Transpl Int (1996) 9 [Suppl 1]: S49–S53

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Is kidney transplantation in sensitized recipients justified?

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Abstract The objective of the study was to determine if it is justified to use the scarce resources of cadaveric kidneys on HLA-sensitized patients, by reviewing the initial and long-term outcome of cadaveric renal transplantation at Uppsala University Hospital, Sweden. Between January 1988 and December 1994, 402 renal transplantations were performed. The patients were divided into one group of sensitized recipients (peak panel antibody reactivity $\geq 25\,\%$; $n = 84$) and a second of non-sensitized recipients (panel reactive antibodies $< 25\,\%$; $n = 318$). The groups were comparable in terms of recipient and donor age, gender, HLA-A, -B and -DR mismatches and numbers of diabetics. None of the sensitized patients received a six-antigen-matched kidney. For the non-sensitized group, life table analysis showed a 1-year actuarial graft survival (GS) of 91.8 % and a 4-year GS of 84.4 %. The corresponding GSs for the sensitized group were 79.9 % and 68.7 %, respectively ($P < 0.01$). The statistical significance vanished if patients with primary non-function were excluded. When excluding donors above 55 years of age, kidneys with cold ischemia time above 20 h, and two-antigen (HLA-DR) mismatches, there was no detectable difference between the non-sensitized and sensitized groups at 1-year or 4-year GS. Although there is a statistical significance in GS between non-sensitized and sensitized recipients of a kidney transplant, this does not differ from other risk groups such as diabetics, rheumatoid disease sufferers or elderly recipients. We therefore conclude that the sensitized patient should be accepted on the waiting list for a kidney transplant and that it is worthwhile to do the utmost to transplant this category of patients. Our data indicate that kidney GS in sensitized recipients is more affected by negative risk factors such as older donors, long cold ischemia time and two-antigen HLA-DR mismatch, than the non-sensitized recipient. To improve the outcome, those negative factors should be avoided or reduced.

Key words Kidney transplantation · Graft survival · Immunization

Introduction

With the increasing shortage of cadaveric kidneys, the accumulation of patients on the waiting list for kidney transplantation is becoming a critical problem. One possibility of reducing this problem would be to limit the opportunity of a transplant to any individual that stands an increased risk of a reduced graft survival. A group that could be targeted by such a policy is sensitized patients, with panel reactive antibodies (PRA), who are steadily increasing in numbers on waiting lists for kidney transplantation in Europe and North America [2].

Table 1 Demographic data, expressed as mean with standard deviation when appropriate or percentage of population. (*PRA* Panel reactive antibodies, *NS* not significant)

	Peak PRA < 25 %	Peak PRA ≥ 25 %	*P*
n	318	84	
Time on waiting list (months)	8.8 ± 6.1	11.7 ± 7.8	< 0.01
Gender			
Female	40.3 %	44.0 %	NS
Male	59.7 %	56.0 %	NS
Age (years)	48.2 ± 12.7	44.3 ± 12.8	NS
Retransplant	8.5 %	59.2 %	< 0.01
Cold ischemia time (min)	1030 ± 366	1119 ± 302	< 0.05
Donor age (years)	44.5 ± 16.5	44.1 ± 17.1	NS
Mismatch HLA-A, -B, -DR	4.3 ± 1.4	4.2 ± 1.3	NS
Mismatch HLA-DR	1.4 ± 0.7	1.4 ± 0.7	NS
Six-antigen matched	2.2 %	0 %	
Two-DR antigen matched	11.3 %	13.1 %	NS
Diabetes	25.2 %	19.0 %	NS
Number of blood transfusions prior to transplant	4.3 ± 10.8	11.6 ± 17.9	< 0.01

A decision to exclude a group of patients from the potential benefit of a kidney transplantation due to any level of PRA would be highly controversial. The influence on graft survival of an increase in PRA levels has not been fully determined. Both inferior and equal results compared with the outcome for non-sensitized recipients have been reported [7, 8, 10, 15]. However, it is undisputed that sensitized recipients pose a problem in finding a suitable cross-matched negative donor [9, 10], which prolongs their time on the waiting list.

At our unit we have always had a positive and aggressive policy of accepting sensitized patients on the waiting list for a kidney transplant. The controversial question mentioned earlier has also been raised at our centre, and therefore we were interested in a retrospective evaluation of our present policy, in particular, bearing in mind that we are facing a decline in the frequency of cadaveric donors.

In this paper we have defined the sensitized group as having a historical or current PRA value of 25 % or higher, since this group was found to have a prolonged time on the waiting list.

Materials and methods

Between January 1988 and December 1994, a total of 402 cadaveric renal transplantations were performed. Recipients were divided into two groups: the sensitized group, with peak PRA reacting to at least 25 % of the cells, consisted of 84 patients, and the other consisted of 318 patients who were considered to be non-sensitized. The PRA reactivity was measured by testing the recipient serum against a panel of lymphocytes from 24 different blood donors. This panel was selected to cover the most common HLA antigens. A panel cell was considered positive if a cytotoxic activity could be detected by the NIH technique.

Most of the kidneys were harvested locally. A few were obtained through the kidney exchange program from other centres in Scandinavia, allocated by Scandiatransplant [5]. However, none of the sensitized patients received a six-antigen-matched kidney.

All patients were treated with a cyclosporine-based immunosuppressive protocol and had a negative current serum cytotoxic T-cell cross-match. Twenty patients, who where either considered as highly sensitized (PRA > 50 %) or had had a prolonged time on the waiting list, were included in a pretransplant program consisting of plasmapheresis aimed at decreasing their PRA levels [1]. In patients with delayed onset of graft function, the cyclosporine treatment was temporarily halted and substituted with anti-lymphocyte globulin (ALG). Rejections were initially treated with Solu-Medrol and, if resistant, with anti-thymocyte globulin (ATG) or OKT-3.

The two groups were comparable in terms of recipient and donor age, recipient and donor gender, HLA-A, -B and -DR mismatches, and whether the kidney was harvested locally or shipped. The sensitized group had a significantly longer time on the waiting list, longer cold ischemia time, a higher proportion of retransplants, and more blood transfusion before transplantation (Table 1). Actuarial graft survival was computed using the Kaplan-Meyer life table method, where patient death was handled as lost to follow-up. For comparison, an overall graft survival was calculated in the same manner but managing patient death as graft loss instead. In reality, none of the patients were actually recorded as lost to follow-up. Statistical analysis was performed using the Student *t*-test for comparison of groups and the Cox-Mantel log-rank test for evaluation of Kaplan-Meyer survival tables, utilizing the Winstat software package.

Table 2 Results, expressed as mean with standard deviation when appropriate or percentage of population

	Peak PRA < 25 %	Peak PRA ≥ 25 %	*P*
n	318	84	
Number of rejections	1.1 ± 1.1	1.0 ± 1.3	NS
Free from rejections	40.9 %	46.4 %	NS
First rejection within 1 month	44.5 %	34.5 %	NS
No onset	2.5 %	8.3 %	< 0.05
Graft lost within 1 month (no-onset excluded)	6.3 %	7.2 %	NS
Delayed onset (no-onset excluded)	19.0 %	28.6 %	NS
Actuarial graft survival, 1 year	91.8 %	79.9 %	
Actuarial graft survival, 4 years	84.4 %	68.7 %	
Overall graft survival, 1 year	82.0 %	70.1 %	
Overall graft survival, 4 years	65.9 %	54.2 %	
Creatinine at 1 year	160 ± 74 (*n* = 216)	162 ± 82 (*n* = 48)	NS
Creatinine at 4 years	153 ± 63 (*n* = 97)	120 ± 38 (*n* = 27)	< 0.05

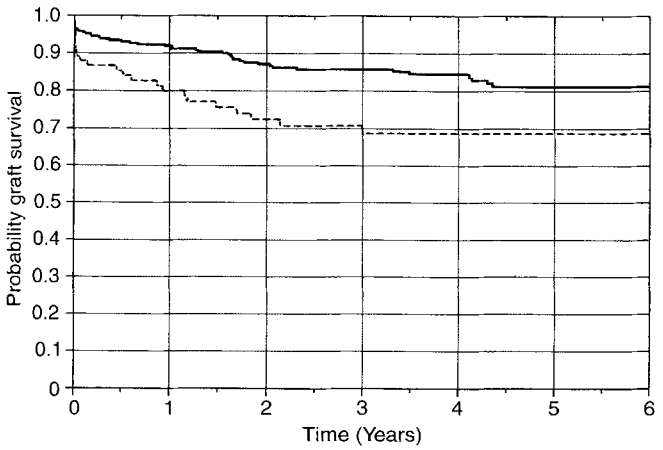

Fig. 1 Actuarial graft survival. (*Solid line* non-sensitized, *dotted line* sensitized, $P < 0.01$)

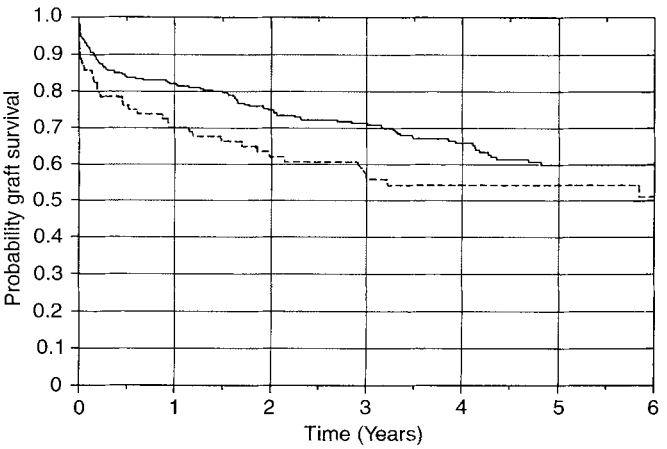

Fig. 2 The overall graft survival for cadaveric grafts. (*Solid line* non-sensitized, *dotted line* sensitized, $P = 0.06$)

Results

The non-sensitized group had significantly higher actuarial 1-year and 4-year graft survivals than did the sensitized group (Table 2, Fig. 1). Looking at the overall graft survival and including patient death as graft loss, a similar difference was obtained (Fig. 2), although without statistical significance.

When looking at graft outcome in the sensitized patients, the only significant negative factor was donor age below 55 years. Cold ischemia time above 20 h and DR antigen mismatch tended to have an influence on graft survival but was not significant. Recipients over 65 years, gender, PRA > 50 %, and total antigen mismatch did not significantly affect the outcome. We have calculated overall graft survival in our patients, excluding donors over 55 years, kidneys with longer cold ischemia time than 20 h, and two-antigen DR mismatch. The overall graft survival between sensitized and non-sensitized groups was then almost equivalent (Table 3). Neither the rejection frequency nor the percentage of patients free from rejection or frequency of early rejections varied between sensitized and non-sensitized groups. Also, creatinine levels at 1 year were fully comparable, but at the 4-year follow-up the sensitized group had significantly better values.

In the sensitized group, grafts with no onset (i.e., never functioning) were strikingly more frequent, this difference also accounted for an increase in early loss of graft. Delayed graft function was also more apparent in the sensitized population. Analysis of grafts which never functioned among the sensitized patients showed that all but one were totally DR antigen mismatched. The cold ischemia time tended to be longer and donors tended to be older in the no-onset group, although not significantly. An interesting finding was that the no-on-

Table 3 Comparison of overall graft survival (%) when excluding patients with negative factors for graft outcome

	Non-sensitized, 1 year	Sensitized, 1 year	Non-sensitized, 4 years	Sensitized, 4 years
Total	82.0	70.1	65.9	54.2
Excluding no-onset	84.1	76.5	67.6	59.1
Excluding donors over 55 years	85.2	79.3	71.1	61.7
Excluding cold ischemia time over 20 h	84.2	75.0	66.0	59.5
Excluding two-DR antigen mismatch	80.0	78.5	66.6	64.8
Excluding donors over 55 years, cold ischemia time over 20 h, two-DR antigen mismatch	84.3	81.2	72.7	72.4

Table 4 Sensitized patients grouped on the basis of functioning or no-onset (primary non-function) grafts

	Functioning graft	No onset	
n	77	7	
Age (years)	44.1 ± 12.9	46.5 ± 11.9	NS
Retransplant	70.1 %	57.1 %	NS
Donor age (years)	42.9 ± 17.1	56.8 ± 11.8	< 0.05
Cold ischemia time (min)	1100 ± 284	1332 ± 420	0.05
Patients with peak PRA above 50 %	33.8 %	28.6 %	NS
Kidneys received via exchange program	28.6 %	42.9 %	NS
Peak PRA (T-cell, %)	59.2 ± 22.2	56.0 ± 24.7	NS
Latest PRA (T-cell, %)	27.0 ± 24.0	41.7 ± 32.5	NS
Change in PRA peak, latest (% PTA)	− 32.2 ± 24.7	− 14.3 ± 12.9	0.06
Mismatch HLA-A, -B, -DR	4.2 ± 1.2	4.1 ± 1.9	NS
Mismatch HLA-DR	1.3 ± 0.7	1.7 ± 0.8	NS

Table 5 Comparison of overall graft survival (%) for different risk groups

	One year	Four years
All (n = 402)	79.5	63.4
Sensitized (n = 84)	70.1	54.2
Diabetic (n = 96)	79.1	55.1
Systemic lupus erythematosus, rheumatoid arthritis (n = 18)	54.3	43.5
Recipient over 65 years (n = 31)	77.4	48.7

set group, despite similar peak PRA% as the functioning graft group, displayed different PRA% in current serum (Table 4).

In a subgroup consisting of 20 patients treated with plasmapheresis pretransplantation, we found significantly higher peak PRA levels than in the rest of the sensitized group. Three grafts (15 %) never functioned and a total of five (25 %) was lost within 1 month. The delayed graft function rate was 35 %. This treatment did reveal an overall graft survival at 1 year of 65 % and at 4 years of 57 %.

Discussion

The question of denying a sensitized patient the opportunity of a kidney transplant is highly controversial. In the literature, most reports published show a trend or significance for a better graft survival in the non-sensitized population [2, 8, 14]. Our own results, with an overall 1-year graft survival of 70.1 % for sensitized compared to 82.0 % for non-sensitized recipients are not significantly lower. Although the numerical difference cannot be ignored, the figures are not dramatically lower than for other risk groups such as diabetic patients, rheumatoid disease sufferers and the elderly (Table 5). The difference noted at 1 year in comparison with other risk groups is often diminished at 4 years due to the higher mortality in the other groups. We conclude that our previous liberal policy of accepting sensitized patients on the waiting list for kidney transplantation, irrespective of the number of previous grafts, PAR levels or blood group, is justified. The aim should be, instead, to improve the result for this group of patients.

Many of the previous publications aim to justify a wider usage of exchange schemes to achieve a better HLA match. In our patients, no attempts at HLA

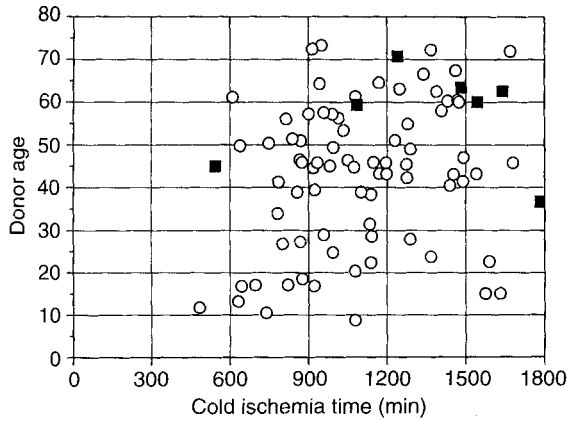

Fig. 3 Sensitized patients dependending on donor age and cold ischemia time. Grafts which never functioned are indicated by *solid boxes*, others *open circles*

matching were done (Table 1). Nevertheless, our results both for sensitized and non-sensitized groups are comparable to those of others, although the six-antigen-matched recipients reported by others show a better 1-year graft survival [12]. A policy aiming at very good matching has, however, the disadvantage of a long time on the waiting list [14] and long cold ischemia times also tend to have a negative influence on primary non-function (Fig. 3) as well as on graft survival. Therefore, a more extensive exchange program to improve HLA match does not appear to be of any advantage. One exception might be DR matching. Our results indicate that sensitized patients transplanted with two DR mismatches do worse, including a higher frequency of recipients undergoing primary non-function and lower graft survival. Thus, one way of further improving the transplant results for HLA-sensitized patients would be to aim for a two-antigen DR match.

Primary non-function is one of the major problems in transplanting sensitized recipients [3]. The main cause for no-onset could be of immunological origin [4] and could therefore perhaps be prevented with better cross-matchtechniques in the future [11]. Although none of our cases showed positive B-cell cross-match or flow cytometric cross-match, we highly recommend the usage of these tests, as previous reports have shown a better graft survival [6, 13]. Another strategy for the prevention of the primary non-function, assuming the cause to be an antibody-mediated rejection, is to use an aggressive treatment with plasmapheresis and polyclonal antibodies, although we still need further evidence before recommending such a combative regime. Graft survival among sensitized recipients is more affected by negative risk factors than the normal transplant population and donors over 55 years of age present an even greater risk and, if possible, should be avoided.

In summary, this retrospective review of our experience employing a liberal policy of accepting sensitized patients for kidney transplantation, has encouraged us to continue this liberal approach. The graft survival is about 10% lower for the sensitized cohort, which we feel is acceptable. To maintain and improve these results, the use of sensitive cross-match techniques such as flow cytometric cross-match, is highly recommended. Other factors, such as avoiding kidneys from elderly donors in this group and aiming at DR-matching kidneys, might further improve the results. Furthermore, new immunosuppressant drugs could hopefully be beneficial for this patient group and make it even more justified to freely accept HLA-sensitized patients.

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