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Studies on Eleven Kidney Transplants from Non-Heart-Beating Donors

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ABSTRACT

This study was performed to analyze postoperative courses and complications, retrospectively, following transplants from non-heart-beating donors and to examine the correlation between early graft function and clinical parameters. We experienced 11 cases of kidney transplants from non-heart-beating donors during the period from April 1995 to May 2003. Warm ischemic time was less than 30 min in all cases, and total ischemic time ranged from 8.4 hours to 27.9 hours. Rejection reactions occurred in seven cases, two of which were vascular rejections. Infectious disease complications included CMV in two cases, interstitial pneumonia in one case and fungal infection in one case. One patient died from interstitial pneumonia, and three patients had to be restarted on dialysis due to loss of function of the grafted kidney. The remaining seven patients all made full recoveries. All of the 16 patients who underwent living related kidney transplantations during the same period made full recoveries. Both the donor's gender and the latest creatinine level of the donor influenced the posttransplant dialysis period. The posttransplant dialysis period significantly influenced the creatinine level one month after transplant. These results suggest that patients who undergo kidney transplants from non-heart-beating donors have higher rates of complications than patients who undergo living related kidney transplantation. It is important that, in cases where the donor's creatinine level is high, especially when the donor is male, the kidney is carefully retrieved and transported to the recipient hospital to shorten the ischemic period as much as possible.

Key words: *Renal transplantation, Non-heart-beating donors, Early graft function*

As the shortage of donor kidneys is a big problem not only Japan but also worldwide, it is important to prolong graft survival in every kidney transplant from non-heart-beating donors. Graft survival is affected by multiple factors such as ischemic time and donor age, and these factors interact in a complex manner. Delayed graft function is well recognized to affect graft survival[6,11-13)]. In this study, we retrospectively analyzed postoperative courses and complications that occurred following kidney transplants from non-heart-beating donors and studied the effects of clinical parameters on early graft function.

SUBJECTS AND METHODS

From September 1971 to May 2003, we experienced 178 cases of kidney transplantation, consisting of 145 cases of living related renal transplants and 33 cases of kidney transplants from non-heart-beating donors; 135 were male and 43 female. The median age at transplant was 33.0 years old. In kidney transplants from non-heart-beating donors, 11 cases were performed in our hospital during the period from April 1995 to May 2003. These recipients were decided by the Japan Organ Transplant Network according to the recipient selection criteria[15)]. We carried out comparative analysis of HLA matching, immunosuppressive agents used, occurrence of acute rejection, development of infectious disease and outcome in each of the 11 cases of kidney transplants from non-heart-beating donors. The correlation between early graft function (posttransplant dialysis period and creatinine level one month after transplantation) and clinical parameters was analyzed by stepwise multiple regression analysis, with $F \geqq 4.0$ indicating a significant correlation. Analyses were performed with Stat View 5 software (Abacus

Table 1. Renal transplant recipients from non-heart-beating donors

Case	Age	Gender	Primary disease	HLA mismatching (DR locus-A and B locus)	Total ischemic periods (hours)	Post transplant dialysis periods (days)	Immunosuppressant	Rejection	Infection	Outcome
1	43	female	CRF	0–4	14.5	0	CY, MF, AZ, S, ALG	no	CMV	full recovery
2	46	male	CRF	0–2	14.9	2	CY, MZ, S, ALG	no	no	full recovery
3	60	male	CGN	0–1	11.9	3	CY, AZ, S, ALG	AR (1)	interstitial pneumonia	died of interstitial 32 months after the operation
4	47	male	CRF	0–3	18.7	6	CY, MF, S, ALG	AR (1)	no	full recovery
5	46	male	naphrotic syndrome	0–4	20.6	34	CY, AZ, CP, S, ALG	VR (1)	no	graftectomy one month after the operation
6	53	male	CGN	1–2	14.1	4	CY, MZ, S, ALG	no	no	full recovery
7	58	male	DM	0–2	16.1	7	CY, MZ, AZ, S, ALG	AR (3)	fungal infection	hemodialysis due to chronic rejection 18 months after the operation
8	42	male	CGN	1–1	10.7	3	CY (FK), AZ (MF), S, ALG	AR (4)	no	hemodialysis due to chronic rejection 22 months after the operation
9	59	male	CGN	0–2	8.4	0	CY, AZ, S, ALG	no	no	full recovery
10	45	male	CGN	1–1	27.9	5	CY, MF, S, ALG	AR (1)	no	full recovery
11	44	male	CGN	1–3	16.4	12	CY, MF, S, ALG	VR (1)	CMV	full recovery

CY; cyclosporine A, MF; mycofenolate mofetil, AZ; azathioprine, ALG; anti-lymphocyte globulin, S; steroid, CP; cyclophosphamide, FK; FK506 (tacrolimus), MZ; mizoribine, AR; acute rejection, VR; vascular rejection

Concepts, Inc., CA).

RESULTS

We experienced 11 cases of kidney transplants from non-heart-beating donors (10 males and 1 female,aged 42 to 60 years) during the period from April 1995 to May 2003 (Table 1). The underlying diseases in the patients were chronic glomerulonephritis in six patients, nephrotic syndrome in one patient, diabetes mellitus in one patient and chronic renal failure in three patients. As for HLA matching, one of the DR antigens was mismatched in 4 patients, but both DR antigens were matched in the other 7 patients. Warm ischemic time was less than 30 min (mean: 7.36 min) in all cases, and total ischemic time ranged from 8.4 hours to 27.9 hours (mean: 15.8 hours). Cases 5, 6 and 8 underwent re-transplantations.

The immunosuppressants used were mainly cyclosporin A as well as mycofenolate mofetil, azathioprine or mizoribine, steroid and ALG. Cyclophosphamide was used in case 5 because this case was positive in warm B-lymphocyte cross match. Rejection reactions occurred in seven cases, two of which were vascular rejections. Treatments with steroid pulse therapy and plasma exchange were performed. Infectious disease complications included CMV in two cases, interstitial pneumonia in one case and fungal infection in one case. The outcomes were as follows. One patient died from interstitial pneumonia, and three patients had to be restarted on dialysis due to loss of function of the grafted kidney. The creatinine level in case 7, due to the high creatinine level in the donor (2.7 mg/dl), gradually rose after a temporary decline to 2.5 mg/dl, and a diagnosis of chronic rejection was made. Since transplantation of the contralateral kidney in another hospital showed a primary graft nonfunction, it was

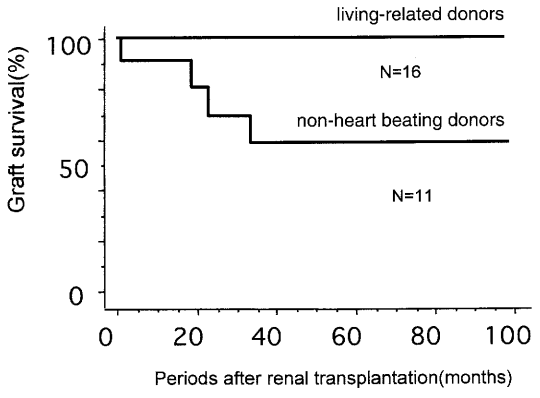

Fig. 1. Graft survivals in transplants from living-related donors and those from non-heart beating donors.

Table 2. Non-heart-beating donors for renal transplantation

Case	Age	Gender	Cause of brain death of non-heart beating donor	Latest creatinine level (mg/dl)
1	60	male	cerebro-vascular accident	1.1
2	48	female	head trauma	1.2
3	61	male	subarachinoidal bleeding	1.2
4	21	male	head trauma	1.2
5	55	male	cerebral infarction	3.5
6	28	male	epilepsy	0.9
7	43	female	subarachinoidal bleeding	2.7
8	35	male	subarachinoidal bleeding	0.8
9	41	female	cerebral infarction	0.5
10	59	male	meningitis	1.2
11	56	female	subarachinoidal bleeding	3.3

Table 3. Correlation between early graft function and clinical parameters

	Correlation coefficient	F value
Age	—	1.289
Gender	—	1.201
Diabetes mellitus	—	0.367
Number of rejections	—	2.355
DR mismatching	—	0.009
Ischemic periods	—	0.175
Donor's age	—	0.293
Donor's gender	6.86	4.201
Donor's creatinine	8.22	s26.345

thought that ischemic renal function disorder might be the main cause of the loss of function of the grafted kidney. The remaining seven patients all made full recoveries. All of the 16 patients who underwent living related kidney transplantations in our hospital during the same period made full recoveries (Fig. 1). The graft survival rates of these 11 cases of kidney transplants from non-heart-beating donors at 1, 3 and 5 years were 92%, 58.5% and 58.5%, respectively (Fig. 1).

Table 2 shows the backgrounds of donors used for the kidney transplants from non-heart-beating donors. The donors included seven males and four females with ages ranging from 21 to 61 years (mean age: 44 years). Five donors were older than 55 years old. The primary diseases in the donors were all cerebral disease, with cerebro-vascular lesions present in more than half of the donors. Cases 5, 7 and 11 showed relatively high creatinine levels.

Table 3 shows the correlation between post-transplant dialysis period and clinical parameters. Both the donor's gender and the latest creatinine level of the donor influenced the posttransplant dialysis period. Other factors such as the recipient's gender, age, the number of mismatched HLA-DR antigens, total ischemic time and donor's age did not influence the posttransplant dialysis period. The posttransplant dialysis period significantly influenced the creatinine level one month after transplant. However, the other clinical parameters did not influence the creatinine level one month after transplant.

DISCUSSION

Organ shortage has become a more critical problem for transplant therapy and this makes prolongation of graft survival even more important. The great reduction in the graft survival rate during the first year of transplantation observed in the period 1971 to 1985 suggests poor control of acute rejection when conventional immunosuppression was used (Fig. 2). Recent progress in immunosuppression, mainly by the introduction of calcineurin inhibitors, improved graft survival by reducing the incidence of acute rejection[4-6]. Acute rejection is one of the major factors for later graft loss and chronic rejection[7,8]. Our data also showed a marked improvement of graft survival by calcineurin inhibitor immunosuppression after renal transplantation (Fig. 2).

The effect of donor age on early graft function has been well documented in a large series[8-10]. Although a young donor is preferable for long-term graft survival, donor age is not a significant

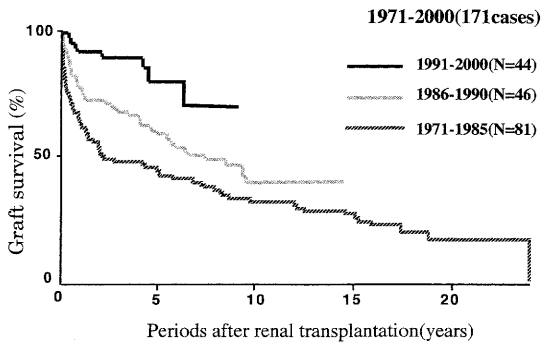

Fig. 2. Changes in graft survivals in renal transplantation.
Striped line represents graft survival during the period 1971 to 1985 (classical immuno-suppression). Gray line shows graft survival during the period 1986 to 1990 (introduction of cyclosporine A). Black line shows graft survival during the period 1991 to 2000 (introduction of FK 506 and mycofenolate mofetil).

factor in hesitating to perform kidney transplants from non-heart-beating donors. In our study, donor age was not a significant factor contributing to early graft function. However, Mizutani et al[9] reported that graft survival decreased with the increase in donor age, when donor age was above 55 years old. A similar line of evidence was also reported by others[12]. These reports including ours may suggest that elderly donors have the potential to become marginal donors.

Ischemic time is also an important factor contributing to early graft function. Longer ischemic time leads to lowered graft survival[1,13]. Delayed graft function is also widely recognized to affect graft survival[1-4]. In our study, a longer period of ischemic time tends to affect early graft function, but the differences are not significant. It has been reported that results of multicomponent analysis of short-term kidney functions in patients that received kidney transplants from 759 heart-arrested donors showed significantly better kidney functions at 3, 6, 12 and 24 months postoperatively in cases in which the total ischemic time was less than 12 hours than in cases in which total ischemic time was 12 hours or longer[14]. Yoshida et al[16] reported that a combination of delayed graft function and acute rejection apparently resulted in short-term graft survival, and this effect continued over the long-term. These data suggest that early function is critical to the success of renal transplantation.

In our study, the latest creatinine value of the donor and the donor gender (male) were significant factors contributing to early graft function. It is difficult to explain the reason why donor gender significantly influenced early graft function. Teraoka et al[14] reported that these are not influential factors on early graft function. Further clinical studies are necessary to clarify these points. It is important that in cases where the donor's creatinine level is high and especially where the donor is male, the kidney is carefully retrieved and transported to the recipient hospital to shorten the ischemic period as much as possible.

In conclusion, patients who have undergone kidney transplants from non-heart-beating donors have higher rates of complications than do patients who have undergone living related kidney transplantation. Moreover, there is a need to establish effective methods for prevention and early treatment of infectious diseases, appropriate methods for management of marginal donors and effective immunosuppressive therapy, especially for re-transplantation cases in order to improve the outcome of kidney transplants from non-heart-beating donors.

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