Living-related and unrelated donors in kidney transplantation: a single center experience

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Riassunto

Premessa. **Nel corso degli ultimi anni, anche in seguito alla nuova normativa sulla sicurezza stradale adottata dai governi occidentali che ha contribuito a ridurre il numero di morti cerebrali causate da traumi cranici, in diversi Centri Trapianto si è progressivamente incrementata la donazione da vivente per i pazienti in lista d'attesa per trapianto di rene (TxR).**

Metodi. **Nel periodo Gennaio 1983-Giugno 2008 presso il nostro Centro sono stati eseguiti 117 TxR da donatore vivente. Di questi, 97 sono stati effettuati da donatore vivente correlato in ambito familiare (LRD), mentre nei restanti 20 casi il donatore era un vivente non correlato (LUD) e legato al ricevente solo da parentela legale (sposi). Per il grado di compatibilità D/R sono stati considerati il gruppo AB0, la tipizzazione HLA-A,B,DR ed il test del Cross-Match. Tutti i riceventi presentavano al momento del TxR negatività della ricerca di anticorpi linfocitotossici contro un panel linfocitario.**

Risultati. **Confrontando le variabili continue dei gruppi LRD e LUD, una differenza significativa è stata riscontata per l'età dei riceventi (LRD: 27.7±14 anni; LUD: 50.6±6.5 anni; p<0.001) ed il numero di HLA mismatches (LRD: 2.2±1; LUD: 4.2±1.2; p<0.001). Il confronto della sopravvivenza di pazienti (SP) ed organi (SO) non ha rivelato differenze significative tra i due gruppi [SP a 5 e 10 anni - LRD *vs.* LUD: 96% *vs.* 92% (p = 0.542); 93% *vs.* 91% (p = 0.938), rispettivamente; SO a 5 e 10 anni - LRD *vs.* LUD: 77% *vs.* 92% (p = 0.276); 58% *vs.* 81% (p = 0.177), rispettivamente]. L'appartenenza al gruppo LUD non è risultata significativa in modelli univariati di regressione di Cox in cui era stata assunta come variabile dipendente SP (β = 0.138; p = 0.900) od SO (β = -1.01; p = 0.170). In modelli multivariati di regressione di Cox in cui sono state inserite come variabili indipendenti anche l'età dei pazienti, il sesso ed il numero di HLA mismatches, l'appartenenza al gruppo LUD non è risultata significativa per SP (β = -0.379, p = 0.780), mentre una significatività con β negativo è emersa per SO (β = -1.645, p = 0.043).**

Conclusioni. **L'analisi della nostra casistica suggerisce come il TxR da LUD possa costituire una valida alternativa all'utilizzo di LRD al fine di aumentare il pool di donatori e ridurre il numero di pazienti in lista d'attesa.**

Summary

Background. In recent years, even after the new road safety legislation adopted by Western governments that have helped reduce the number of deaths caused by brain injuries, in many Transplant Centers has gradually increased the use of living donors (LD) for patients in waiting list for kidney transplantation (KT).

Methods. In the period January 1983-June 2008, in our Center were performed 117 KT from LD. Of these, 97 were from living related donors (LRD) and 20 from living unrelated donors (LUD). The latter were related to the recipients only by legal relationship (spouses). For the D/R degree of compatibility was considered the AB0 blood group, HLA-A,B,DR typization, and cross-matching. At the time of KT, all the recipients were negative for detection of antibodies against a panel of cytotoxic lymphocytes.

Results. By comparing continuous variables between LRD and LUD groups, a significant difference was found for recipient age (LRD: 27.7±14 years; LUD: 50.6±6.5 years; p<0.001) and number of HLA mismatches (LRD: 2.2±1; LUD: 4.2±1.2; p<0.001). No significant difference was observed for patient survival at 5 and 10 years after kidney transplantation between LRD and LUD group (96% vs. 92%, p = 0.542; 93% vs. 91%, p = 0.938), as well as for graft survival

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at the same time points (77% vs. 92%, p = 0.276; 58% vs. 81%, p = 0.177). Belonging to LUD group was not significant in univariate Cox regression model for patient survival (β = 0.138; p = 0.900) or graft survival (β = -1.01; p = 0.170). In multivariate Cox models in which were included as independent variables also patient age, sex, and number of HLA mismatches, belonging to LUD group was not significant for patient survival (β = -0.379, p = 0.780), whereas a statistical significance with negative regression coefficient occurred for graft survival (β = -1.645, p = 0.043).
Conclusions. The analysis of our series suggests that the KT from LUD can provide an alternative to LRD in order to increase the donor pool and reduce the patients on the waiting list.
Key-words: Kidney transplantation; Living Related Donors; Living Unrelated Donors; patient survival; graft survival; HLA-mismatches; R software.

Introduction

In the last years, the shortage of cadaveric donors (CD) worldwide has led to an increased number of kidney transplants from living donors (LD)[1-3]. Renal transplanted patients from living-related donors (LRD) display a superior function and a longer graft survival than those obtained from CD. A large part of these better results is due to the optimal conditions under which LRD kidneys are obtained, such as healthy non-traumatized donors with a minimal cold ischaemia time and to the higher HLA matching[1]. Recent reports have shown that kidney graft outcome from living-unrelated donors (LUD) is not worse than that from one HLA-haplotype matched LRD[4-7], thus giving a new stimulus to transplant programs using LUD, especially between spouses. In this study we report our experience of LRD and LUD kidney transplant in 117 cases. This analysis was aimed to knowing whether LUD transplantation utilizing spouses as donors may be comparable to LRD, particularly under Cyclosporin or Tacrolimus immunosuppressive regimen.

Patients and methods

Patients

In the period between January 1, 1983 and June 30, 2008, in our Center were performed 117 kidney transplantation procedures from living donors. Of these, 97 were from living related donors (LRD) and 20 from living unrelated donors (LUD). The latter were related to the recipients only by legal relationship (spouses). In 97 kidney grafts the donor was genetically related to the recipient. In the LRD group (female/male: 68/29), the mean age was 27.7±14 years, whereas the mean number of HLA mismatches was 2.2±1. A total of 20 recipients received a LUD kidney graft. All of them were spouses. The mean age of the LUD recipients was 47.6±7.9 years (female/male: 16/4), whereas the mean number of HLA mismatches was 4.2±1.2. All adults patients were informed about the details of the procedure and they consented to undergo kidney transplantation at the time of acceptance, while they were on the waiting list. They repeated their consent when called for transplantation.

HLA typing

All recipients and their potential family related or unrelated donors were typed for HLA-A, B and DR loci by standard serological and low-resolution genomic methods (PRC-SSP or PCR-SSO). T and B cell cross-match were performed both by complement dependent cytotoxicity (CDC) and more recently by flow cytometry techniques.

Immunosuppressive therapy

Sandimmune®, Neoral® and Prograf® were the main immunosuppressant with Azathioprine (or MMF) and steroids. The follow up period ended on December 2008. Acute rejection was diagnosed by clinical parameters and confirmed, at least in the last 5 years, by core biopsy, scored according to the Banff criteria.

Statistical analysis

The results are expressed as mean ± standard deviation (SD) or percentage. Continuous and categorical variables were compared by Mann-Whitney test and Pearson's chi-squared test, respectively. Patient and graft survival were evaluated by the Kaplan-Meier method. Comparison of the survival differences was performed by using the log-rank test[8]. Uni-and multivariate robust Cox proportional hazard models were performed by entering continuous and categorical variables as independent variables. For each independent variable entered in a Cox model, regression coefficient (β) and p value were in the output. The hazard ratio (HR) was provided only for independent variables with p value <0.05. The likelihood ratio test and the Wald test were used to calculate the overall significance of each Cox model. To determine whether the fitted Cox regression models adequately described the data, the proportional-hazards assumption for each covariate and global model was tested by correlating the corresponding set of scaled Schoenfeld residuals with a time transformation based on the Kaplan-Meier estimate of the survival function[9]. Survival curves were provided as crude curves and as adjusted curves according to the Cox's analysis[10]. Statistical significance was assumed for a p value <0.05 with a two-tailed null hypothesis. Statistical analyses were carried out by using R software/environment[11]. R is an open source project that is distributed under the GNU General Public License (Copyright 2008 Free Software Foundation, Inc. In:

Table I. Characteristics of kidney recipients grouped for living-related donors (LRD) and living-unrelated donors (LUD).

Characteristics	LRD (n = 97)	LUD (n = 20)	p value
Donor age (years)	48.6 ± 9.2	47.6 ± 7.9	0.717
Donor sex (F/M)	36/61	5/15	0.301
Family relationship			
Parent	72	-	-
Sibling	25	-	-
Spouses			
Wife	13	-	-
Husband	5	-	-
Recipient age (years)	27.7 ± 14	50.6 ± 6.5	<0.001
Recipient sex (F/M)	68/29	16/4	0.370
Number of HLA mismatches	2.2 ± 1	4.2 ± 1.2	<0.001
Original nephropathy			
Chronic glomerulonephritis	36 (37.1%)	10 (50%)	0.282
Chronic interstitial nephritis	8 (8.2%)	1 (5%)	0.619
Reflux nephropathy	15 (15.5%)	-	-
Alport's Syndrome	5 (5.2%)	-	-
Renal dysplasia	6 (6.2%)	-	-
Renal hypertension	8 (8.2%)	2 (10%)	0.798
IgA nephropathy	7 (7.2%)	1 (5%)	0.720
Others	12 (12.4%)	6 (30%)	0.144
Pre-transplant dialysis			
Mean duration (months)	13.5 ± 12.7	24.3 ± 15.7	0.001
Number of non dialysed patients	16 (16.5%)	3 (15%)	0.868
Total ischaemia time (min)	158 ± 78	156 ± 85	0.925

Table II. Causes of patient deaths and graft losses in kidney transplantation performed by using living-related donors (LRD) and living-unrelated donors (LUD) occurring during the first post-transplant year.

Characteristics	LRD (n = 97)	LUD (n = 20)	p value
Causes of patient death			
Unknown	3 (3%)	-	-
Heart failure	1 (1%)	1 (5%)	0.212
Pancreatitis	1 (1%)	-	-
Causes of graft loss			
Arterial thrombosis	2 (2%)	-	-
Irreversible acute rejection	3 (3%)	-	-
Chronic rejection	15 (15.4%)	2 (10%)	0.527
Recurrence of primary disease	3 (3%)	-	-
De novo cancers	3 (3%)	-	-
CMV infection	1 (1%)	-	-

http://www.gnu.org/licenses/gpl.html). Sources, binaries, documentation, and additional packages for R can be obtained from the Comprehensive R Archive Network (CRAN) mirror sites[12]. At the time of this writing, R-2.8.1 was available.

Results

Characteristics of kidney recipients grouped according to LRD and LUD are shown in Table I. Significantly higher age (p<0.001), number of HLA mismatches (p<0.001), and duration of pre-transplant dialysis were found in kidney recipients of LUD group. Conversely, donor age, sex, and graft ischaemia time did not differ significantly in both recipient groups. The causes of patient deaths and graft losses are summarized in Table II.

Five- and 10-year patient survival rates were 96% group LRD *vs.* 92% LUD (p = 0.542) and 93% group LRD *vs.* 91% LUD (p = 0.938), respectively. Five- and 10-year graft survival rates were 77% group LRD *vs.* 92% LUD (p = 0.276) and 58% group LRD *vs.* 81% LUD (p = 0.177), respectively.

In a first series of univariate Cox models carried out by entering donor group (target: LUD) as indepen-

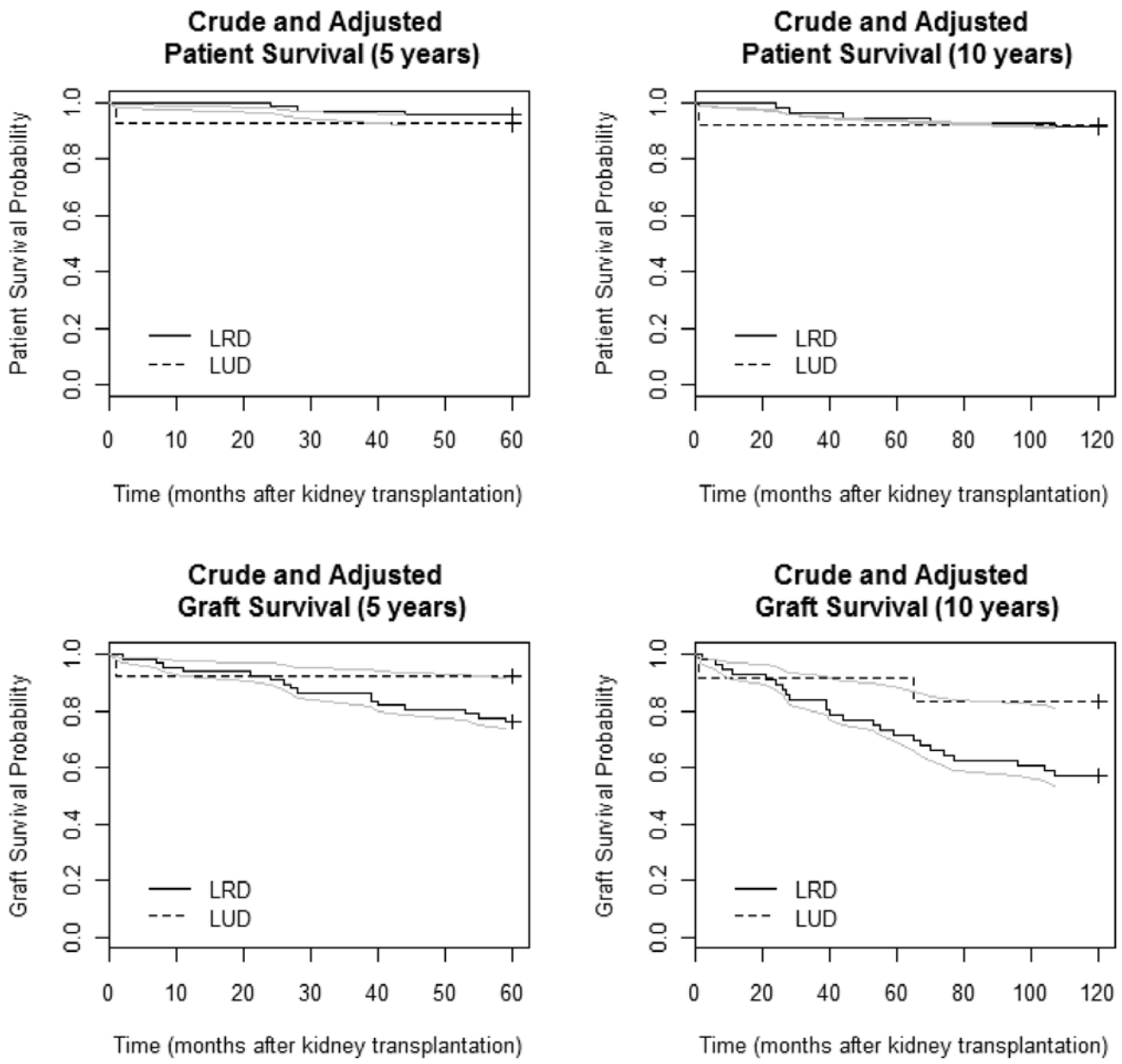

Figure 1. Cox crude survival curves (continuous and dotted black lines) and adjusted survival curves (continuous grey lines) for patient age, sex, and number of HLA mismatches in LDR and LUD groups (patient and graft survival at 5 and 10 years after kidney transplantation).

dent variable, no statistical significance was found for patient survival (β = 0.138, likelihood ratio test = 0.901, Wald test = 0.900, p = 0.900) and graft survival (β = -1.01, likelihood ratio test = 0.111, Wald test = 0.169, p = 0.170). Cox model diagnostics based on scaled Schoenfeld residuals supported the proportional hazard assumption for both patient survival (p = 0.139) and graft survival (p = 0.358) univariate models. In a second series of multivariate Cox models carried out by entering donor group (target: LUD), patient age, patient sex (target: male), and number of HLA mismatches as independent variables, no statistical significance was found for patient survival (Group: β = -0.379, p = 0.780; Age: β = 0.017, p = 0.570; Sex: β = 19.491, p = 0.999; number of HLA mismatches: β = -0.036, p = 0.920; likelihood ratio test = 0.442; Wald test = 0.988), whereas for graft survival a statistical significance occurred only for patient group (Group: β = -1.645, HR: 0.193, p = 0.043; Age: β = 0.012, p = 0.360; Sex: β = 0.303, p = 0.510; number of HLA mismatches: β = 0.187, p = 0.280; likelihood ratio test = 0.239; Wald test = 0.277). Both Cox multivariate models passed diagnostics based on scaled Schoenfeld residuals (p = 0.621; p = 0.567, respectively). The Cox crude survival curves at 5 and 10 years for patients and grafts, as well as the adjusted survival curves for patient age, sex and number of HLA mismatches are presented in Figure 1.

Discussion

Our experience in kidney transplantation using LD demonstrates that although transplanted patients from LUD had higher age and number of HLA mismatches than LRD (Table I), the patient and graft-survival rates in LUD group were similar or better than those observed in LRD group (Fig. 1). These findings confirm the high survival rates of kidney transplants from spousal and LUD previously reported[1,13]. In our series, late graft losses were largely due to chronic rejection and de novo cancers, whereas patient deaths were mainly caused by heart failure in the presence of well-functioning graft (Table II). Although in our LUD group there were more patients than in previous series[13], we have adopted several conservative strategies for statistical analysis. Thus, a robust Cox regression was performed to evaluate potential independent predictors for patient and graft survival. Moreover, to determine whether the fitted Cox regression models adequately described the data, the proportional-hazards assumption was tested for each covariate and global model. In a first series of univariate Cox models for patient and graft survival, donor group was entered as independent variable. In these models, no statistical significance was found. In a series of multivariate Cox models performed by entering also patient age, sex, and number of HLA mismatches, no significance was found for patient survival, whereas the kidney recipients of the LUD group showed a slight significance for a better graft survival than LRD group, although with a very low HR. On the other hand, the likelihood ratio test and the Wald test did not support the overall significance of this model. In any case, the adjusted survival curves for potential confounding variables confirmed the high survival rates for both patients and grafts of the LUD group (Fig. 1).

The strategies adopted in our statistical analysis makes the results of this series more reliable than previous studies concerning living kidney transplantation, in which only Kaplan-Meier and log-rank test were used[13,14]. In addition to the better kidney quality, shorter ischaemia time, and better compliance with spousal transplantation, others factors such as the availability of a potent array of immunosuppressive drugs as well as a possible allo-hyporesponsiveness induced by sexual intercourse, could contribute to the long-term satisfactory kidney graft survivals observed in HLA mismatched spousal grafts. The results of this study suggest that LUD utilization should be greatly encouraged in kidney transplantation programs.

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