		323 (65.5)	314 (63.7)	
24-h creatinine clearance, mL/min (SD)	117.4 (38.5)	116.8 (26.9)	0.704	117.5 (31.7)	117.1 (27.4)	0.814
24-h urine protein, mg/day (SD)	90.4 (51.4)	96.2 (90.8)	0.143	93.8 (74.1)	94.0 (32.8)	0.960
Kidney graft weight, g (SD)	189.7 (51.8)	192.3 (100.3)	0.446	192.7 (68.9)	88.2 (36.2)	0.199
eGFR (CKD-EPI), % (SD)	103.9 (14.5)	104.6 (14.5)	0.290	105.3 (14.4)	104.4 (14.7)	0.321

SD, standard deviation; ESRD, end-stage renal disease; FSGS, focal segmental glomerulosclerosis; HLA, human leukocyte antigen; PRA, panel reactive antibody; DSA, donor-specific antibody; CYT, cyclophosphamide; eGFR, estimated glomerular filtration rate; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration.

Impact of the duration of pre-transplant dialysis on long-term mortality, graft failure, and BPAR

In order to verify the difference in clinical outcomes according to the duration of pre-transplant dialysis, the cohort was classified into three groups; PKT, pre-transplant dialysis < 19 months, and pre-transplant dialysis ≥ 19 months.

In unmatched cohort, patient survival (p=0.024), overall graft survival (p<0.001), and death-censored graft survival (p=0.001) were significantly lower in recipients with pre-transplant dialysis ≥ 19 months compared with the other groups (Figure 3).

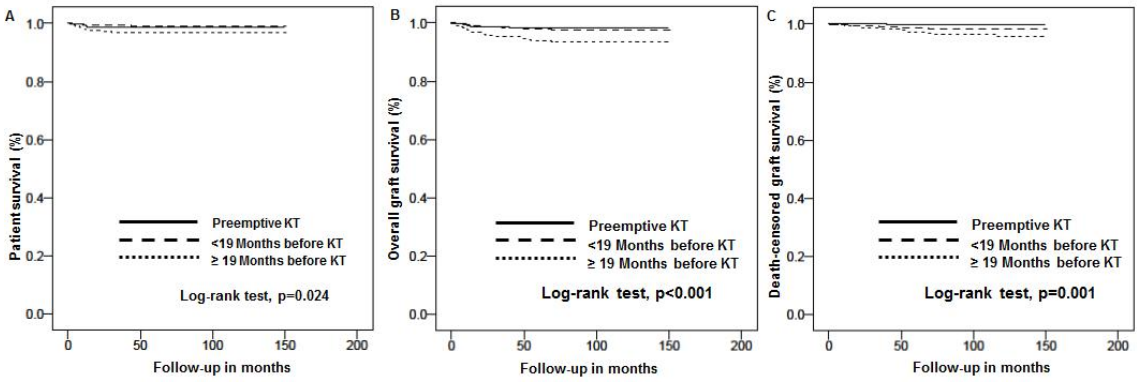

Figure 3. Kaplan-Meier curves of unmatched cohorts for 11-year overall patient survival (A), overall graft survival (B) and death-censored graft survival (C) according to duration of dialysis before kidney transplantation.

In matched cohort, it is likely that patient survival was lower in those with pre-transplant dialysis ≥ 19 months but with marginal significance (p=0.095) (Figure 4A). However, overall graft survival (p=0.006) and death-censored graft survival (p=0.037) were significantly lower in those with pre-transplant dialysis ≥ 19 months compared with the other groups (Figure 4B, 4C).

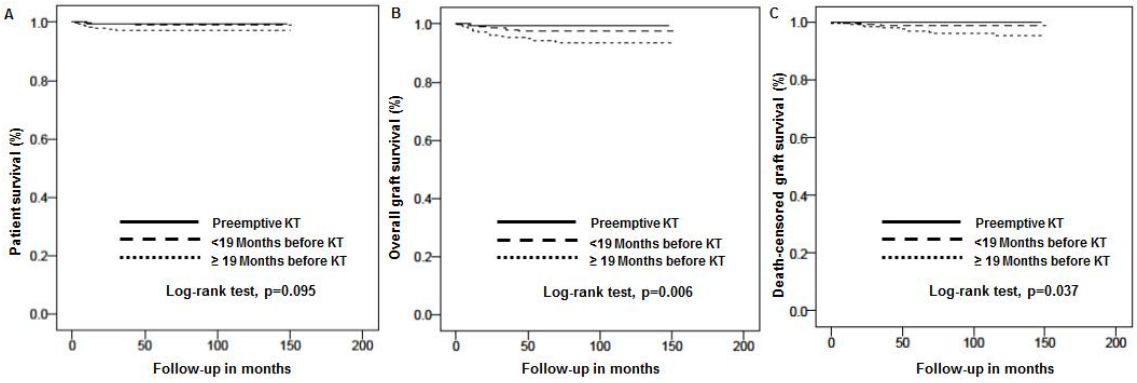

Figure 4. Kaplan-Meier curves of matched cohorts for 11-year overall patient survival (A), overall graft survival (B) and death-censored graft survival (C) according to duration of dialysis before kidney transplantation.

In unmatched cohort, a total 32 recipients of the 1,984 recipients had died during the follow-up period. Infections (50%, n=16), cardiovascular events (21.9%, n=7), and malignancy (9.4%, n=3) were three major causes of death after LDKT. Other causes of death were suicide, bowel perforation, and adrenal insufficiency. On the other hand, there were 17 cases (1.7%) of mortality in the matched cohort. Of them, one, three, and thirteen patients belong to PKT, pre-transplant dialysis < 19 months, and pre-transplant dialysis ≥ 19 months group, respectively. Infection (52.9%) and cardiovascular accidents (23.5%) were the most common causes of mortality. Of the 19 (1.9%) cases of death-censored graft failure, four and fifteen recipients belong to pre-transplant dialysis < 19 months and ≥ 19 months group, respectively. There was no death-censored graft failure in the PKT group during the follow up period.

It seems that the BPAR rate was higher in those who had pre-transplant dialysis ≥ 19 months compared with those who had a PKT or had pre-transplant dialysis < 19 months not only in the unmatched cohort (p=0.083) (Figure 5A) but also in the matched cohort (p=0.053) (Figure 5B).

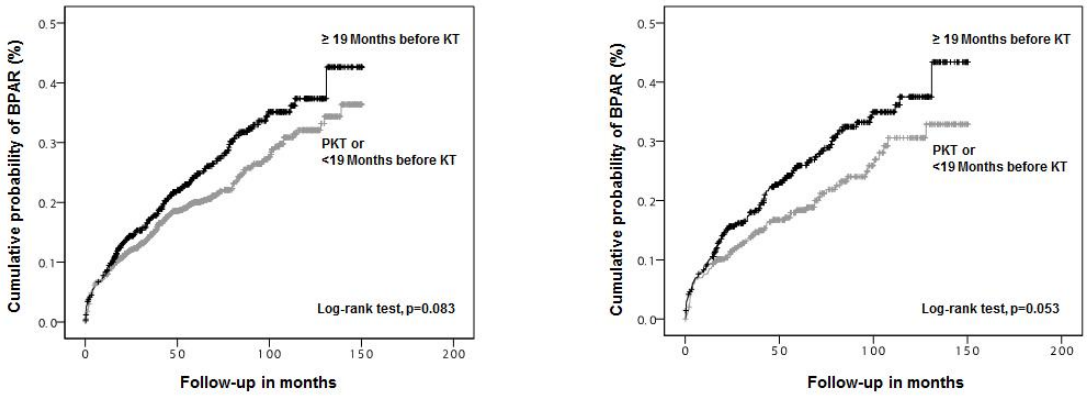

Figure 5. Kaplan-Meier curves of matched cohorts for 11-year BPAR according to duration of dialysis before kidney transplantation.

Discussion

This study reveals that recipients who underwent LDKT after a short period of pre-transplant dialysis had similar long-term outcomes compared with those with PKT in terms of patient survival and allograft survival. In addition, better allograft survival in a short pre-transplant dialysis group compared with a long pre-transplant dialysis group is attributed, in part, to a lower incidence of BPAR.

Long-term outcomes of PKT in this study are consistent with previous reports. Mange et al. demonstrated that LDKT without long-term dialysis was associated with a 52, 82, and 86 percent reduction in the risk of allograft failure during the first, second, and subsequent years after transplantation, respectively, as compared with transplantation after dialysis (12). A study in a Japanese cohort revealed that PKT could be beneficial to reduce mortality, graft failure, and post-transplant cardiovascular disease (1). Kasiske et al. demonstrated that PKT was associated with improved patient and graft survival in DDKT as well as LDKT (3). On the other hand, this study is distinguished from previous reports in that long-term outcomes of kidney transplant recipients from a living donor were assessed whereas a majority of previous studies dealt with outcomes of DDKT recipients according to a pre-transplant dialysis duration (8,13,14,15).

Although waiting time on dialysis is a significant risk factor for mortality and graft failure, it is not well known how long a patient can maintain dialysis before kidney transplantation to minimize deleterious effects of long-term dialysis on patient and graft survival. This study suggests that recipients with a pre-transplant dialysis time of ≥ 19 months have worse patient survival and graft survival. Furthermore, it is likely that the incidence of BPAR is higher in recipients who

maintain pre-transplant dialysis ≥ 19 months. Although this cut-off value of pre-transplant dialysis duration needs to be further validated, the duration is much shorter compared with previous reports. Recently, it was reported that recipients with pre-transplant dialysis time of ≥10 years had worse outcomes than those pre-emptively transplanted or transplanted with shorter dialysis time according to the analysis of United Network for Organ Sharing registry data (13). Goto et al. also demonstrated that PKT could be beneficial to reduce the rate of clinical events including mortality, graft failure, and post-transplant cardiovascular disease (3.3%) while the rate of clinical events for those having pre-transplant dialysis time of < one year is significantly increased (10.8%) (1). On the contrary, the present study verifies that recipients with a short period of dialysis (less than 19 months) had favorable long-term outcomes similar to PKT recipients. Unlike western countries, candidates for DDKT hardly have the chance of PKT in South Korea unless they are on dialysis according to regulations established by Korean Network for Organ Sharing (KONOS). Furthermore, average waiting time for DDKT exceeds five years in South Korea according to 2016 KONOS annual report (Data not shown). Therefore, a physician has to be able to recommend an optimal time of transplantation when a patient with ESRD consider LDKT in order to minimize the length of dialysis duration for favorable long-term outcomes. Although Okumi et al. compared clinical outcomes of PKT with those of non-PKT in a propensity score matched cohort, they just revealed that PKT was associated with neither improvement of post-transplant renal function nor a lower rate of common post-transplant complications than non-PTK (2). In a propensity score matched cohort of this study, however, it is evident that recipients with a short pre-transplant dialysis had similar long-term outcomes to those with PKT whereas they had superior results compared with those with a long pre-transplant dialysis in terms of mortality, graft survival, and BPAR.

There are some limitations to this study. First, a cut-off value of pre-transplant dialysis duration to differentiate clinical outcomes was determined from a retrospective, single-center data even though we used propensity score matching to remove potential confounding variables. For general application, therefore, it is necessary to validate in a larger, multi-center cohort. Second, assessment of pre-transplant DSA was available since January, 2009 when single antigen bead assay by Luminex was introduced at our center. Therefore, it is difficult to confirm a positive correlation between a duration of pre-transplant dialysis and the presence of pre-transplant DSA. Third, ABO-incompatible KT was performed in about 16% of recipients who had desensitization treatments including rituximab and total plasma exchange. Although there was no significant difference in the incidence of ABO-incompatible KT between short and long pre-transplant dialysis groups, it is possible that desensitization might have an influence on clinical

outcomes. Nevertheless, to our knowledge, this study is the first to suggest optimal duration of pre-transplant dialysis to get long-term clinical outcomes comparable to those in PKT.

In conclusion, compared with a pre-transplant dialysis time of ≥ 19 months, a pre-transplant dialysis time of < 19 months was associated with superior clinical outcomes which are similar to those in PKT in a propensity score matching cohort. It is necessary to set up an appropriate cut-off value of pre-transplant dialysis duration using a national or international database to improve long-term patient survival and graft survival in LDKT.

Abstract

It is unclear what extent of pre-transplant dialysisis permissible in terms of patient and allograft survival. We retrospectively evaluated outcomes of living donor kidney transplantation(LDKT) according to the duration of pre-transplant dialysis in both unmatched (n=1,984) and propensity score matched cohorts (n=986). The most appropriate cut-off value of pre-transplant dialysis duration to differentiate clinical outcomes was 19 months. Of 1,984 patients who had LDKT at our center between January 2005 and September 2016, preemptive kidney transplantation (PKT) was performed in 429 patients. The duration of pre-transplant dialysis was less than 19 months in 962 recipients while the duration was equal to and longer than 19 months in 593 recipients. There was no significant difference in mortality and death-censored graft survival (DCGS) between PKT and non-PKT recipients with pre-transplant dialysis less than 19 months. Meanwhile, patient survival (p=0.024) and DCGS (p=0.001) turned out to be worse in non-PKT recipients with pre-transplant dialysis equal to and longer than 19 months. In the matched cohort, DCGS was significantly lower in non-PKT recipients with pre-transplant dialysis equal to and longer than 19 months (p=0.037). Furthermore, it is likely that the incidence of biopsy-proven acute rejection was higher in this group (p=0.083). In conclusion, patient survival and DCGS were worse when pre-transplant dialysis duration was equal to and longer than 19 months in a propensity score matched LDKT cohort.

References

1. Goto N, Okada M, Yamamoto T, Tsujita M, Hiramitsu T, Narumi S, Katayama A, Kobayashi T, Uchida K, Watarai Y: Association of dialysis duration with outcomes after transplantation in a Japanese cohort. Clin J Am Soc Nephrol 11: 497-504, 2016

2. Okumi M, Sato Y, Unagami K, Hirai T, Ishida H, Tanabe K, Japan Academic Consortium of Kidney Transplantation (JACK): Preemptive kidney transplantation: a propensity score matched cohort study. Clin Exp Nephrol 21: 1105-1112, 2017

3. Kasiske BL, Snyder JJ, Matas AJ, Ellison MD, Gill JS, Kausz AT: Preemptive kidney transplantation: The advantage and the advantaged. J Am Soc Nephrol 13: 1358-1364, 2002

4. Arze Aimaretti L, Arze S: Preemptive Renal Transplantation-The Best Treatment Option for Terminal Chronic Renal Failure. Transplant Proc 48: 609-611

5. Fissell RB, Srinivas T, Fatica R, Nally J, Navaneethan S, Poggio E, Goldfarb D, Schold J: Preemptive renal transplant candidate survival, access to care, and renal function at listing. Nephrol Dial Transplant 27: 3321-3329

6. Yoo SW, Kwon OJ, Kang CM: Preemptive living-donor renal transplantation: outcome and clinical advantages. Transplant Proc 41: 117-120

7. Ahn C, Koo TY, Jeong JC, Kim M, Yang J, Lee J, Min SI, Lee JE, Kim MS, Kwon OJ, Kim SJ, Kim YH, Kim YH, Choi BS, Choi SJ, Lee DH, Chung SY, Cho WH, Kim YS; Korean Organ Transplantation Registry Study Group: Initial report of the Korean Organ Transplant Registry: the first report of national kidney transplantation data. Transplant Proc 46: 425-430, 2014

8. Rose C, Gill J, Gill JS: Association of kidney transplantation with survival in patients with long dialysis exposure. Clin J Am Soc Nephrol 12: 2024-2031, 2017

9. Liem Y, Weimar W: Early living-donor kidney transplantation: a review of the associated survival benefit. Transplantation 87: 317-318, 2009

10. Meier-Kriesche HU, Kaplan B: Waiting time on dialysis as the strongest modifiable risk factor for renal transplant outcomes a paired donor kidney analysis. Transplantation 74: 1377-1381

11. Meier-Kriesche HU, Port FK, Ojo AO, Rudich SM, Hanson JA, Cibrik DM, Leichtman AB, Kaplan B: Effect of waiting time on renal transplant outcome. Kidney International 58: 1311-1317

12. Mange KC, Joffe MM, Feldman HI: Effect of the use or nonuse of long-term dialysis on the subsequent survival of renal transplants from living donors. N Engl J Med 344: 726-731, 2001

13. Aufhauser DD Jr, Peng AW, Murken DR, Concors SJ, Abt PL, Sawinski D, Bloom RD, Reese PP, Levine MH: Impact of prolonged dialysis prior to renal transplantation. Clin Transplant 15: e13260, 2018

14. Keith DS: Preemptive deceased donor kidney transplant not associated with patient survival benefit in minority kidney transplant recipients. Clin Transplant 26: 82-86, 2012

15. Grams ME, Chen BP, Coresh J, Segev DL: Preemptive deceased donor kidney transplantation: considerations of equity and utility. Clin J Am Soc Nephrol 8: 575-582, 2013