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ORIGINAL ARTICLE

KIDNEY TRANSPLANTATION AT HIROSAKI KIDNEY TRANSPLANT UNIT -INITIAL 5-YEAR EXPERIENCE

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Abstract **Introduction** Kidney transplantation has been widely accepted as a definitive therapy for patients with renal failure. The Hirosaki Kidney Transplant Unit was organized in June 2006 in conjunction with the Departments of Urology, Cardiology, Respiratory Medicine and Nephrology, and Gastrointestinal Surgery, from the Hirosaki University School of Medicine. Herein, we introduce our current results and discuss our future strategies.
Patients and Methods From June 2006 to December 2011, 36 kidney transplants were performed with 31 living donors and 5 deceased donors. Immunosuppression therapy included an inductor treatment of anti-CD25 antibody and triple therapy with calcineurin inhibitor, mycophenolate mofetil, and steroids. **Results** Recipients included 25 males and 11 females. The patients' average age was 41.8 years. Nine living–pairs were ABO incompatible. Deceased donors were performed at Oyokyo Hospital. Median follow-up period was 27.6 months. Acute cellular rejection occurred in 8.3% of patients. Positive antigenemia for cytomegalovirus happened in 16.7% of patients, but none developed invasive diseases. All recipients are currently surviving. Graft survival rates at 1, 3, and 5 years are 100%, 94.7%, and 94.7%, respectively. **Conclusion** Successful kidney transplantations have been performed by a multidisciplinary unit at Hirosaki University. Our next step is a promotion to increase organ donation.

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Key words: kidney transplantation; transplant unit.

原　著

弘前大学移植ユニットにおける腎移植—初期５年の経験

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抄録　【緒言】腎移植は慢性腎不全に対する最終的な治療である．2006年に弘前大学泌尿器科，循環器・呼吸器・腎臓内科，および消化器外科による弘前腎移植ユニットが設立され腎移植が開始された．これまでの成績と将来の展望について述べる．【対象と方法】2006年６月からの生体腎31例，献腎５例を対象とした．免疫抑制剤は抗CD25抗体を用いた導入による３剤併用にて行った．【結果】男性25人，女性11人で平均年齢は41.8歳であった．９症例が血液型不適合移植で，献腎移植は鷹揚郷病院で行った．平均観察期間は27.6ヶ月．急性拒絶反応は8.3％で生じた．サイトメガロウイルス血症は16.7％に見られたが侵襲性病変には至らなかった．全症例が生存中で１，３，５年グラフト生着率はそれぞれ100％，94.7％，94.7％であった．

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Introduction

Kidney transplantation has been widely accepted as a definitive therapy for patients with renal failure. The number of hemodialysis patients in Japan has been continuously increasing and had reached almost 300,000 by the end of 2010 (http://www.jsdt.or.jp/index_e.html). Even though the necessity of kidney transplantation has increased, no kidney transplantation surgery was performed throughout 2004 in the Aomori Prefecture, Japan, mainly because of lack of manpower[1]. The Hirosaki Kidney Transplant Unit (HKTU) was organized in June 2006 to perform renal transplantations in conjunction with the Departments of Urology, Cardiology, Respiratory Medicine and Nephrology, and Gastrointestinal Surgery from the Hirosaki University School of Medicine, Hirosaki City, Aomori Prefecture, Japan. Herein, we introduce our current results and discuss our future strategies.

Patients and Methods

From June 2006 to December 2011, 36 kidney transplants were performed with organs from 31 living donors and 5 deceased donors. All living donor renal transplantations (LDRTs) were performed at the Hirosaki University Hospital and all deceased donor renal transplantations (DDRTs) were performed at the Oyokyo Kidney Research Institute, Hirosaki Hospital. Immunosuppression therapy included an inductor treatment using anti-CD25 antibody (Basiliximab) and a triple therapy of calcineurin inhibitor, mycophenolate mofetil (MMF), and steroids. All statistical analyses were calculated using SPSS software. A p-value <0.05 was considered statistically significant.

Results

Patient demographics are provided in Table 1. Organ recipients included 25 males and 11 females with an average age of 43.1 years. LDRT patients were slightly younger than those receiving DDRTs (41.8 years vs. 51.6 years) (n.s.). Nine living–pairs were ABO incompatible (29.0%). The median follow-up period was 27.6 months. Etiologies of renal failure included chronic glomerulonephritis in 10 patients, IgA nephropathy in 8, diabetic nephropathy in 4, and hypoplastic kidney in 2 patients. Five patients underwent peritoneal dialysis. Pre-emptive transplants were performed in 5 patients. Relation between donor and LDRT patients were as follows: the mother in 8, the father in 7, a sibling in 6, and a spouse in 8. The median human leukocyte antigen mismatch was 3. The average dialysis period lasted 28.0 months in LDRT patients and 196.4 months in DDRT patients ($p < 0.05$). The average operation time was 248 min. The average estimated blood loss was 246 ml. The total ischemic time was 81 min in LDRT patients and 537 min in DDRT patients ($p < 0.05$). Postoperative complications are described in Table 2. Four patients required surgical interventions, of which all are fully recovering. Biopsies revealed acute cellular rejection had occurred in 8.3% of patients, but all responded to anti-rejection therapy. Positive antigenemia for cytomegalovirus was detected in 16.7% of patients, but none developed an invasive disease. All recipients are currently surviving. One graft was lost due to chronic rejection in a patient who suffered colonic ulcers possibly due to MMF and was converted to azathioprine therapy. Graft survival rates at 1, 3, and 5 years were 100%, 94.7%, and 94.7%, respectively.

Table 1 Summary of kidney transplant recipients

	Age	Sex	Etiology	Dialysis period (months)	type of dialysis	Relation	Donor age	ABO blood type compatiblity	HLA mismatch	operative time (min)	blood loss (ml)	total ischemic time (min)
LDRT#1	39	Male	DMN	3	HD	sister	41	identical	2	226	50	60
LDRT#2	33	Male	IgA nephropathy	4	HD	mother	59	identical	2	256	660	76
LDRT#3	54	Male	CGN	0	preemptive	sister	57	identical	2	280	370	49
LDRT#4	45	Male	CGN	125	HD	mother	68	identical	0	198	175	48
LDRT#5	44	Male	DMN	2	HD	mother	70	identical	2	239	50	90
LDRT#6	35	Male	IgA nephropathy	24	CAPD/HD	mother	53	identical	2	278	558	68
LDRT#7	23	Male	Hypoplastic kidney	24	HD	brother	25	identical	0	227	70	62
LDRT#8	18	Female	IgA nephropathy	7	CAPD	father	44	identical	3	343	200	98
LDRT#9	32	Male	CGN	9	HD	father	54	incompatible	3	240	390	115
LDRT#10	40	Female	IgA nephropathy	0	preemptive	father	75	identical	1	243	150	85
LDRT#11	19	Male	Hypoplastic kidney	4	HD	grandfather	71	identical	5	327	370	73
LDRT#12	24	Male	CGN	31	HD	mother	44	incompatible	3	229	100	73
LDRT#13	37	Male	CGN	47	HD	father	60	identical	2	225	100	82
LDRT#14	46	Male	Hypertension	18	CAPD	sister	43	identical	0	250	250	82
LDRT#15	36	Female	ANCA associated nephropathy	4	HD	mother	60	incompatible	3	258	120	67
LDRT#16	71	Male	IgA nephropathy	2	HD	son	35	compatible	3	198	120	91
LDRT#17	64	Male	polycystic kidney	0	preemptive	wife	62	incompatible	4	189	390	77
LDRT#18	25	Male	FGS	2	HD	mother	56	compatible	3	207	280	81
LDRT#19	43	Female	SLE	3	HD	father	76	identical	3	190	120	75
LDRT#20	63	Female	CGN	22	CAPD	sister	65	identical	3	305	211	74
LDRT#21	54	Female	CGN	139	HD	sister	52	compatible	1	233	100	77
LDRT#22	37	Male	IgA nephropathy	8	HD	father	61	incompatible	2	219	390	88
LDRT#23	65	Male	CGN	30	HD	wife	64	identical	5	224	150	72
LDRT#24	28	Male	DMN	0	preemptive	mother	50	identical	2	343	630	168
LDRT#25	43	Female	unkonwn	26	HD	husband	49	identical	0	240	130	91
LDRT#26	19	Male	Alport syndrome	5	HD	father	43	identical	1	284	230	92
LDRT#27	41	Male	unkonwn	0	preemptive	wife	43	incompatible	3	252	300	72
LDRT#28	51	Female	pregnancy	245	HD	husband	51	incompatible	3	307	1150	71
LDRT#29	56	Female	unkonwn	46	HD,PD	husband	53	incompatible	4	226	200	65
LDRT#30	46	Male	unkonwn	10	HD	wife	49	incompatible	6	237	250	61
LDRT#31	64	Male	DMN	29	HD	wife	61	identical	5	161	50	53
DDRT#1	50	Female	IgA nephropathy	233	HD	brain dead donor	50's	identical	3	218	142	321
DDRT#2	62	Female	membrenous nephropathy	201	HD	DCD	50's	identical	2	197	316	734
DDRT#3	55	Male	CGN	228	HD	brain dead donor	50's	identical	3	243	209	558
DDRT#4	33	Male	CGN	170	HD	brain dead donor	60's	identical	4	173	86	278
DDRT#5	58	Male	IgA nephropathy	150	HD	brain dead donor	60's	identical	4	267	364	364

* LDRT: living donor renal transplant, DDRT: deceased donor renal transplant, HLA: human leukocyte antigen, CGN: chronic glomerulonephritis, DMN: diabetic nephropathy, ANCA: anti-neutrophil cytoplasmic antibody, FGS, focal glomerular sclerosis, SLE: systemic lupus erythematosus, HD: hemodyalysis, CAPD: continuous ambulatory peritoneal dialysis, DCD: donor after cardiac death

Table 2 Postoperative complications

Complications	Treatment	Prognosis
hemorrhage after percutaneous kidney biopsy	exploratory hemostasis	full recovery
lymphocele	course observation	full recovery
urinary leakage	endoscopic ureteral stent placement	full recovery
pneumocystis pneumonia	antibiotics	full recovery
colonic ulceration due to MMF	conversion to Azathiopurine	graft failure due to chronic rejection
repeat urinaly infection	antibiotics	full recovery
convulsion due to FK506	conversion to CSA	full recovery
wound dehescience	wound closure	full recovery
VUR	temporary bladder drainage	full recovery

MMF: mycophenolate mofetil, FK506: tacrolimus, CSA: cyclosporin, VUR: vesicoureteral reflux

Discussion

The necessity of renal transplantation has been rising because of a continuous increase in the number of patients suffering from chronic renal failure which lead to huge medical expenses. Renal transplantation in Aomori Prefecture had been performed in a few medical centers, but was stopped in 2004 mainly because of lack of manpower[1]. A scarcity of medical personnel was problematic at the Hirosaki University, until the HKTU was organized in June 2006 with staff from the Departments of Urology, Cardiology, Respiratory Medicine and Nephrology, and Gastrointestinal Surgery from the Hirosaki University School of Medicine. Since most of the HKTU staff had little experience in kidney transplantation, observational education in kidney transplant services was offered multiple times. The University of California, San Francisco Medical Center (UCSF) was selected as an observatory institute, as transplant services were performed using a similar system, and more than 300 renal transplants per year were performed. Observation at UCSF enabled our staff to better understand kidney transplant procedures.

In the HKTU system, preoperative examinations and workups, as well as preconditioning for ABO-incompatible transplants, were performed by the Department of Cardiology, Respiratory Medicine and Nephrology. Perioperative care was the responsibility of urologists and surgeons. Patients were transferred to the nephrology ward 2 weeks post-transplant and follow-up care was provided by nephrologists. During this time, 31 LDRT were successfully performed. Most awaiting DDRT were patients of Oyokyo Hospital, where manpower was a major concern. Therefore, we formulated a solution in which a transplant team traveled to Oyokyo Hospital to perform transplant surgeries when a deceased kidney was available for a patient. Following the procedure, the local staff provided postoperative care, since the two hospitals are located within a relatively short distance. Hence, this system has alleviated the lack of manpower in each department. Five LDRT were successfully performed so far.

The incompatibility of ABO blood-typing presents a significant barrier to transplantation. Japanese transplant surgeons have contributed much to the current knowledge in this subject[2,3]. Hyperacute antibody-mediated humoral rejection occurs in incompatible ABO blood type transplantations, thereby requiring preoperative management. In 2008, an ABO incompatible transplant was performed using

preoperative rituximab, MMF, and plasma exchange. Preconditioning was performed for 3 weeks prior to transplantation surgery. Till date, there have been no severe adverse effects reported with this current regimen. ABO incompatible transplants at HKTU occurred in 29.0% of LLRT patients. The Japanese transplant registry reported 273 cases in 1041 LDRT patients (26.2%) performed in 2009[4]. All transplant patients are currently recuperating well at HKTU. These results are encouraging and should promote living donor transplantation.

The period of dialysis lasted approximately 28 months in LDRT patients and 200 months in DDRTs. The average waiting time in the Japanese Organ Transplant Network is reported to be an average of 3.8 years (45.6 months) for LRDTs and 17.1 years (205.2 months) for DDRTs. Our DDRT recipient seemed to wait shorter even we have limited local donors[1]. Pre-emptive transplants were performed in 5 LDRT patients (16.1%) and 17.2% from the Japanese registry[4]. Efficacy of preemptive transplants has been reported from multiple institutions[5-7]. In pre-emptive transplants, graft and patient survival rates were superior, complication rates were low and cost effectiveness was apparent. The advantages of pre-emptive renal transplant should be widely disseminated.

Operative data, including ischemic time and blood loss, were satisfactory. Extended ischemic time was reported as a significant risk factor for graft survival[8-10]. The average total ischemic time was approximately 80 min for LDRT patients and 537 min for DDRTs. This is shorter than indicated by the Japanese registry data (722 min for DDRTs)[4]. Urination in all LDRT patients was achieved in the operative field with average time of 5 min. At HKTU, coordination with the donor team seemed flawless.

Surgical complications included many components. Vascular complications, especially arterial anastomosis, were the most critical. The incidence rate had been reported to be approximately 10%, but is currently less than 5%. End-to-side anastomosis, which we use as a standard procedure, has greatly contributed to this progress[11]. In only 1 recipient, whose external iliac artery was very narrow and had 2 arteries in the allograft, end-to-end anastomoses with the internal iliac arterial branches were performed and provided sufficient flow. Till date, we have not encountered vascular complications.

Urinary leakage occurs in 1−8% of patients[3, 12]. One recipient, with an unusually thick bladder and anuric period of longer than 10 years experienced urinary leakage that required transurethral stenting. After this experience, we decided to continue using a Foley's catheter for 2 weeks in patients with an extended anuric period or thick bladder.

With improvements in immunosuppressive drug therapy, episodes of acute rejection have dramatically decreased, especially in the last 2 decades[13, 14]. After the introduction of MMF and induction therapy, short-term survival rates of allografts markedly improved. Therefore, we decided to incorporate both MMF and induction therapy with the anti-CD25 antibody to further decrease episodes of acute cellular rejection. In Japanese transplant centers, MMF is used in 92.0% of cases, whereas anti-CD25 antibody therapy is applied in 95.6% of LDRTs performed in 2009[4]. Biopsy-proven rejection was detected in 3 recipients (8.3%) in HKTU, which is very convincing.

Cytomegalovirus (CMV) infection is the single most frequent infectious complication in renal transplant recipients[15-17]. We encountered a 16.7% CMV antigenemia incidence rate, but none developed an invasive disease. The combination of CMV positive donors to negative recipients (CMV P-N) has been reported to be a major risk for acute rejection[18]. In our series, 3 donor/recipient pairs were CMV P-N and

all developed positive antigenemia, even with valganciclovir prophylaxis. However, only 1 patient developed acute cellular rejection. CMV P-N recipients should be carefully monitored and treatment for CMV initiated.

Polyomavirus type BK (BKV)-associated nephropathy has emerged as a cause of allograft failure linked to immunosuppressive regimens containing tacrolimus or MMF[19, 20]. In our series, 3 recipients were found to be BKV-positive; 2 of who had suffered episodes of acute therapy rejection. The patients' serum creatinine levels were elevated and their immunosuppressive dosage were reduced. Fortunately, none lost graft function. The possibility of BKV infection should not be ignored and PCR-monitoring should be performed, as described previously[3, 21].

It is regrettable that 1 patient returned to hemodialysis (twice per week) due to chronic rejection 27 months after transplantation surgery. Severe diarrhea developed in this patient; however, a full work-up was unable to identify its etiology. Hence, a diagnosis of erosive enterocolitis associated with MMF was made[22, 23]. We reduced immunosuppression therapy, which consequently led to graft dysfunction. Current graft survival rates at 1, 3, and 5 years are 100%, 94.7%, and 94.7%, respectively, which is in agreement with data from the Japanese national registry (97.0%, 94.2%, and 90.7%)[24]. Currently, the patient survival rate is 100%, and we hope to maintain these results.

Till date, the transplantation regimen at the HKTU is functioning very well. This system not only replenishes the lack of manpower, but also improves diagnostic and therapeutic quality with multidisciplinary medical specialties. Satisfactory results should be maintained and will allow for better public understanding of the transplantation process and foster future organ donations.

Conclusion

Successful kidney transplantations have been performed by the multidisciplinary HKTU. Our next step is a promotion to increase organ donations.

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