Surgical aspects of renal transplantation

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CHAPTER 9

10-year results of the transatlantic kidney transplant airlift between the Dutch Caribbean and the Netherlands

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The prevalence of end-stage renal failure in Curaçao (Dutch Caribbean) is one of the highest in the world. In 1998, the St. Elisabeth Hospital started a unique transatlantic collaboration with the Academic Medical Center (AMC) in Amsterdam, the Netherlands, and the Eurotransplant Foundation. The partnership aimed to achieve a structured transplantation programme for patients in the Dutch Caribbean, who otherwise would need lifelong dialysis. The distance between the Dutch Caribbean and the Netherlands is 8000 km. This study is an analysis of the 10-year transplantation results of this transatlantic programme. In 41 consecutive transplantations performed between January 1998 and April 2007 1-year graft survival and complication rates were retrospectively studied. Twenty-four males and 17 females with a median age of 54 years were transplanted. The median dialysis period prior to transplantation was 6.8 years. The 1-year graft survival rate was 69% (95% confidence interval: 52% to 80%). Initially 28 graft functioned (68%); 4 grafts showed primary non function (10%) and delayed graft function (DGF) developed in 9 patients (22%). Ten recipients had 16 postoperative complications. Acute rejection was diagnosed in 11 patients; in 5 this episode was superponed on DGF. Our transatlantic programme affords patients with end stage renal failure, who otherwise would need lifelong dialysis, a chance to be transplanted. Taking the circumstances into consideration graft survival is acceptable. Currently we are approaching these patients slightly differently, aiming to improve graft survival.

INTRODUCTION

The prevalence of end-stage renal failure in the Dutch Caribbean is one of the highest in the world with an estimated prevalence of 145 per 100.000 residents[1]. Only in Japan the prevalence is higher with 202 cases per 100.000[2]. In contrast: in the Netherlands the prevalence is 70 per 100.000[3]. The population of the Dutch Caribbean originates from a highly variable ethnic background and is a mixture of African, Arawak Indian, Hispanic, Jewish, Portuguese and Dutch origins.

The high prevalence of end-stage renal disease (ESRD) in the Dutch Caribbean is partly explained by the high incidence of well-known risk factors for developing renal failure such as hypertension, diabetes, obesity and dyslipidemia[4-7]. As a result the Dutch Caribbean has a relatively large dialysis population.

In 1998, the St. Elisabeth Hospital in Curaçao and in 2003 the Dr. Horacio E. Oduber Hospital in Aruba, in collaboration with the Academic Medical Center (AMC) in Amsterdam, the Netherlands, the Eurotransplant Foundation, Sanquin Diagnostic Services and the Dutch Transplantation Working Group, aimed to achieve a structured transplantation programme for patients in the Dutch Caribbean, who otherwise would need lifelong dialysis. These patients were offered the opportunity to be put on the waiting list of Eurotransplant to receive a deceased donor kidney or to participate in the living donor transplantation programme, when a living donor was available. An agreement with the Dutch Royal Airlines was made. In this agreement a seat on the first flight to Amsterdam was guaranteed for the renal transplant candidate in case of a donor kidney offer. This resulted in an airlift between the islands of Aruba, Curacao (both part of the Dutch Caribbean) and the AMC. This study is an analysis of the 10-year transplantation results of this transatlantic transplantation programme.

PATIENTS AND METHODS

Forty-one consecutive transplantations in Dutch Caribbean recipients performed between January 1998 and April 2007 were retrospectively analysed.

Patients

Dialysis patients of the Dutch Caribbean were prepared locally according to a protocol of the AMC based on general accepted guidelines[8,9]. Blood samples of the aspirant recipients were sent to the department of Immunogenetics, Sanquin Diagnostic Services for Human Leukocyte Antigen (HLA) typing and antibodies screening. Then the patient was placed on the Eurotransplant waiting list in the Amsterdam region. The distance between the Dutch Caribbean and the Netherlands is 8.000 km, with a flying time of approximately nine hours.

The airport in the Netherlands is within a distance of 25 km from the transplant center. The time difference is 5 hours. Donor kidneys, all harvested in countries affiliated to Eurotransplant, were machine-preserved in order to optimize its quality. The Eurotransplant International Foundation is responsible for the mediation and allocation of organ donation procedures in Austria, Belgium, Croatia, Germany, Luxemburg, the Netherlands and Slovenia. The maximum distance in the Eurotransplant area is 1.300 km. A cold ischemia time (CIT) of 48 hours maximally was accepted. After arrival in the AMC the recipient could be transplanted within 1.5 hours. Implantation of the kidney was done via the extra peritoneal approach in the iliac fossa. Immunosuppressive therapy consisted of prednisone, a calcineurin inhibitor and mycophenolate mofetil. From 2006 prophylactic anti-CD25 monoclonal antibody (basiliximab) was added as induction therapy. After successful transplantation all recipients were seen at the outpatient clinic of the AMC in the Netherlands for at least 6 weeks of follow-up, before returning to the Dutch Caribbean.

End-points

Immediate graft function, one-year graft survival and complications were studied. The graft survival was compared with a matched Dutch residents group corrected for ethnic background. In addition CIT and acute rejection episodes up to six months after transplantation were recorded. An urological complication was defined as any urinary fistula (leakage) and/or ureteral obstruction, which a percutaneous nephrostomy and/or operation was necessary. First episodes of acute rejection were treated with pulse doses of methylprednisolone; second episodes with thymoglobulin. Delayed graft function (DGF) was defined as the need for dialysis within the first postoperative week.

Statistical analysis

Survival analysis was performed by Kaplan–Meier technique and log-rank test. A p-value of < 0.05 was considered statistically significant. For statistical analyses the SPSS software package (SPSS 14.0.2., Chicago, Illinois, USA) was used.

RESULTS

Twenty-four males and 17 females with a median age of 54 years (range 23 - 68) were transplanted. The primary renal diseases of the recipients are listed in Table 1. Thirty-six patients were on haemodialysis and 5 patients were on peritoneal dialysis. The median dialysis period prior to transplantation was 6.8 years (range 1 – 20). Twenty-seven patients (66%) were treated for hypertension and 6 patients (15%) were treated for type 2 diabetes mellitus. The median body mass index was 29 kg/m^2 (range 19 - 47). Thirty-eight patients underwent a first kidney transplantation, 2 patients a second kidney transplantation and

Table 1: Primary renal disease of recipients

Primary renal disease	(n=41)
Hypertension	17
Diabetic nephropathy	3
Systemic lupus erytematosus	3
Chronic glomerulonephritis	2
Polycystic kidney disease	2
Hypoplastic/dysplastic kidney	2
IgA nephropathy	1
Reflux nephropathy	1
Acute tubular necrosis due to eclampsia	1
Lithium nephrotoxicity	1
Unknown aetiology	8

one patient a third kidney transplantation. Donor characteristics are presented in Table 2. Current panel-reactive antibody (PRA) level was 0% to 6% PRA in 35 (85%) and 6% to 85% PRA in 6 (15%). Historical panel reactivity was 0% to 6% PRA in 25 (61%), 6% to 85% PRA in 13 (32%) and 2 patients (5%) with more than 85% PRA (Table 3). In 3 transplantations no mismatches were present between the donor and recipient. One or two HLA mismatches were present in 9 (22%) patients, 3 or 4 HLA mismatches in 20 (49%) and 5 or 6 HLA mismatches in 9 (22%) patients. Twenty-nine patients (71%) received a graft mismatched for 1 HLA-DR allele. In 38 donors University of Wisconsin preservation solution was used and in 3 donors kidney Histidine-Tryptophan-Ketoglutarate (HTK) solution.

Table 2: Donor characteristics

Variables	
Age median years (range)	48 (12-68)
Left kidney (%)	21 (51%)
Female sex (%)	16 (39%)
Non-heart beating donor (%)	5 (12%)
Cause of death	
Trauma (%)	27 (66%)
Stroke (%)	5 (12%)
Subarachnoid hemorrhage ((%)	8 (20%)
Suicide (%)	1 (2%)

Surgical technique

Thirty-three kidneys were implanted in the right fossa iliaca and 8 kidneys in the left. Median CIT was 31 hours (range 16 – 48 hours), median operating time 150 minutes (range 102 – 257) with an anastomosis time of 30 minutes (range 13 – 80). Renal transplant arterial

Table 3 Immunological characteristics

Variables	
Historical panel reactive antibody (PRA) level	
0% to 6%	25 (61%)
6% to 85%	13 (32%)
> 85%	2 (5%)
Current PRA level	
0% to 6%	35 (85%)
6% to 85%	6 (15%)
HLA mismatch	
0	3 (7%)
1 or 2	9 (22%)
3 or 4	20 (49%)
5 or 6	9 (22%)

reconstructions were performed in four cases, venous reconstructions in three of which one was performed with a Poly Tetra Fluor Ethylene (PTFE) graft. Intraoperative complications occurred in 2 recipients (5%): during implantation the renal artery ruptured in 2 recipients requiring sutures for repair.

Postoperative outcome

Initially 28 graft functioned (68%); 4 grafts showed primary non function (10%) and DGF developed in 9 patients (22%). Ten recipients had 16 postoperative complications (39%) (Table 4). Acute rejection was diagnosed in 11 patients; in 5 of them this episode was superponed on DGF. Five patients suffered from an urological complication treated with a percutaneous nephrostomy catheter. In one patient a surgical revision was necessary to correct the urological complication. Eight grafts were lost within 3 months, due to therapy resistant rejection (3), sepsis (3) or thrombosis (2) (Table 5). The one-year graft survival rate was 69% (95% confidence interval (CI): 52% to 80%) (Figure 1). The one-year patient survival rate was 91%. All patients returned to the Dutch Caribbean within 3 months. In this cohort two patients died. The 1-year graft survival of the matched Dutch residents group corrected for ethnic background was 93% and the 1-year patient survival of 94%.

DISCUSSION

Our study shows that a transatlantic programme affords patients with end stage renal failure a chance to be successfully transplanted. However, as compared to our centre 1-year graft survival of 93% corrected for the ethnic background of Dutch residents, the 1-year graft survival rate of 69% is rather low.

Table 4: Postoperative outcome

Postoperative outcome	
Postoperative complications (no.)	16 (39%)
Major complications	5 (12%)
Re-operation due to bleeding	2
Urosepsis	2
Peritonitis	1
Minor complications	11 (27%)
Urinary tract infection	2
Supraventricular tachycardia	2
Deep vein thrombosis	2
Lymphoceles	2
Pyelonephritis	1
Wound infection	1
Pneumonia	1
Delayed graft function (no.)	9 (22%)
Acute rejection (no.)	11 (27%)
Urological complication (no.)	5 (12%)
1-week postoperative serum creatinine (µmol/L) [median (range)]	317.0 (63-1116)
1-month postoperative serum creatinine (µmol/L) [median (range)]	145.5 (61-750)
3-months postoperative serum creatinine (µmol/L) [median range)]	136.5 (97-500)
1-year graft survival (95% confidence interval)	69% (52-80)

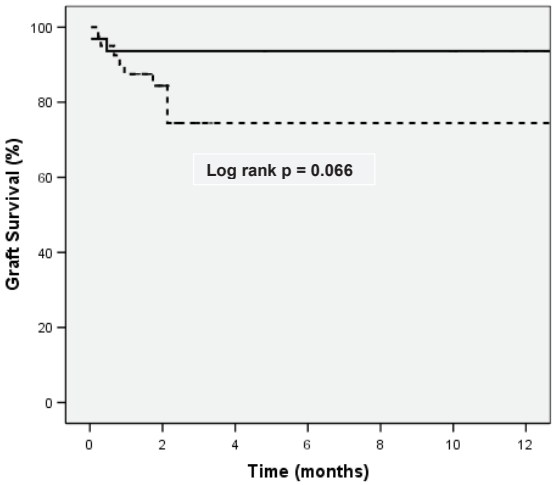
Table 5: Characteristics of the kidney graft losses

patient	original disease	years on dialysis	HLA mismatch	PRA %	CIT	direct postoperative function	rejection	immune suppression	Cause
1	unknown aetiology	9	2-2-1	0	1.810	yes	no	0	thrombosis
2	hypertension	6	2-2-1	0	2.850	no	yes	0	rejection
3	hypertension	7	1-1-1	0	1.440	yes	yes	0	rejection
4	hypertension	20	2-2-2	0	1.920	yes	no	0	sepsis
5	unknown aetiology	9	1-1-1	23	1.440	yes	no	1	sepsis
6	hypertension	5	1-2-1	0	2.837	no	yes	1	rejection
7	hypoplastic kidney	9	1-2-1	0	1.954	yes	no	1	thrombosis
8	reflux nephropathy	7	1-2-0	0	2.040	yes	no	1	urosepsis

immune suppression 0 = prednisone, a calcineurin inhibitor and mycophenolate mofetil
immune suppression 1 = prednisone, a calcineurin inhibitor, mycophenolate mofetil and basiliximab
CIT = cold ischemia time in minutes

Kidney transplantation is considered to be the optimal treatment for ESRD; compared with long-term dialysis, it confers a better quality of life, a longer life expectancy and lower costs[10-13]. However, previous research mainly from the United States, has demonstrated the

Figure 1. Renal graft survival at one year. The dashed line represents the transatlantic group and the other line represents the reference group.



No. at risk							
Transatlantic group	34	14	4	3	3	3	2
Reference group	32	29	28	27	26	23	18

presence of significant barriers to access to transplantation services for racial minorities, women, and patients with low socioeconomic status or inadequate insurance[14-17]. The factors contributing to this disparity in access to renal transplantation, include perceived differences in patient preferences, differential rates and timing of referrals, variation in the rates and timeliness of the completion of transplant evaluations, and organ allocation policies favoring highly matched donors and recipients[18-22]. Another explanation for disparity in access to renal transplantation is remote living location[23,24].

Several factors might explain our 1-year graft survival rate. First, mean cold ischemia time was rather long. Prolonged CIT (>24 hours) is a strong risk factor for DGF and graft loss[25,26] and adversely affects graft survival[27-31]. Additionally, DGF and acute rejections episodes are also significant determinants of short- and late graft survival[25]. The median CIT of 31 hours (range 16 – 48 hours) in our study is mainly a result of the travelling distance between both places. A longer distance travelled by the kidneys increases the risk of long term graft loss[31]. However this factor cannot easily be changed. Secondly, when the transatlantic airlift was started, the first recipients were those on haemodialysis for a long time (mean 6.8 years). Prolonged dialysis is a risk factor for allograft loss due to cardiovascular and infectious complications. Indeed, mean dialysis time in the group with an unsuccessful transplantation was 8.9 years. Thirdly, our group of transatlantic patients experienced a relatively high incidence of rejections and these rejections were relatively frequent steroid resistant.

In order to improve the results in this particular patient group, we decided to accept only heart beating donor kidneys, since for non-heart beating donor kidneys rapid implantation

is even more important. We try to speed up the logistical and pre-operative preparations even more to diminish cold ischemia time. We adjusted the immunosuppressive protocol and all new patients will be treated with basiliximab and with tacrolimus, cellcept en prednisolone. Fourthly, we decided to accept only kidney donors with at least one HLA-DR match. Even with the present use of very effective immunosuppressive therapy fully HLA matched kidney grafts are still superior in graft survival, showing the lowest graft survival in six HLA mismatched patients[32]. Of two major classes of major histocompatibility complex (MHC) antigens, class II antigens (HLA-DR) matching is the most important resulting in a significant improvement in graft outcome[33,34]. And we renewed our pretransplant screening protocol, trying to avoid risk factors for graft failure, such as an elevated PTH and obesity.

In conclusion, our transatlantic programme affords patients with end stage renal failure, who otherwise would need lifelong dialysis, a chance to be transplanted. Taking the circumstances into consideration graft survival is acceptable.

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