Ten-year experience of kidney transplantation at the Hospital of Kaunas University of Medicine: demography, complications, graft and patient survival

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***Key words**: kidney transplantation; complications; delayed graft function; survival; renal replacement therapy.*

***Summary.** During 10 years, 163 cadaveric kidney transplantations were performed at the Hospital of Kaunas University of Medicine. The aim of this study was to analyze the first 10-year experience in kidney transplantation and to evaluate the most frequent early and late complications after transplantation, graft and patient survival, and impact of delayed graft function on graft survival.*

Material and methods. A total of 159 patients were included into the study. Graft and patient survival was calculated at 1, 3, and 5 years after transplantation using the Kaplan-Meier method; graft function was also analyzed.

Results. Fifty-three patients (33.3%) in the early period and 72 (55.4%) in the late period had at least one episode of urinary tract infection. Less than half (47.2%) of patients had complications related to immunosuppressive treatment, mostly cytomegalovirus infection, in the late period. The risk of CMV reactivation was 3.98 times higher among recipients who received prophylaxis only with intravenous ganciclovir as compared to patients who received valganciclovir after a brief course of ganciclovir (OR, 3.98; 95% CI, 1.48–8.19; P=0.003).

Delayed graft function was observed in 53 cases (33.3%); 37 (23.3%) grafts were lost. Graft and patient survival at 1, 3, and 5 years after transplantation was 85%, 82%, and 71% and 97%, 94%, and 94%, respectively. Graft survival at 1, 3, and 5 years was worse among patients with delayed graft function as compared to patients with good graft function (69%, 69%, 50% vs. 93%, 86%, 84%, respectively; P<0.05).

Conclusions. Urinary tract infection was the most frequent complication after kidney transplantation. Reactivation of cytomegalovirus infection was present only in a quarter of our patients. The administration of valganciclovir was associated with a significantly lower incidence of CMV infection/disease. Graft and patient survival was sufficiently good. Delayed graft function was an independent risk factor for worse graft survival.

Introduction

The number of patients with end-stage renal disease is increasing every year. The most of them are on dialysis, but transplantation is the treatment of choice for many patients. Successful renal transplantation improves survival and quality of life and costs less than dialysis (1, 2).

Kidney transplantation in Lithuania was started in Vilnius in 1970. The first transplantation of cadaveric kidney at the Hospital of Kaunas University of Medicine was performed on May 4, 2000. During the next 10 years, 163 cadaver kidney transplantations were done in Kaunas.

Success of transplantation depends not only on surgery, but also on management and nursing of post-ransplant patients, and on the treatment of early and late complications after kidney transplantation. Immediate allograft function after kidney transplantation is very important. In kidney transplantation, the absence of immediate allograft function is known as delayed graft function (DGF) and is defined as the need for dialysis during the first week after transplantation. The frequency of DGF ranges from 5 to 50% in cadaveric donor kidney transplantations (3–5). DGF makes the

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management of patients more difficult, prolongs hospital stay, increases the costs of transplantation, has a negative impact on the rehabilitation of transplant recipients, and reduces graft survival rate (6, 7).

The aim of the present study was to analyze the results of kidney transplantations during the first 10 years after initiation of kidney transplantation program at the Hospital Kaunas University of Medicine and to evaluate the most frequent early and late complications after transplantation and impact of delayed graft function on survival of transplanted kidney.

Material and methods

We studied a population of 163 patients who had consecutively received a cadaveric kidney transplant at the Hospital of Kaunas University of Medicine between May 2000 and April 2010. Fig. 1 shows the dynamics of transplantation rate at the Hospital of Kaunas University of Medicine.

All the data concerning recipients were collected using a questionnaire and stored in a computerized database. Four patients were children (<16 years); they were excluded from analysis. Finally, 159 patients were involved into the study. The mean follow-up was 39.78±29.22 months (range, 0.33–118.8 months).

We analyzed posttransplant complications in the early period (postoperative period in the hospital after kidney transplantation) and late period (outpatient observation period). The patients who died or lost transplant or whose data were missing in the early postoperative period (n=29) were excluded from the analysis of late complications. According to graft function after transplantation, we divided patients into two groups: with immediate graft function and with delayed graft function (defined as the need for dialysis in the first week after transplantation). We studied the impact of DGF after transplantation on graft survival. Graft and patient survival was calculated at 1, 3, and 5 years after transplantation.

The presented data were expressed as mean±SD. Significance was assessed with the Student's *t* test for unpaired data. Patient and graft survival was calculated by the Kaplan-Meier method, and the log-rank test was employed to compare survival between groups. Comparison of nonparametric data was done by the χ test or Fisher's exact test. A *P* value of <0.05 was considered significant. All analyses were performed using the SPSS statistical software.

Results

Among 159 patients who underwent cadaveric kidney transplantation, 96 were males (60.4%) and 63 females (39.6%). The mean age of recipients at the time of transplantation was 43.21±12.31 years (range, 16–69 years). A total of 150 patients (94.3%) were transplanted for the first time, while 9 (5.7%) underwent their second transplantation. Chronic glomerulonephritis was the primary kidney disease of recipients in 72 patients (45.3%), diabetic nephropathy in 22 (13.8%), polycystic kidney disease in 21 (13.2%), hypertensive nephropathy in 15 (9.4%), chronic pyelonephritis in 10 (6.3%), and other diseases in 19 (11.9%) patients. The mean duration of chronic dialysis until kidney transplantation was 36.18±30.09 months. Nine (5.7%) patients were at high risk for CMV infection (R–/D+ serostatus), 140 (88%) patients at intermediate risk (R+/D+ and R+/D–), and 10 (6.3%) patients at low risk (R–/D–).

The mean HLA mismatch was 3.14±0.84 (range, 0–5). Two (1.3%) patients had 0 mismatch, 3 (1.9%) patients 1 mismatch, 22 (13.8%) patients 2 mismatches, 79 (49.7%) patients 3 mismatches, 50 (31.4%) patients 4 mismatches, 3 (1.9%) patients 5 mismatches. The standard immunosuppressive regimen consisted of cyclosporin, steroids, and mycophenolate mofetil or azathioprine triple therapy. One hundred fifty-one (95%) patients received mycophenolate mofetil and 8 (5%) patients received azathioprine. Induction

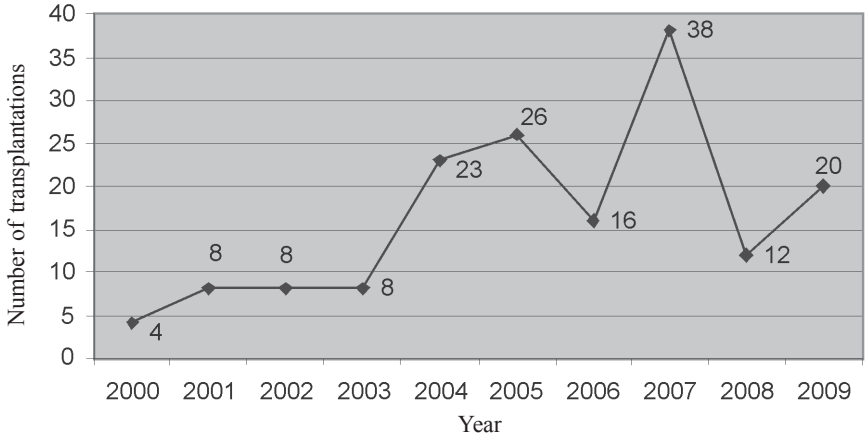

Fig. 1. Number of cadaveric kidney transplantations at the Hospital of Kaunas University of Medicine

therapy with monoclonal antibodies (daclizumab or basiliximab) was prescribed only for patients (71.7% of patients) at moderate and high immunological risk (due to ≥3 HLA mismatches and/or lymphocytotoxic antibodies ≥50 %).

In the early postoperative period, only 50 (31.4%) patients had no complications. The frequency of early and late complications is presented in Table 1. Fifty-three patients (33.3%) in the early and 72 (55.4%) in the late period had at least one episode of urinary tract infection. Urosepsis was diagnosed in 5% and 13.1% of patients in the early and late periods, respectively. Biopsy-proven acute rejection (Banff I–II) occurred in 12 (7.5%) and in 5 (3.8%) patients in the early and late periods, respectively. In the late period, 47.2% of patients had complications due to immunosuppressive treatment; most of them were cytomegalovirus (CMV) infections (n=31, 23.8%). CMV disease was diagnosed only in 4 (3.1%) patients. A total of 88 episodes of CMV infection/disease occurred in 35 patients: 14 patients had one episode of CMV infection, 15 patients had 2 episodes each, 6 patients had from 3 to 12 episodes each. As there was no valganciclovir in Lithuania until 2007, anti-CMV prophylaxis only with intravenous (IV) ganciclovir was prescribed during the period of hospitalization (28.7±11.5 days) in all cases, except the combination of D–/R– and when the transplant in the early period after transplantation had to be removed. Prophylactic therapy during outpatient period was not possible. In 2007, we adopted an antiviral prophylaxis regimen for renal transplant recipients using oral valganciclovir after a brief course of IV ganciclovir. In our study, 63 (51.2%) patients received CMV prophylaxis only with IV ganciclovir during the period of hospitalization, and 60 (48.8%) patients received oral valganciclovir after a brief course of IV ganciclovir for a total of 3 months. Reactivation of CMV was documented in 26 (41.3%) patients from the first group and 9 (15.0%) from the second group (Table 2). Kidney recipients who received only IV ganciclovir during the period of hospitalization and did not receive prophylaxis with valganciclovir later on were at 3.98 times higher risk of CMV reactivation than those who received valganciclovir (OR, 3.98; 95% CI, 1.48–8.19; *P*=0.003). No lethal outcomes of CMV disease developed.

Complications due to malignancies were as follows: 2 (1.5%) patients developed prostatic carcinoma and 3 (2.3%) patients developed skin basalioma.

The frequency of urological-surgical complications was as follows: lymphocele in 7.5% in the early and in 8.4% of patients in the late periods, urinary leak in 9.4% of patients in the early period, and ureteral stenosis in 7.7% of patients in the late period (3.1% required reanastomosis).

Table 1. Frequency of early and late complications after cadaver kidney transplantation

Complication	Early period	Late period
Lymphocele	7.5%	8.4%
Urinary leak	9.4%	–
Infectious complications:		
Wound	11.9%	–
Urinary tract	33.3%	55.4%
Urosepsis	5.7%	13.1%
Acute rejection	7.5%	3.8%
Complications due to immunosuppressive treatment:		
CMV infection	0.6%	23.8%
Myelosuppression	1.3%	4.6%
Polyoma virus	–	0.8%
Herpes virus	0.6%	2.3%
Malignancy:	–	6.9%
Prostate carcinoma	–	1.5%
Skin basalioma	–	2.3%
Others	–	3.1%
Aseptic osteonecrosis	–	3.1%
Myocardial infarction	3.1%	3.8%

Table 2. The rate of cytomegalovirus CMV reactivation depending on a prophylaxis regimen

Prophylaxis regimen	With CMV reactivation	Without CMV reactivation
IV ganciclovir	26 (41.3%)	37 (58.7%)
IV ganciclovir + oral valganciclovir	9 (15%)	51 (85%)

P=0.003.

During the follow-up of 39.78±29.22 months (median, 35.23 months; range, 0.33–118.8 months), 37 (23.3%) grafts were lost, more than half (n=24) of them during the first year after transplantation. Mortality of patients with a functioning graft during the first year after transplantation was 3.1% (3 patients) and was caused by ischemic stroke, septic shock, and myocardial infarction.

The causes of graft loss were chronic transplant nephropathy in 13 (8.2%) cases, graft infection in 10 (6.3%) cases, patient's death with a functioning graft in 8 (5%)cases, and acute rejection in 3 (1.9%) cases. Three (1.9%) grafts were lost due to other reasons.

The overall graft and patient survival at 1, 3, and 5 years after transplantation was 85%, 82%, and 71%, and 97%, 94%, and 94%, respectively (Figs. 2 and 3). DGF was observed in 53 cases (33.3%). Patients in both groups (with immediate or DGF) were similar

regarding gender and age. Graft survival at 1, 3, and 5 years was worse among patients with DGF in comparison to patients with immediate graft function (69%, 69%, 50% vs. 93%, 86%, 84%, respectively) (Fig. 4). DGF was an independent risk factor for worse graft survival (RR, 3.58; 95% CI, 1.85–6.92; $P<0.001$).

Discussion

Lithuania is a small country, so it is difficult to find a recipient of appropriate tissue compatibility for each procured cadaver donor kidney. National rationing of donor organs to achieve minimal mismatching and maximal matching could potentially decrease the average number of HLA mismatches from 3.6 to 1.2 (8). In our study, the mean HLA mismatch was 3.14. Held et al. reported a 84.3% adjusted one-year graft survival for grafts with no mismatches and 77% for grafts with 4 mismatches (8).

In our study, graft survival at 1, 3, and 5 years after transplantation was 85%, 82%, and 71%, respectively. Other studies reported 88–90%, 79%, and 68–76% graft survival at 1, 3, and 5 years after transplantation, respectively (9, 10). This comparison shows that graft survival was a little worse or similar. However, patient survival was better in our study than in other reports (97% vs. 95–96% at 1 year after transplantation; 94% vs. 88% at 3 years after transplantation; and 94% vs. 81–88% at 5 years after transplantation) (9, 10). Analyzing the impact of transplant kidney function on graft survival, we found that patients with DGF had a 3.58-fold higher relative risk for worse graft survival. Defined as the necessity for dialysis in the first postoperative week, DGF developed in 33.3% of patients in our study. Others reported DGF in 20–50% of patients receiving a first cadaveric graft (4, 5, 7). In some studies, DGF was an independent risk factor for allograft survival (7), the same as in our study. In the Hospital of Kaunas University of Medicine, transplantation program is on primary stage; therefore, our survival results are sufficiently good comparing with other reports.

Acute rejection is a very serious and important complication of a kidney transplant. Patients with a history of acute rejection episodes are more likely to have late allograft failure (11, 12). The reported frequency of acute rejection is less than 10–15% at the recent time due to improvements in immunosuppression (10, 13, 14). We observed a rather low rate of acute rejection in 7.5% and 3.8% of cases in the early late periods, respectively, that could be explained by use for induction therapy of monoclonal antibodies in moderate and highly sensitized patients.

Our study showed that infection, particularly of the

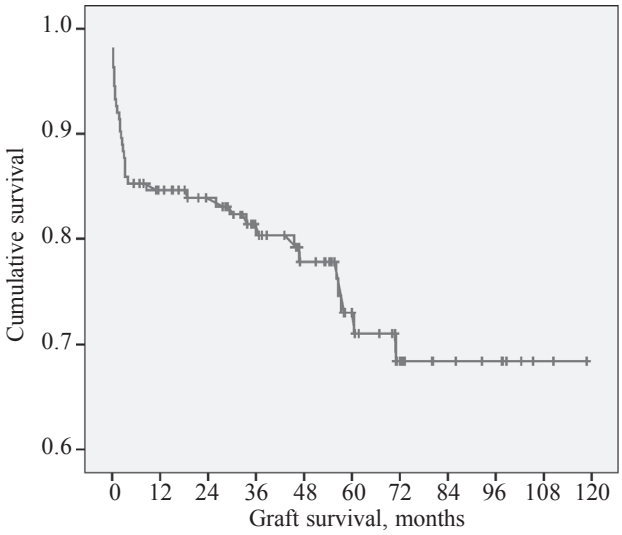

Fig. 2. Kaplan-Meier graft survival curves of kidney transplant recipients (n=159)

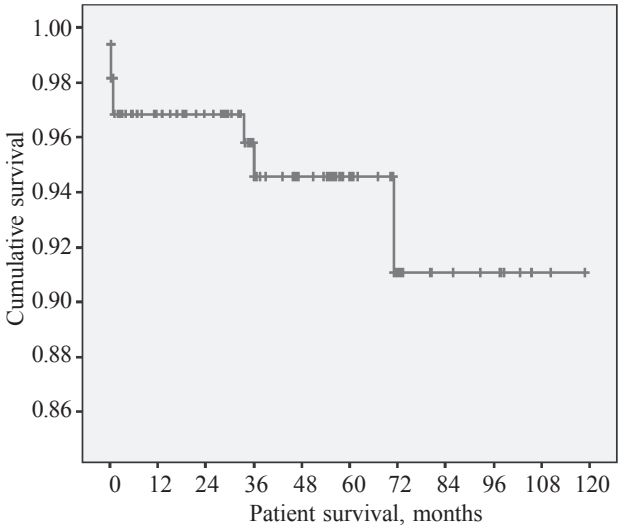

Fig. 3. Kaplan-Meier patient survival curves of kidney transplant recipients (n=159)

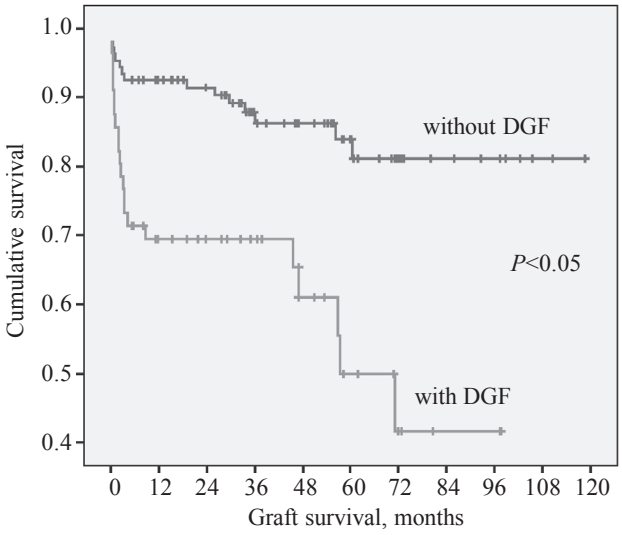

Fig. 4. Graft survival according to early posttransplant graft function (presence of DGF)

urinary tract, was the most frequent early and late complication. It occurred in 33.3% and 55.4% of patients in the early and late periods, respectively. Similar data were reported in others studies, with an incidence of urinary tract infection ranging from 35% to 79% (15–19). Viral infections mainly occurred in the late period. According to literature, one-third of patients in the late period suffer from viral complications, mostly from CMV infection (16–36%). Prophylaxis with antiviral medications reduces CMV disease- and CMV-associated mortality in solid organ transplant recipients, and it should be used routinely in CMV-positive recipients and in CMV-negative recipients of CMV-positive organ transplants (16, 18). In our study, CMV infection was observed in 23.8% of patients. Because of anticytomegalovirus prophylaxis after transplantation with IV ganciclovir until 2007 and 3-month anticytomegalovirus prophylaxis with valganciclovir from 2007, there were no CMV infection-related deaths, and CMV disease was very rare (3.1%).

It is known that due to immunosuppression treatment in the late period after kidney transplantation, the prevalence of neoplastic diseases in patients with transplanted kidneys is 4 to 5 times higher than in general population of similar age and gender (20). We observed new cases of oncologic diseases in 6.9% of patients, mostly cases of skin basalioma and prostatic carcinoma. Several studies have reported that the incidence of malignancies after renal transplantation ranges from 3 to 12% (21, 22).

Development of immunosuppressive therapy significantly improved early outcomes of kidney transplantation. However, improvement was not so great in long-term graft survival (23, 24). Chronic allograft nephropathy was reported as the main cause of late graft loss in other transplant centers (14, 25). Incidence of others causes varied. We also observed that chronic allograft nephropathy (proven by biopsy or clinic) was the main cause of late graft loss, documented in 8.2% of our patients.

Summarizing the 10-year experience, we can conclude that kidney transplantation program is going well as patient and graft survival and complication rate was sufficiently good or similar to others transplantation centers. Relative risk for worse graft function was higher in the group with DGF in our kidney transplant recipients. Urinary tract infection was the most frequent complication after kidney transplantation. In the late period, we observed an increase in the number of cases of viral complications, particularly CMV infection. Our report prompts us to continue the optimizing of the management of kidney transplant recipients.

Conclusions

1. Graft survival at 1, 3, and 5 years after cadaveric kidney transplantation was 85%, 82%, and 71% and patient survival was 97%, 94% and 94%.
2. Delayed graft function was an independent risk factor for worse graft survival, being present in 33.3% of patients.
3. Among complications after cadaveric kidney transplantation, urinary tract infection was most prevalent; acute rejection developed in a few cases.
4. Reactivation of cytomegalovirus infection was present only in a quarter of the patients.
5. The administration of valganciclovir was associated with a significantly lower incidence of cytomegalovirus infection reactivation as compared to prophylaxis only with ganciclovir.

Inkstų transplantacijų dešimties metų patirtis Kauno medicinos universiteto klinikose: demografiniai duomenys, komplikacijos, transplantato ir paciento išgyvenamumas

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Raktažodžiai: inksto transplantacija, komplikacijos, pavėluota transplantuoto inksto funkcija, išgyvenamumas, pakaitinė inkstų terapija.

Santrauka. Kauno medicinos universiteto klinikose per dešimt metų buvo transplantuoti 163 kadaveriniai inkstai. Šio *darbo tikslas* – išanalizuoti pirmųjų dešimties metų Kauno medicinos mniversiteto klinikose atliktų inksto transplantacijų rezultatus, įvertinti dažniausias ankstyvąsias ir vėlyvąsias potransplantacinio laikotarpio komplikacijas, paciento ir transplantuoto inksto išgyvenamumą bei nustatyti pavėluotos inksto funkcijos įtaką transplantuoto inksto išgyvenamumui.

Medžiaga ir metodai. 159 pacientai buvo įtraukti į šį tyrimą. Transplantato išgyvenamumas skaičiuotas po 1, 3 ir 5 metų po transplantacijos ir analizuotas atsižvelgiant į inksto funkciją.

Rezultatai. Bent vienas šlapimo takų infekcijos epizodas ankstyvajame potransplantaciniame periode buvo

nustatytas 53 recipientams (33,3 proc.), o vėlyvajame – 72 (55,4 proc.). Vėlyvajame potransplantaciniame periode 47,2 proc. pacientų pasireiškė imunosupresinio gydymo sąlygotos komplikacijos, dažniausiai citomegalo viruso infekcija. CMV reaktyvacijos rizika buvo 3,48 karto didesnė pacientų, gavusių profilaktiktinį gydymą tik stacionariniu laikotarpiu ir negavusių ambulatorinio gydymo valganciloviru (ŠS, 3,48; 95% PI, 1,48–8,19); p=0,003. Pavėluota inksto funkcija buvo stebima 53 pacientams (33,3 proc.). Stebėjimo laiku buvo prarasti 37 (23,3 proc.) transplantuoti inkstai. 1, 3 ir 5 metų inkstų išgyvenamumas po transplantacijos buvo atitinkamai 85 proc., 82 proc. ir 71 proc., o pacientų – 97 proc., 94 proc. ir 94 proc. Transplantato 1, 3 ir 5 metų išgyvenamumas buvo prastesnis grupėje su pavėluota inksto funkcija, atitinkamai 69 proc, 69 proc., 50 proc. ir 93 proc., 86 proc., 84 proc.

Išvados. Dažniausia potransplantacinio laikotarpio komplikacija buvo šlapimo takų infekcija. Vėlyvajame potransplantaciniame periode citomegaloviruso reaktyvacija nustatyta ketvirtadaliui pacientų. Valgancikloviro vartojimas ambulatoriniu laikotarpiu susijęs su patikimai mažesniu CMV reaktyvacijos dažniu. Transplantuoto inksto ir pacientų išgyvenamumas buvo palyginti geras, lyginant su kitų autorių duomenimis. Pacientų, kuriems buvo stebima pavėluota inksto funkcija po transplantacijos, transplantato išgyvenamumas buvo blogesnis, nei pacientų su gera inksto funkcija iš karto po transplantacijos.

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