Title page

Deceased donor-initiated Chains: first report of a successful deliberate case and its ethical implications

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"KIDNEY -Incorporating patients' preferences in kidney transplant decision protocols”

Abbreviations page

CDC, complement dependent cytotoxicity

CIK, chain initiating kidney

DBD, Donor after brain-dead

DEC-K, KPD started from DD kidney

DD, Deceased donor

DSA, Donor Specific Antibodies

ESRD, end-stage renal disease

HLA, human leucocyte antigen

KDPI, Kidney Donor Profile Index

KDRI, Kidney Donor Risk Index

KPD, Kidney Paired Donation

KT, kidney transplant

LKDPI, Live Kidney Donor Profile Index

NITp, Nord Italia Transplant program

NT, no-transplanted recipients

PNI, national program for immunized patients

UT, unlikely transplantable recipients

WL, waiting list

Abstract

Background: The utilization of deceased donor kidneys to initiate chains of living donor kidney paired donation (KPD) has been proposed, although the potential gain of this practice needs to be quantified and the ethical implications must be addressed before starting its application.

Methods: The gain of implementing deceased donor-initiated chains has been measured through a mathematical algorithm, using retrospective data on the pool of donor/recipient incompatible pairs at a single Center. Allocation rules of chain ending kidneys and characteristics/quality of the chain initiating kidney (CIK) are described.

Results: the quantification of benefit analysis showed that with a pool of 69 kidneys from deceased donors and 16 pairs enrolled in the KPD program, over a period of 3 years it is possible to transplant 8/16 recipients (50%). Following the approval of the Bioethical Committee of the Veneto Region and the revision of the allocation policies by the Italian National Transplant Center, the first successful case has been performed. The waiting time of the recipient (male, 53 yo) after entering the program for the CIK with a kidney donor risk index (KDRI) equal to 0.61 and a kidney donor profile index (KDPI) of 3%, was 4 days. His willing donor (female, 53 yo) with a living kidney donor profile index (LKDPI) of 2, donated 2 days later to a chain ending recipient (male, 47 yo,) who had been on dialysis for 5 years.

Conclusions: This is the first report of a deliberate deceased donor-initiated chain, which has been successfully performed. This has been made possible thanks to an extensive phase of evaluation of the ethical issues and allocation policy impact. This paper includes a preliminary efficacy assessment and the development a dedicated algorithm.

Introduction

Living donor renal transplantation is the most promising solution for closing the gap between organ demand and supply. Despite growing efforts to implement this option for patients with end-stage renal disease (ESRD), the percentage of living donations has been decreasing in the United States from 50.1% in 2000 to 38.2% in 2017 of the total number of kidney transplants (1).

Figures are different in the European countries, where the expansion of living transplantation programs is still underway. ABO-incompatible or KPD programs are not fully and uniformly developed: beside the Dutch and the UK programs, that have already successfully optimized these processes, other European countries such as Spain, France, Italy, Czech Republic, Austria, Belgium, Switzerland, Poland and Scandinavia have just started these programs or are striving to implement one.

In Italy, 2.221 kidney transplants have been undertaken in 2017 and among these 310 were from living donors, with an increase of 61 % compared to 2012 and 1.7 fold compared to 2007 (2), and desensitization techniques for AB0 incompatibility are now applied in the highest-volume centres. However, KPD programs have only been performed in few cases, mainly due to the low number of patients enrolled in such programs. Nevertheless, KPD seems to represent the best option for candidates with circulating human leucocyte antigen (HLA) antibodies directed against their willing donors.

Several options to expand KPD have been proposed in the last few years, with dissimilar applicability: 1. A proposal for a nationwide and international KPD registry and match run, using optimization algorithms to match pairs, including three-way matches; 2. The inclusion of altruistic donors to initiate chains of KPD: 3. The combination of KPD with desensitization to relax the requirement for a negative crossmatch for highly sensitized patients; 4. The inclusion of compatible pairs into small single-centre pools to achieve match rates that might even surpass those attainable in a nationwide list made up of only incompatible pairs; 5. List exchange and non-directed donation, where a living incompatible donor provides a kidney to a candidate on the deceased donor (DD) list and in return the list exchange intended recipient receives priority on the DD waiting list (WL) (3,4,5).

More recently, the utilization of DD kidneys to initiate living donor chains has been proposed (6, 7), hypothesizing that a pilot program would show a positive impact also on patients on the DD waiting list, improving the quality of kidneys allocated to waitlisted patients, independently from ethnicities and blood types. However, important issues when implementing such program may raise ethical and logistical concerns: 1. The parameters of prioritization in the WL for the CIK recipient, 2. The acceptable quality and risk characteristics of the donors of CIK, 3. The number of DD kidneys that might be used as CIKs, 4. The allocation strategies of the chain ending kidney, 5. The estimation of the quality of the living donor kidney compared to that of a DD kidney, 6. The risk for reneging of the living donors due to the non-

simultaneity of the operations, 7. The impact of cold ischemia time in the realization of the chains in large regions.

As previously stated by Wall et al (7), in order to be implemented, such an innovation needs to take into consideration all these challenges. Here we describe how the ethical and logistical concerns were addressed in order to perform the first case of DD-initiated chain.

Methods

Quantification of benefit

In order to measure the potential gain of the program and to establish the number of DD-CIK that could ideally be diverted from the standard waiting list, we used retrospective data on the pool of donor/recipient incompatible pairs at a single centre. We simulated the gain of implementing KPD transplants at a local level, starting KPD chains from a DD organ, continuing by means of consecutive donations among pairs of incompatible living donor-recipients, and ending with a transplant to a patient on the WL for a DD organ who does not have a willing donor.

Our sequential algorithm was previously described (8) and the details of the studied population are available as Supplemental Documents.

In our simulation, the recipient of the DD organ could be any of the ESRD patients (n=16) with an incompatible living donor who were not transplanted during the period. Receiving a transplant, even from a DD, would certainly represent a gain for those patients who were not transplanted, but one may argue that this policy would subtract organs from the pool available for waitlisted candidates. It should be pointed out, however, that the organ provided by the living donor of the last pair of the chain will terminate to a DD waitlisted patient. Therefore, at least in theory, waitlisted patients without a potential living donor do not suffer from the introduction of this allocation procedure also because the expected graft survival of a living donor kidney is higher than that of a DD organ (9). Nevertheless, there has to be some equity warranted for the waitlisted candidates with a lower probability of finding a compatible organ. We identified two categories of waitlisted candidates who merit special consideration. These are represented by recipients unlikely to be transplanted for immunological reasons (UT recipients) and by blood-type 0 recipients.

UT recipients were defined based on the classification of the NITp, which considers UT recipients those patients on the WL for more than 5 years or on dialysis for more than 7 years due to immunological reasons (PRA>80%, referred to either class I or class II HLA antigens). During the period of study, 35 UT recipients were listed at our Centre and were considered available for running the algorithm. UT recipients deserve absolute protection against any detrimental effect of the procedure, as also a favorable treatment to increase their chance of receiving an organ, because they have already experienced a long waiting time; blood-type 0 recipients, who may experience longer waiting time than other waitlisted candidates due to

the unbalanced distribution of blood-type 0 donors, should not be at a disadvantage. We therefore added three constraints to our algorithm. First, DD organs that were directly allocated to UT recipients were excluded from the algorithm, and we only considered organs allocated to patients in the standard WL. Second, whenever there was more than one living donor chain with maximal length, we select the one, if any, that ended with an UT recipient. Third, if a blood-type 0 organ was used to start the donor chain, then the chain had to end with either an UT recipient or return a blood-type 0 organ to the standard WL.

Allocation policy and characteristics of CIK

For a proper allocation of the CIK, the following immunological variables of donors and recipients were taken into account: AB0 identity, HLA typing for both class I (A, B, C) and class II (DP, DQ, DR) antigens;, unacceptable antigens were those with demonstrated single antigen beads assay (Luminex®) with MFI>3000.

Using DD kidneys for chain initiation by incorporating this program into the allocation algorithms would change patient selection. Indeed, even if the kidney at the end of the chain is returned to a patient on the DD donor waiting list, it would probably not be allocated to the patient who would have been at the top of the match list if this program had not been implemented. Taking due account of such a possible flaw, we defined for patients on the DEC-K program a DD allocation strategy that would not disadvantage specific patient categories with higher allocation priority. In the inter-regional NITp program, that covers an area of more than 19 million inhabitants, DD kidneys are allocated to a single WL with an overall number of about 2.800 patients. Recipients in the DEC-K program could be selected for any given organ available in the NITp area. Such an allocation takes place only if not competing with high-priority national programs such as the urgency program (ESRD patients with lack of vascular access for dialysis), the PNI (national program for hyper-immunized patients), the kidney-pancreas program, or other inter-regional priorities (0-1 HLA mismatched or UT recipients).

The quality of the CIK was calculated with the KDRI and the KDPI calculator, and the score was expected to be comparable with the LKDPI of their willing living donor. Moreover, the DDs were defined as standard in terms of infectious or neoplastic risk.

The living donor kidney ending the chain was assigned according to the Italian allocation policies: in the absence of recipient in emergency list or PNI compatible patients, the graft was allocated with the NITK4 algorithm, which takes into account blood type, HLA matches and time on dialysis (10).

Logistical and ethical issues

In order to keep as short as possible the cold ischemia time of the CIK, the pilot program was limited to a single Centre (Padua University Hospital) and its region of procurement (Veneto region). A CDC crossmatch was performed with a recipient current serum.

The ethical implications were clearly and extensively exposed to the Bioethical Committee of the Veneto Region (exempting further IRB approval) obtaining a favorable opinion in November 2017, and the program was defined to conform to the principle of benevolence, with high social and healthcare value. A specific informative and consent form for the recipients and their willing donors was elaborated with the collaboration of psychologists, bioethical and legal medicine experts. It was explained to the involved subjects by two physicians of the Transplant team (one surgeon and one nephrologist). When the CIK became available, before starting the surgical procedures, a confirmation of the consent was requested to both subjects, to avoid the risk of withdrawal of the living donor.

Results

Quantification of benefit

Results of the retrospective simulation are summarized in Table 1. Given a cohort of 16 incompatible pairs, and a pool of 69 standard DDs allocated to the Padua Transplant Centre, it turns out that by using 7 grafts from DDs to start a chain, it was theoretically possible to transplant 50% of the patients who would have not been otherwise able to receive a transplant in a time span of three years. This means that only 10% of the entire pool of standard grafts available was utilized to enter the program.

Moreover, in most of the cases (6/7) the chains ended to a UT recipient who therefore received a living donor kidney instead of a DD organ.

Report of the first case

The recipient was a 53 year old male, affected by ESRD due to IgA nephropathy who had received a first kidney transplant from a deceased donor in 2003 and had lost his graft function for chronic damage. He restarted hemodialysis in May 2017. His blood type was A negative, and he had received previous blood transfusions. His pre-transplant workup displayed no contraindications to a second kidney transplant. His 53 year old wife (blood type A positive) intended to donate him a kidney and presented no clinical or psychological contraindications to donation. Although the patient was not broadly sensitized (PRA class I: 50%; PRA class II: 65%) the couple had CDC positive crossmatch, and the Luminex® single bead assay demonstrated DSA (anti-A2, MFI: 20.185; DQ06:03, MFI: 1.368). Moreover, HLA-A2 was a repeated mismatch with his previous transplant. The couple was enrolled in the cross over national program KPD in October 2017, and the patient was active in the WL for a

DD since then. The couple was offered the option to enter the DEC-K program in February 2018, and completed the psychological and immunological work-up on March 9th 2018.

Four days later, a deceased CIK was offered to the patient. The donor was a 28 year old white male, height 183 cm, weight 94 kg, DBD due to a head trauma, with no history of hypertension or diabetes, HCV negative, and serum creatinine of 0.57 mg/dL (KDRI 0.61, KDPI 3%), 2 HLA-A, 2 HLA-B, 1 HLA-DR, 1 HLA-DQ, 2 HLA-DP mismatches.

The kidney transplant was performed the next day with standard technique; cold ischemia time was 6 hours and the post-operative course was uneventful, with immediate recovery of renal function. The patient was discharged on post-operative day 9 with a serum creatinine of 0.9 mg/dL.

Two days after her husband's transplant, the wife underwent laparoscopic left nephrectomy, without complications, and she was discharged on post-operative day 3.

The living donor kidney was allocated following the NITp algorithm to a WL recipient (male, 47 yo, group A, positive). The chain-ending patient was at his first transplant, on dialysis since April 2013, affected by Schoenlein Henoch purpura, height 165 cm, weight 62 kg. The LKDPI calculated for the pair was 2, being the donor non hypertensive, non-smoker, with eGFR 102 ml/min, BMI 20.5, 2 HLA-B mismatches and 1 DR mismatch.

The kidney transplant procedure was performed with a cold ischemia time of 1 hour and 45 minutes, renal function recovered promptly The CIK recipient did not display any complication and was discharged on post-operative day 10, with a serum creatinine of 1.0 mg/dL.

Discussion

The utilization of DD grafts as source of CIK to start chains has been proposed previously (6 7). The underlying ethical issues have been detailed and can be summarized as follows: 1. The proper allocation strategy of a CIK from a DD and of the chain ending kidney, 2. The value of exchanging a living donor kidney for a DD kidney, 3. The risk of living donor withdrawal, 4. The consent of the parties.

The precedent for using a DD kidney in kidney exchanges has been reported by Delmonico et al (11). Their experience, however, can be better described as a List Exchange procedure, since "following transplant of the kidney from the living donor to the highest ranking appropriate individual identified by the transplant center's list, the incompatible recipient for whom the donor kidney was originally intended receives the right of first refusal for the next AB0 identical (crossmatch negative) deceased donor kidney available within the Region".

Contrary to the present report, in the list exchange one will donate before his intended recipient receives an organ from a DD, and the degree of uncertainty of the prioritization in the WL, mostly in case of highly sensitized patients as those involved in our program would become an ethical concern when asking a donor to anticipate his donation.

Nevertheless, the allocation strategy of the chain ending kidney was following the rules of their match run, and a similar approach has been used in our experience, according to the allocation strategy of the NITp (NITK4 algorithm).

More challenging, in our opinion, is the selection of the adequate CIK from a DD. This decision should take into account the expected graft survival and the risk of disease transmission of a DD kidney compared to a living donor kidney. Our protocol, therefore, considers the KDRI and the KPDI score of the DD kidney and compares them with the LKDPI (12) of the subsequent matches; it also excludes those donors with risk for transmissible disease. The predictive value of the LKDPI compared with KDPI of DD has been recently validated in a European cohort, and based on these findings, corresponding subgroups of LKDPI and KDPI showed comparable graft survivals (13). Nevertheless, each CIK and LD should be evaluated comprehensively, taking into account several clinical aspects which are not currently or only partially included in these indexes such as male/female and donor/recipient weight ratio, HLA mismatches, pre-emptive status of the recipients, specific comorbidities of the donors. In the reported case, the HLA match was not high even though better than that of the intended living donor (8MM for the CIK vs 10MM for the intended living donor). However, the patient was sensitized against her HLA antigens to such an extent that even the CDC cross-match turned out to be positive. When applying the immunological analysis to the HLA antigens considered conventionally (HLA loci A, B and DR), the recipient had 5 MM with the CIK donor, whereas he had 6 MM with the intended LD. Although the difference in the outcome between a 5 and a 6 MM is probably not substantial, it has to be observed that: 1. The class II DR mismatch are known to be associated with worse outcome (14) ; 2, the DQ mismatch was 1 with the CIK donor, compared with 2 of the original LD, and this is also quite relevant if one considers that sensitization against DQ antigens is the most frequent following transplantation; 3. The KDPI and LKDPI scores, although imperfect, include and give weight to HLA MM; therefore the importance of the HLA match is somehow taken into account when the scores are calculated. 4. Finally, the requirement for a high degree of HLA compatibility would have unavoidably impacted negatively on the waiting time, certainly exceeding the “4 days” of waiting that we have been able to offer to our case. The shortening of the waiting time and dialysis duration is known to impact significantly on the graft and patient survival and transplantation outcome, and this fact should be considered in addition to the degree of HLA match.

One further argument to address is the quantification of the diversion of kidneys from patients on the WL. The CIK may be allocated to any recipient with an incompatible living donor, irrespective of his/her PRA. Indeed, even patients with low PRA may find themselves with an incompatible living donor. In our simulation, we have observed that in the retrospective population of DD and incompatible pairs, only 10% of the standard DD kidneys (7 grafts)

would have been diverted from the WL allowing to transplant 50% of the incompatible pairs. Furthermore, our approach would have returned to the donor pool 7 additional high quality grafts (from living donors), which would have been transplanted into UT or blood group 0 patients. The chain ending kidney (from LD) will be allocated to a wait-list candidate, preferentially to UT recipients, applying the above-mentioned NITK4 allocation policy. Such an allocation policy is the one applied also to the chain ending kidney started from altruistic donors. The usefulness of the proposed program results undeniable, since it increases the overall number of kidneys available for transplantation and, consequently, the aggregate quality and quantity of life of ESRD patients.

One last important issue to address is the management of the consent process for all the involved subjects. The key points of an adequate information have to make clear to the prospective living donors and CIK recipients the level of prioritization that the program allows, the quality of the DD grafts considered and the respect of their freedom to withdrawal at any time of the program. It emerges of paramount importance to avoid the occurrence of donor reneging, given that the simultaneity of more surgeries would be logistically very difficult to achieve within the DEC-K program. To minimize this risk, both the donor and the recipient of each pair undergo an extensive educational process held by two very experienced transplant physicians (one surgeon and one nephrologist) that will enable them to fully comprehend and appreciate the content of the DEC-K program. The educational process, therefore, will need to be very extensive and will require an amount of time which is neither predictable nor easy to standardize even in a single center, as it will depend on psychological and attitudinal features of both patients and physicians. We believe that experienced surgeons and nephrologists should be dedicated to describing the program to the pairs and should clarify and give answers to their specific queries and address each concern raised. Being far the possibility to make perfectly standardized such a procedure, in our opinion the requirements of the informative process should include as a very minimum:

- a two-steps psychological evaluation
- the commitment by two experienced physicians to explain the program
- a third-party person or committee aimed to assist the pair in their decision process, whose ultimate objective is to assess their degree of understanding of the program and their willingness to participate.

However, it is noteworthy that, differently from in list exchanges, patients participating in a chain of donations receive a kidney before her/his donor donates an organ to another patient. Moreover, for each incompatible pair who can start a chain of donations, it is possible to compute in advance which is the optimal chain to perform, making the logistics easier. As far as real crossmatches, these can be performed as early as the results of the virtual crossmatch are available. In this way, whenever a DD CIK becomes available, there is no need to perform the crossmatch. In agreement with the existing national policy, sera from potential recipients are collected every three months, and an updated assessment of the immunological profile is undertaken as soon as new samples are available. Although the maximum flexibility is applied within the protocol in terms of logistics, the most likely option is that the kidney will travel. This is not expected to be associated with detrimental consequences in terms of cold ischemia injury, depending evidently on the extent of the territory involved in the program. In this first case, we selected to use the local pool of DD in order to minimize the cold ischemia time (in the reported case CIT was 5 hours), whereas the

transplant from LD could be organized similarly to what happens when the chain starts with an altruistic donor (15).

It has to be acknowledged that unspecified LKD to initiate exchange program pose several advantages compared to a program of DD initiating chains, as well as fewer (or at least different) ethical dilemmas, for many reasons: all patients receive a LD, WL recipients will always benefit, it is logistically easier to plan. Nevertheless, there are several differences in the legislation between countries, and for some Countries, for example Germany, altruistic donation is prohibited by law. In addition, in some Countries such as Italy, incentive to start donating altruistically, i.e. soliciting donation through social media or emphasizing the need for a kidney transplant in favor of a specific patient, is not allowed by law, since living donation can take place only in the context of a long-lasting emotional relation or in the frame of anonymity.

In our case, the motivation to explore further options to expand domino chains between incompatible pairs was represented by the scarcity of unspecified LKDs and the Italian law constraints mentioned above. Nevertheless, the opportunity to include deceased donors to implement Kidney Paired Donation may supplement and complement an established KPD program through kidney paired exchanges and altruistic donors. (16)

The present report represents, to the best of our knowledge, the first case of a chain of kidney transplants initiated by a DD kidney. Differently from previous experiences (17), this case was deliberate and programmed following a straightforward process aimed to address ethical and logistical issues. The extension of the program to a national level will confidently allow to optimize the allocation strategies and obtain longer chains, thus minimizing waiting times for highly immunized recipients with incompatible willing donors.

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References

1. OPTN data as of January 12, 2017 (https://optn.transplant.hrsa.gov/data/view-data-reports/national-data)

2. CNT (Centro Nazionale Trapianti) National Data, Italy. http://www.trapianti.salute.gov.it/imgs/C_17_pubblicazioni_2591_allegato.pdf

3. Roth AE, Sonmez T, Unver MU, et al. Utilizing list exchange and non-directed donation through “chain” paired kidney donation. Am J Transplant 2006; 6:2694-2705

4. Veale JL, Capron AM, Nassiri N et al. Vouchers for future kidney transplants to overcome “chronological incompatibility” between living donors and recipients. Transplantation 2017; 101 (9): 2115-2119.

5. Liu W, Treat E, Veale JL et al. Identifying Opportunities to Increase the Throughput of Kidney Paired Donation. Transplantation 2015; 99(7): 1410-5.

6. Melcher ML Roberts JP, Leichtman AB, et al. Utilization of deceased donor kidneys to initiate living donor chains. Am J Transplant. 2016 May;16(5):1367-70.

7. Wall AE, Veale JL, Melcher ML. Advanced donation programs and deceased donor-initiated chains- 2 innovations in kidney paired donation. Transplantation 2017; 101 (12): 2818-2824

8. Silvestre C, Nicolò A. Cornelio C et al. Potential gain of utilizing kidneys from deceased donors to initiate "chain" kidney paired donations: quantification of benefit through a real-world retrospective analysis. Transplant Int 2017; 30 S2:82

9. Hart A, Smith JM, Skeans MA, et al. Kidney. Am J Transplant. 2016 Jan;16 Suppl 2:11-46

10. Poli F, Cardillo M, Scalamogna M. Clinical relevance of human leukocyte antigen antibodies in kidney transplantation from deceased donors: the North ItalyTransplant program approach. Hum Immunol. 2009 Aug;70(8):631-5.

11. Delmonico FL, Morrissey PE, Lipkowitz GS et al. Donor Kidney Exchanges. Am J Transplant 2004; 4:1628-1634

12. Massie AB, Leanza J, Fahmy LM et al. A risk index for living donor kidney transplantation Am J of Transplant 2016;16:2077-2084

13. Rehse G, Halleck F, Khadzhynov D et al, Validation of the living kidney donor profile index in a European cohort and comparison of long-term outcomes with US results. NDT 2018; 1-8

14. Shi X, Lv J, Han W, et al. What is the impact of human leukocyte antigen mismatching on graft survival and mortality in renal transplantation? A meta-analysis of 23 cohort studies involving 486,608 recipients. BMC Nephrol. 2018, 19(1):116

15. Bofill M, Calderon M, Castro F et al. The Spanish kidney exchange model: study of computation-based alternatives to the current procedure. Artificial Intelligence in Medicine. AIME 2017. Lecture Notes in Computer Science, vol 10259. Springer, Cham

16. Flechner SM, Thomas AG, Ronin M et al. The first 9 years of kidney paired donation through the national Kidney Registry: Characteristics of donors and recipients compared with National Live Donor Transplant Registries. Am J Transplant 2018;18(11):2730-2738

17. Flechner SM, Leeser D, Pelletier R et al. The incorporation of an advanced donation program into kidney paired exchange: initial experience of the National Kidney Registry Am J Transplant 2015; 15:2712-2717

18. Pierobon ES, Sandrini S, De Fazio N, et al. Optimizing utilization of kidneys from deceased donors over 60 years: five-year outcomes after implementation of a combined clinical and histological allocation algorithm. Transpl Int. 2013 Aug;26(8):833-41.

Deceased donor kidneys used to start a chain	7/69 (10%)
NT patients who received an organ	8/16 (50%)
UT patients who received an organ	6/35 (17%)
Living donor kidneys returned to the standard waiting-list.	1

Table 1: Results of the retrospective analysis