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Similar Outcome 3 and 12 Months after Kidney Transplantation during the Last Two Decades with Different Immunosuppressive Therapy – A Single Centre Study

Introduction: During the last decades immunosuppressive therapy of kidney transplanted patients has changed completely. Complications after kidney transplantation (KTR) mainly occur during the first 3 months. In this study we investigated the outcome of patients with KTR before 1987 using cyclosporine and patients with KTR after 1986 using tacrolimus.

Patients and methods: A total of 406 patients were included in the study, patients were divided into 2 groups: in group I with KTR 1986-1996 (n=182), immunosuppressive therapy was azathioprine and cyclosporine and group II with KTR 1997-2007, using mofetil mycophenolat (MMF) and tacrolimus for immunosuppression. In each group we evaluated the incidence of complications as well as incidence of kidney graft loss and death of patients 3 and 12 months after KTR

Results: During the three months after KTR the incidence of acute graft rejection was significantly lower in the last decade (20% versus 38%), in contrast to that, the incidence of infections was higher during the same period (30% versus 20%). The prevalence of non-functioning grafts 3 months after KTR was slightly higher in the years 1986-1996 (20% versus 12%). Death of patients was a cause of graft loss in 12 patients in each group (33% versus 44%). Severe rejection was the cause of non functioning graft in 20 patients during 1984-1996 but only in 10 patients during the last decade (41% versus 11%, $p < 0.01$).

Conclusion: In group I rejections were more often the cause of kidney graft loss within the first 3 months after KTR compared to group II. However, the prevalence of non-functioning grafts 3 months after transplantation was only slightly lower during the last decade. The 1-year mortality was nearly the same in both groups.

Key words: kidney transplantation, early graft function, complication

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Vergleichbares Ergebnis 3 und 12 Monate nach Nierentransplantation während der letzten zwei Jahrzehnte mit unterschiedlicher immunsuppressiver Therapie – eine Einzell-Zentrum-Studie

Einführung: Während der letzten zwei Jahrzehnte wurde die immunsuppressive Therapie bei Nierentransplantation (NTX) komplett geändert. Komplikationen treten bekanntlich nach NTX vor-

wiegend während der ersten 3 Monate auf. In dieser Studie wurde die Erfolgsrate bei Patienten mit NTX vor 1987 (unter Cyclosporin) und nach 1986 (unter Tacrolimus) untersucht.

Patienten und Methode: Insgesamt wurden 406 Patienten in die Studie aufgenommen. Die Patienten wurden in 2 Gruppen eingeteilt: in Gruppe I mit NTX 1986-1996 (n=182), immunsuppressive Therapie mit Azathioprin, und Cyclosporin sowie in Gruppe II mit KTR 1997-2007 (n=224), Immunsuppression mit Mofetil Mycophenolat (MMF) und Tacrolimus. In jeder Gruppe wurde die Inzidenz von Komplikationen sowie die Häufigkeit eines Nieren-Transplantatversagens und eines Patienten-Todesfalls 3 und 12 Monate nach der NTX evaluiert.

Ergebnisse: Während der ersten 3 Monate nach NTX war die Inzidenz einer akuten Abstoßung in der letzte Dekade signifikant niedriger (20 versus 38%), im Gegensatz dazu war während der selben Zeit die Infektionshäufigkeit höher (30 versus 20%). Die Häufigkeit eines nicht-funktionierenden Transplantats 3 Monate nach NTX war in den Jahren 1986-1996 nur gering höher (20 versus 12%) als 1997-2007. Todesfall war die Ursache für einen Transplantatverlust bei 12 Patienten in jeder Gruppe (33 versus 44%). Eine schwere Abstoßung war in den Jahren 1986-1996 bei 20 Patienten die Ursache eines Transplantatverlustes, in der letzten Dekade nur bei 12 Patienten (41 versus 11%, $p < 0.01$)

Schlussfolgerung: In Gruppe 1 war eine Abstoßung in den ersten 3 Monaten nach NTX häufiger die Ursache für einen Transplantatverlust als in Gruppe 2. Jedoch war 3 Monate nach NTX die Häufigkeit eines Transplantatverlustes nur wenig niedriger als in der letzten Dekade. Die 1 Jahres Mortalität war in beiden Gruppen annähernd gleich.

Schlüsselwörter: Nieren-Transplantation, frühe Transplantatfunktion, Komplikationen

Introduction

By introducing cyclosporine for immunosuppression in 1983 the 1-year kidney graft survival could significantly be improved (1). The introduction of tacrolimus and mofetil mycophenolat (MMF) instead of cyclosporine and azathioprine led to a further reduction of graft rejections (2). The long-term graft and patient survival during the last decade was limited due to higher age of the recipients and acceptance of higher aged kidney donors. Usually, the highest rate of rejections and graft-related complications can be seen during the first 3 months after kidney transplantation (KTR). There are controversial data in the literature concerning changes in the early outcome of kidney graft and transplanted patients

within the first 3 months after transplantation, comparing the last two decades (3, 4).

In our study we evaluated the complications and the outcome 3 and 12 months after KTR in the years 1986-1996 with prednisolon, azathioprine and cyclosporine for immunosuppression, and the years 1997-2007 with prednisolon, MMF and tacrolimus. Aim of the study was to investigate the occurrence of complications, the frequency of non graft function and/or early loss of graft function as well as early death of transplanted patients 3 and 12 months after KTR comparing the period 1986-1996 as well as the period 1997-2007. Moreover, we wanted to find out the causes of non-function and/or early graft loss as well as for early death after transplantation. Hypothe-

sis was that the occurrence of complications and the outcome in the first year after KTR have been changed during the last decades.

Patients and Methods

In this study we included a total of 406 patients who received kidney transplantation (KTR) 1986-2007 in our centre. The patients were divided into two groups: group I: patients who received their kidney transplant during the years 1986-1996 (n=182) with prednisolone, azathioprine and cyclosporine for immunosuppression, and group II: patients with KTR during 1997-2007 (n=224) and a combination therapy with prednisolone, mofetil mycophenolate (MMF) and tacrolimus. Patients who primarily used an other immunosuppressive therapy during the two decades were excluded from the study (n=12), as well as type 1 diabetic patients with simultaneous kidney pancreas transplantation during the same period (n=36). The baseline data of the patients are presented in table 1. Additionally, we evaluated donor age, cold and warm ischemic time and number of mis-matches in both patient groups. All kidney graft related data are summarized in table 2. We estimated the cumulative incidence of acute rejections and the frequency of infectious diseases and other complications 3 and 12 months after KTR. Moreover, we compared in both decades the well known risk factors for poor outcome, such as diabetes, heart insufficiency and severe atherosclerosis. Finally, we compared the prevalence of non-functioning grafts (dialysis requiring) 3 and 12 months after KTR as well as the cumulative incidence of death with and without functioning graft during the same period. Finally, we estimated the causes of death and reasons for no function of grafts in both periods. We also calculated the 3 month- as well as the 1-year-graft and patient survival in both groups. Acute rejection was assumed in case of increasing serum-creatinine after exclusion of other reasons for worsening of renal function. Diagnosis of rejection was confirmed by kidney biopsy in 66% of all cases. Therapy of rejection was 250 mg methyl-prednisolone for 3-5 days, in steroid resistant cases 200 mg ATG daily for 4-10 days. Cardiovascular disease was defined as the presence

Tab. 1: Baseline data of the patients with kidney transplantation

	1986-1996 (n = 182)	1997-2007 (n = 224)
Age (years)	44 ± 14*	52 ± 12*
Female (%)	42%	41%
BMI	25 ± 3	24 ± 3
Dialysis duration (years)	3.2 (0-12)	2.6 (0-8)
Primary renal disease (%)		
Glomerulonephritis	33%	29%
Diabetic nephropathy	12%	10%
Vascular nephropathy	22%	21%
Interstitial nephritis	12%	11%
Reflux nephropathy	3%	4%
Polycystic kidney disease	3%	2%
Unknown	15%	13%
Immunosuppressive therapy (%)		
Azathioprine	97%**	3%**
Cyclosporine	97%**	0**
MMF	0**	97%**
Tacrolimus	0**	91%**
Sirolimus	0	12%
Everolimus	0	3%
IL-2-blocker	0**	91%**

*p<0.05, **p<0.01

Tab. 2: Kidney graft related data

	1986-1996	1997-2007
Donor age (years)	48 ± 12*	54 ± 18*
HLA mismatches x + SD	2.2 ± 1.0*	2.9 ± 1.4*
Warm ischemic time (min) x + SD	51 ± 18	57 ± 19
Cold ischemic time (h) x + SD	18 ± 8*	12 ± 6*
Possible risk factors:		
HLA > 4 mismatches (n/%)	18 (10%)	24 (10%)
Warm ischemic time > 60 min (n/%)	7 (4%)	20 (9%)
Cold ischemic time > 20 hours (n/%)	22 /12%	11 (5%)

*p<0.05

of angina pectoris and/or myocardial infarction as well as stent implantation and/or coronary bypass operation in history. Heart failure was classified as heart insufficiency NYHA I-III.

Statistical Analysis

Statistical methods included paired Student's t-test for comparing differences within groups and unpaired Student's t-test to compare data between groups. For comparison of differences between groups with data not normally distrib-

uted the Wilcoxon and the Man-Whitney U-test as non-parametric statistic was used. A p-value <0.05 was considered as significant.

Results

The mean age of the kidney graft recipients (44 ± 14 versus 52 ± 12 years) as well as the age of the donors (48 ± 12 versus 54 ± 18 years) were significantly lower during the years 1986-1996 than during the last decade. During 1997-2007, the numbers of HLA mis-

matches were higher with 2.2 ± 1.0 versus 2.9 ± 1.4 (p<0.05). The incidence of rejections during the first 3 months after KTR was significantly lower in the last decade with 20% versus 38% (p<0.05), in contrast to that, the incidence of infectious diseases was 30% versus 20%. Also diseases with sepsis occurred more frequently during the last decade (9% versus 6%, NS). The prevalence of non-functioning grafts 3 months after KTR was slightly higher in the years 1986-1996 (20% versus 12%). During the same periods death of patients was a cause of graft loss in 12 recipients in each group (33% versus 44%). Severe rejection was the cause of non-functioning graft in 20 patients 1986-1996 but only in 10 patients during the last decade (55% versus 37%, p<0.05). All complications occurred mainly during the first 3 months. Later on, till month 12 after KTR the occurrence of complications was low. These data are presented in table 3.

The prevalence of non-functioning grafts 3 months after KTR was only slightly higher in the years 1986-1996 than in the last decade (20% versus 12%). The risk factors for graft non-function were not significantly different during both periods. Death of patient was the cause of graft loss in 12 patients in each group (33% versus 44%), in six patients with functioning graft rejection was the cause of not functioning graft or loss of transplanted kidney in 20 transplantations during the years 1986-1996 but only in 12 transplantations during the last decade (55% versus 44%). All data are summarized in table 4. Predictors for death were similar in both groups, only the number of recipients aged over 65 years was higher in the period 1997-2007 (4% versus 9%). Causes of death were mainly cardiovascular events.

These data are summarized in table 5. During the years 1986-1996 the 3-month graft survival (80 versus 88%) and patient survival (93 versus 94%) were slightly lower. The 1-year survival was approximately the same for functioning grafts (80 versus 87%) as well as for patients (93 versus 94%) during both periods of observations, as can be seen in figure 1.

Tab. 3: Complications and outcome during the first three months and during the next nine months until the end of the first year after kidney transplantation

	1986-1996		1997-2007	
	3 months	12 months	3 months	12 months
Complications (n/%)				
Rejections	69 (38%)*	73 (40%)	45 (20%)*	47 (21%)
Infectious disease	36 (20%)	44 (24%)	67 (30%)	76 (34%)
Sepsis	11 (6%)	13 (7%)	2 (1%)	2 (1%)
Bleeding	9 (5%)	9 (5%)	11 (5%)	11 (5%)
Ureter leak	9 (5%)	9 (5%)	9 (4%)	9 (4%)
Outcome	3 months	1 year	3 months	1 year
Death of patient (n/%)	12 (7%)	12 (7%)	12 (5.5%)	13 (6%)
Loss of graft (n/%)	36 (20%)	36 (20%)	27 (12%)	28 (12.5%)

*p<0.05

Tab. 4: Causes of non-functioning kidney graft and graft loss respectively during three months after NTX

Lost graft function (n)	1984-1996 (n=36)	1997-2007 (n=27)
Death of patient (n/%)	12 (33%)	12 (44%)
With graft function (%)	66%	50%
Patients alive (n/%)	24 (66%)	15 (56%)
Acute rejection (therapy resistant)	20 (55%)*	10 (37%)*
Ischemic damage	1 (3%)	1 (4%)
Ureter-leak	1 (3%)	1 (4%)
Kidney rupture	1 (3%)	0
Acute pancreatitis	0	1 (4%)
Venous thrombosis	0	1 (4%)
Sepsis	1 (3%)	1 (4%)

*p<0.05

Tab. 5: Causes of death of patients within 3 months after NTX as well as predictors for death

Death (n)	1896-1996 (n=12)	1997-2007 (n=12)
Causes of death (n/%)		
Heart failure	7 (58%)	6 (50%)
Myocardial infarction	2 (17%)	2 (17%)
Sepsis	1 (8%)	2 (17%)
Ileus	0	1 (8%)
Sudden death	0	1 (8%)
Stroke	2 (17%)	0
Predictors for death (n/%)		
Age > 65 yr	8 (4%)	21 (9%)
Diabetes mellitus	23 (12%)	21 (8%)
Cardiovascular disease	23 (12%)	32 (14%)
Heart failure	14 (8%)	14 (6%)

Discussion

Most complications in kidney graft recipients occur within the first few weeks after transplantation. During this period most episodes of acute rejections as well as infectious diseases can be observed. Usually, three months after KTR the decision has fallen if graft is functioning or not (4). In our study the three-month graft survival was approximately the same as the 1-year graft survival, and there was also no significant difference between the patient survival three months and one year after KTR.

Acute rejection (5, 6) is a major cause of kidney graft loss during the first three months after KTR. However, acute rejection of the transplanted kidney has also been identified as the major risk factor for the development of chronic rejection and immunological graft loss during later period of observation. In our study the total cumulative incidence of acute rejections within the first three months after KTR was significantly higher during the earlier years 1986-1996. At that time the patients usually received azathioprine and cyclosporine. In this patient group the occurrence of therapy-resistant rejections with consecutive loss of the graft was significantly more often, too. However, the 1-year graft survival was only slightly higher in group II under immunosuppressive therapy with MMF and tacrolimus. The 1-year patient survival was nearly the same in both groups.

Several studies could demonstrate (6, 7) that both acute rejection and the function of a renal allograft early after transplantation correlate with short as well as long-term survival. The similar outcome in both groups despite a more potent immunosuppressive therapy may be explained by several factors: in the last decade the age of patients was higher, as well as donor age and HLA mismatches, additionally the incidence of infections was higher too, the difference was not statistically significant only due to the too small patient groups.

An additional major cause for loss of kidney graft function is death of the transplanted patients (table 5) The transplantation outcome is reduced in patients with cardiovascular diseases, especially in subjects with diabetes (8). The prevalence of cardiovascular risk factors in renal transplant candidates is high. In several studies diabetic

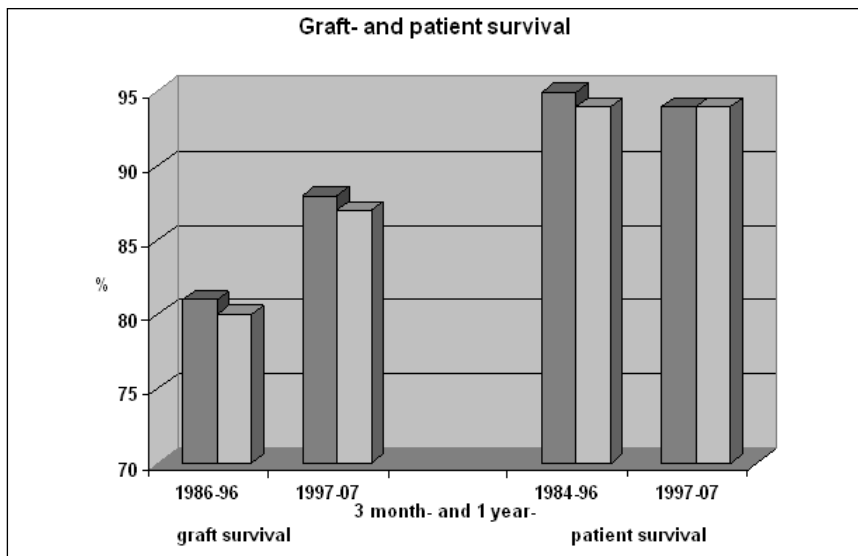


Fig. 1: 3-month- and 1-year survival of kidney grafts and patients after KTR

nephropathy and cardiovascular disease were the most important predictors for cardiovascular events and all-cause mortality after renal transplantation. Early treatment of cardiovascular risk factors and pre-transplant cardiovascular evaluation might improve the prognosis. In our study the prevalence of cardiovascular disease as well as of diabetes was similar during both periods, however, the age of the patients was significantly higher during the last decade. In a recent study (9) was reported that in elderly patients with age over 65 years the risk for complications after KTR is elevated, however, patient survival after KTR is better than under dialysis therapy. In our study the number of elderly patients with kidney transplantation was higher during the last decade; the 3 month patient survival was improved with 78% versus 37% in the earlier period.

Diabetic patients show a higher mortality after KTR (7, 10). Both, pre-transplant diabetes type 1 or type 2 as well as post-transplant diabetes (PTDM) are a serious complication of kidney transplantation. In a further study (11) it was postulated that aggressive detection and treatment of PTDM may significantly reduce cardiovascular morbidity and mortality after KTR. In our study the prevalence of diabetes prior to transplantation was approximately the same. The frequency of PTDM was significantly higher during the last decade due to the use of tacrolimus during this period (2).

Rare complications during the early phase after KTR (12) are urologic com-

plications such as ureter strictures, urine leaks and ureter stone. In our study the incidence of post-kidney transplant urologic complications during both decades was 5% and 4% respectively. Our data are in agreement with the reports in the literature with a mean incidence of 5% of urological complications. They were more common among male recipients and after cadaveric kidney transplantation. In a recent study ureteric stricture was more common among children, urine leak more common in the elderly. Usually the urologic complications can be successfully managed, however in our study one graft was lost three months after KTR.

Conclusion

During the years 1997-2007 frequency of acute rejections was significantly lower than in the years 1986-1996, obviously due to the new immunosuppressive therapy. The incidence of infections was slightly higher during the last decade. During 1986-1996 acute rejections were more often the cause of non-graft function within the first 3 months after KTR. However, the prevalence of non-functioning grafts during the same time after transplantation was only slightly lower compared to the years 1997-2007; the 1-year graft survival was 12 versus 20%. The cumulative incidence of death during the same period was nearly the same in both groups, the 1-year patient survival was 7 versus 6%.

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