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ORIGINAL ARTICLE

Comparison of time on the deceased donor kidney waitlist versus time on the kidney paired donation registry in the Australian program

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Summary

In the Australian kidney paired donation (KPD) program matching is based on acceptable mismatches, whereas deceased donor waitlist (DDWL) patients are allocated kidneys based on HLA antigen matching rules. Herein, we compared waiting time for a KPD match to the waiting time on the DDWL and the occurrence of matching in the DDWL for patients who were registered in both programs. Data on first dialysis, matches on the DDWL, KPD program entry, matches and transplant dates were assessed in 26 KPD recipients of the Australian program. There were 22 recipients who were listed in the DDWL and received kidney transplants by KPD. Time on dialysis until KPD transplantation was 808 ± 646 days. Eleven patients had never been matched with a deceased donor (waiting time 345 ± 237 days) and 11 had been matched on average 3 ± 5 times (waiting time 1227 ± 615 days, $P < 0.0001$ vs. never matched), but did not progress to transplantation because of positive crossmatch or class II donor-specific antibody. Mean time from registration in the KPD program until kidney transplantation was 153 ± 92 days ($P < 0.0001$ vs. DDWL). KPD allocation using the acceptable mismatch approach is effective in identifying suitable live donors for some recipients within a relatively short time-frame.

Introduction

Live kidney donation remains a major source of kidney transplantations in Australia accounting for approximately 35–40% of all kidney transplants [1]. Based on blood type distribution and previous sensitizing events up to a third of willing and healthy living donors are unsuitable to donate a kidney to a loved one because of blood group incompatibility or unacceptable donor-specific antibodies (DSA). One of the solutions to overcome this barrier is kidney paired donation (KPD), which facilitates the exchange of live donor kidneys between the willing donors by pairing two or more incompatible pairs together [2–5]. The success of KPD depends upon several factors, such as the number of incompatible pairs in the database, the type of immunological incompatibility, and the rules for allocation of KPD donors to recipients. In Australia, patients on the deceased donor waiting list (DDWL) are matched to potential deceased donors based on HLA antigen matching rules and time

on dialysis by the National Organ Matching System (NOMS). In contrast, allocation of live donors to suitable recipients in the Australian KPD program is performed using a matching algorithm based on acceptable mismatches excluding donors from matching to recipients with DSA >2000 MFI for any class I or II antibodies and the algorithm does not consider any HLA antigen matching rules for allocation [5]. It is presently unknown whether using these KPD matching rules will help sensitized patients who have been waiting for many years on the DDWL finding a suitable donor within a short period of enrollment in the KPD registry. In its first year of activity, the Australian KPD program successfully achieved a transplant rate of 35% among a small pool of highly sensitized recipients, with 60% of patients having a calculated panel-reactive antibody (cPRA) >90% [6]. Herein, we analyze whether and to what extent allocation based on acceptable mismatches compared to HLA matching rules can provide a benefit to recipients with broad sensitization.

Materials and methods

Between October 2010 and October 2011, 61 donor–recipient pairs and two altruistic donors who satisfied all agreed medical criteria for donor and recipient registration, molecular HLA typing, and HLA alloantibody testing were included in the five quarterly match procedures.

Computer program matching of KPD pairs

Allocation of suitable live donor matches in the KPD program was performed using a software module developed by the NOMS enabling virtual crossmatching as previously described [5]. HLA alleles of each locus and HLA antibody specificities and strength (as mean fluorescence intensity or MFI) were entered in the computer program at the 4-digit level. Donor molecular HLA typing and recipient HLA antibody testing for the loci -A, -B, -C, -DRB1, -DPB1, -DQB1, and DRB3/4/5 were performed as previously reported [5]. Recipients were tested for HLA class I and class II directed IgG antibody in their sera using single antigen bead (SAB) Luminex technology.

The matching algorithm does not consider any HLA antigen matching rules and allocation is only based on acceptable mismatches by excluding donors from matching to recipients with DSA >2000MFI for any class I or II antibodies against any of the donor HLA loci [5]. The program allows the option of ABO-incompatible matching in selected cases. NOMS selects between competing match offers based on prespecified ranking rules, which aim to maximize the number of patients receiving a transplant, while favoring patients with high versus low PRA all other things being equal [5].

Deceased donor kidney allocation

The major criteria used by the NOMS deceased donor allocation algorithm to decide which patient on the transplant list will be allocated a donated kidney are: first, the blood group (identical > compatible); second, HLA antigen matching with the donor; third, how long the patient has been on dialysis (waiting time on dialysis); fourth, the level of sensitization based on class I PRA; and fifth, whether the patient is a child. Waiting time is taken from the commencement of dialysis and not from time of admission to the waiting list, and thus waiting time bonus on the DDWL accrues from the date of first dialysis. The first level of matching in the NOMS database occurs at a national level and involves every patient on the DDWL. It is designed primarily to help patients with high levels of panel-reactive antibodies (PRA >80%), as it is difficult to find a suitable kidney for these patients and their outcome is likely to be better if they receive a very well-matched kidney [7,8]. If a difficult to match patient is identified in NOMS as a very close match to the donor kidney, this kidney can be sent to them from anywhere in Australia. Although emphasis is on good HLA matching, unacceptable antigens are indirectly accounted for as far as in patients with PRA>80% will be allocated kidneys only if they have 0 or 1 HLA mismatches. About 80% of donated kidneys are allocated at the state level and are transplanted in the same state where they were donated. For local allocations, the NOMS database also calculates who should receive the kidneys in each state, according to the state's allocation formula, which uses slightly different weighting to HLA antigen matching and time on dialysis within each state algorithm.

Comparison of time on the deceased donor waitlist versus time on the KPD registry

Prospective, dialysis-dependent, kidney transplant recipients who register in the Australian KPD program are also registered in the DDWL. They remain active on this list until the time of a match run, when they are temporarily off listed until completion of the match run and review of potential matched pairs. Unmatched recipients are reactivated in the DDWL. Date of first dialysis, time on the DDWL, number of matches in the DDWL, date of entry into the KPD program, and KPD match and transplant dates were assessed in 26 recipients who received a live donor kidney transplant through the national KPD program. The time on DDWL to match run date was

Table 1. Calculated panel-reactive antibodies (cPRA) for loci A-, B-, DR-, and DQ- in 61 recipients registered in the first five match runs of the Australian kidney paired donation (KPD) program and cPRA in 26 recipients who were transplanted through the KPD program.

cPRA (%)	Registered (*N* = 61)	Transplanted (*N* = 26)
0–25	11 (18)	8 (30)
25–50	7 (12)	3 (10)
50–75	10 (16)	4 (15)
75–90	8 (13)	3 (10)
90–100	25 (41)	9 (35)

Values within parenthesis are expressed in percentage.

compared with the time in the KPD program until the transplant.

Results

Of the 61 recipients from the pairs enrolled in the program, only 10% were included because of ABO blood group incompatibility without HLA antibody against their co-registered donor (ABOi), whereas 90% of recipients were included because of HLA sensitization against their co-registered donor. There were twice as many blood group O recipients (62%) than there were blood group O donors (30%). A cPRA for loci -A, -B, -DR, -DQ of >75% and >90% was found in 54% and 41% of recipients, respectively (Table 1). Allocation procedures to match compatible combinations were scheduled every 3 months and five match procedures were performed between October 2010 and October 2011. Only pairs who satisfied all agreed medical criteria for donor and recipient registration, molecular HLA typing, and HLA alloantibody testing were included in match run procedures. Eventually, after obtaining negative crossmatches between the new donors and recipients, 26 recipients (24 KPD and 2 orphan donor recipients) received a kidney transplant through the National KPD scheme, resulting in a transplant rate of 39% for KPD recipients. At last follow-up (range 190–552 days), patient survival in the 26 transplanted recipients was 96%; one recipient died at 9 month of systemic fungal infection. Rejection-free survival after a mean follow-up of 347 ± 131 days was also 96%.

Deceased donor waitlist time versus time on the KPD registry

Of the 26 patients who received a KPD transplant, 4 were pre-emptive recipients and 22 were recipients who were listed in the DDWL. Only KPD recipients who were listed in the DDWL were included in the comparison between waiting time on the deceased donor versus KPD registry. Time on the DDWL from commencement of dialysis was 808 ± 646 days (maximum 2003 days) in patients who received a KPD transplant. Time on the DDWL was longer for patients with PRA 50–75% compared with >75% (1199 ± 684 vs. 575 ± 497 days, $P < 0.001$) (Fig. 1). Of the patients on the DDWL, 11 had never been matched with a deceased donor (waiting time 345 ± 237 days) and 11 had been matched on average 3 ± 5 times (waiting time 1227 ± 615 days, $P < 0.0001$ vs. never matched) and 3 of these patients had been matched >13 times each (Fig. 2). In those patients, deceased donor transplantation was not undertaken because of a positive T-cell crossmatch due to Cw-DSA, or the presence of significant class II DSA or positive B-cell crossmatch, when this was available.

After being registered in the KPD program, patients who progressed to KPD transplant had been listed on average for 93 ± 87 days (range of 13–301 days) from the

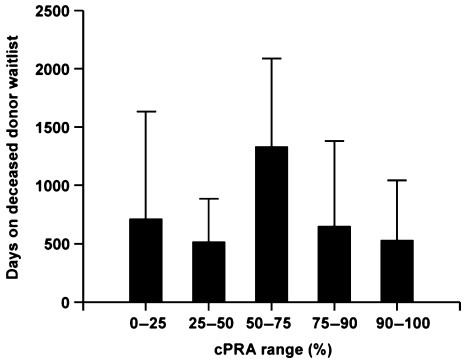

Figure 1 Average (±SD) number of days on the deceased donor waitlist in 22 dialysis patients who received a kidney transplant through the kidney paired donation program by level of sensitization based on cPRA (A, B, DR, DQ).

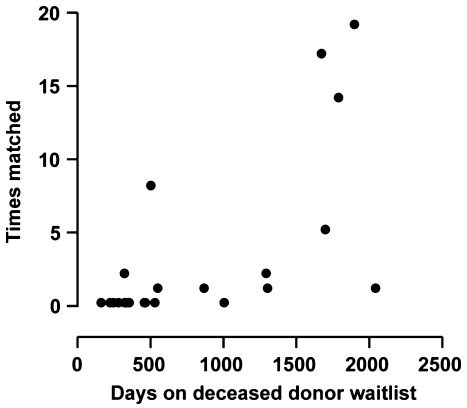

Figure 2 Number of times recipients on the transplant waiting list were matched to a deceased donor using HLA antigen matching of the standard allocation algorithm in relation to time on the transplant waitlist.

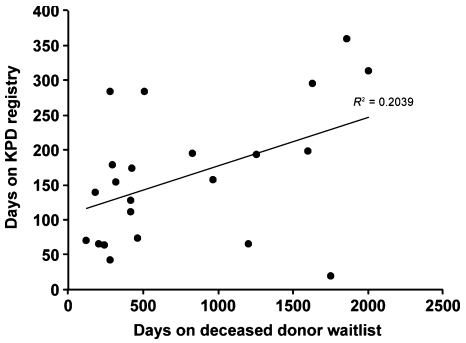

Figure 3 Correlation between time on the deceased donor waitlist and time on the kidney paired donation registry in 22 patients who received a kidney transplant through the kidney paired donation program.

time to registration until a match was found ($P < 0.0001$ compared to time on DDWL) and for 153 ± 92 days (range of 56–360 days) from the time to registration until transplantation. The time between matching in the KPD program until transplantation was 57 ± 24 days. The cPRA in recipients transplanted by KPD is shown in Table 1. There was a weak, but significant correlation ($R^2 = 0.204$, $P < 0.05$) between days on the DDWL and days on the KPD registry until transplant (Fig. 3).

During the time October 2010 and October 2011 when the first 5 KPD match runs took place, six patients registered on both the DDWL and KPD programs received deceased donor kidney transplantation. The time on the DDWL until transplantation was 1413 ± 867 days and the time between registrations in the KPD program until deceased donor transplantation was 125 ± 153 days.

Discussion

The initial experience of the Australian KPD program demonstrates that allocating live donor kidneys using the acceptable mismatch approach is effective in identifying suitable live donors for some sensitized recipients within a relatively short time-frame. These results are of particular importance in view of the relatively small number of unsensitized ABO-incompatible recipients enrolled in the program, reducing the ability to easily match donors to multiple recipients. The trade-off of the unacceptable mismatch approach is that the matched donor is not necessarily well matched to the recipient and this could be used as an argument that inferior outcomes may be expected particularly in patients with high PRA, as their outcomes appear better if they receive a very well-matched kidney [7,8]. On the other hand, survival for nearly any patient with kidney failure is better with a kidney transplant than if they were to remain on dialysis [9] and patient and graft survival in the Eurotransplant acceptable mismatch program for deceased donor organ allocation have been shown to be excellent [10], probably as a result of better epitope matching. Using the acceptable mismatch approach, the early outcomes of recipients in the Australian KPD program were excellent, with a rejection-free survival of 95% after a mean follow-up of 256 ± 131 days [5].

The options for kidney transplant candidates sensitized to a broad range of HLA antigens are limited. Their chance to receive a crossmatch-negative organ from a deceased donor is disproportionately reduced and results in markedly prolonged waiting times [11]. Often they may have a willing live donor, who is immunologically incompatible and if directed donation is not possible because DSA are not amenable to desensitization, the only hope for these highly sensitized recipients could be KPD. The success of a KPD program may be in part dependent on the allocation criteria.

For DDWL allocation, the NOMS database calculates who should receive the kidneys using an algorithm that takes into consideration HLA antigen matching and time on dialysis. As antigens that would be unacceptable in a donor are only indirectly accounted for in the allocation, the number of kidney offers particularly to subjects with moderate to high sensitization that are declined because of a positive crossmatch is not negligible. The current data show that over 20% of patients were matched in excess of five times to a donor in the deceased donor program, but did not progress to transplantation because of positive CDC crossmatch. The main reason for positive crossmatches in HLA antigen-matched recipients is the presence of class II antibodies against the donor, which are not considered in the allocation. Allocation based on the virtual crossmatch approach as utilized by the Australian KPD program has the advantage that the likelihood of a positive crossmatch once a match is identified by computer allocation is exceedingly low [6].

About 80% of donated deceased donor kidneys are allocated by NOMS at the state level and 20% are allocated nationally to patients with PRA >80% kidneys, provided that they have 0 or 1 HLA mismatche. This may explain the longer waiting time observed in our cohort for recipients with cPRA 50–75% compared with those with cPRA >75%. As O recipients wait on average longer for an organ than recipients with other blood groups, this disparity could account for the observed difference in waiting time. Indeed, in our patients with cPRA, 50–75% the proportion of O recipients was higher than in those with cPRA >75% (67% vs. 42%). Interestingly, analysis of the NOMS registry allocation data shows that the average time waiting on dialysis of all patients transplanted with deceased donor kidney in Australia in 2011 by percentage

authorized class I PRA by serology had a similar odd distribution and the mean wait time for deceased donor transplantation was 3.5 years for PRA < 20%, 5.3 years for PRA 21–50%, 5.1 years for PRA 51–80%, and 4.0 years for PRA 81–100%. The shorter waiting time for sensitized patients with PRA >80% to be allocated a deceased donor kidney transplant reflects the priority given by the algorithm to this group of DDWL patients to receive an organ from the larger national donor pool, rather than the smaller state donor pool. Patients with narrow sensitization against a few common antigens are more likely to have a high PRA compared with patients with broad sensitization against less common ones. For instance, having a class I antibody against A2, which is present in 50% of the Australian donor population, will automatically give a PRA of 50%. On the other hand, broad sensitization while not giving a high PRA may result in many potential matches being excluded because of 1 or more DSA.

On the other hand, the Australian KPD algorithm creates possible combinations of 2-way or 3-way chains of suitable donor–recipient pairs using six ranking rules [5]. Although this first rule favors maximizing the number of pairs who can proceed to transplant, the second rule favors recipients with low match probability (MP). The MP range is 0 to 1, 0 indicating no compatible donors and 1 indicating any donor in the run could be a suitable match. The inclusion of this ranking rule explains the large proportion of KPD recipients with cPRA >90% who proceeded to kidney transplantation in our program.

Patients who were long waiters on the DDWL also wait longer to find a match and progress to kidney transplantation in the KPD program. Many of these long waiters have a very high cPRA (>95%) and even if there is a single potential matched donor in the KPD, the latter must be able to reciprocate by being linked in a two-way or three-way chain, which may not necessarily occur in a first matching round. On the other hand, because the KPD matching program gives priority to recipients with low MP [5], when these highly sensitized are matched and linked in a chain combination, they are ranked higher than a chain where pair with the highly sensitized recipient is interchanged for a pair with a recipient with moderate sensitization. In comparison to waiting time on the DDWL, the differences in the waiting time on the KPD registry are rather minute, with an average of 76 days for those who had been on the DDWL for <1 year and 147 days for those waiting on the DDWL for >3 years.

The results of this study show that highly sensitized recipients who traditionally wait for extremely long periods for a suitable deceased donor kidney and have immunologically incompatible live donors that cannot directly donate a kidney to them, because they have high-titer DSA that are not amenable with desensitization, are often able to find suitable donors in a KPD program using a virtual crossmatch approach within 12 months of joining such program. Thus, KPD allocation using an approach based on acceptable mismatches is effective in identifying suitable live donors for some recipients within a relatively short time-frame.

Authorship

PF: data analysis, performance of the research and writing of the paper; SF: data analysis, performance of the research; CW: data collection and performance of the research; GT: performance of the research; LD: data analysis, performance of the research and writing of the paper.

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