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An algorithm for cadaver kidney allocation based on a multivariate analysis of factors impacting on cadaver kidney graft survival and function

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Abstract The large imbalance between cadaver kidney supply and demand makes the implementation of equitable and effective organ allocation systems an urgent need. This has triggered a revision of the criteria used so far for cadaver kidney allocation within the North Italy Transplant program, not least in the light of the many changes that have occurred recently with respect to broader criteria for admission of patients to the waiting list, donor selection, tissue-typing methods, organ preservation and immunosuppressive protocols. We based the critical revision of our cadaver kidney allocation algorithm on univariate and multivariate analysis of a number of immunological, clinical, social and administrative factors that impacted on the transplant outcome in 2,917 patients transplanted in the 12 transplant centers operating within our organization from 1 January 1990 to 30 September 1997. This analysis indicated that younger donor age, absence of pretransplant transfusions, patient dialysis center and level of HLA match showed statistically significant positive associations with graft survival. Younger donor age and male donor gender showed a statistically significant association with excellent graft function at 4 years. The results of this analysis were used to develop a new computer-assisted version of our adult kidney allocation algorithm. It works in two steps (local pool first, then the entire waiting list) and four levels (0–1 HLA MM, PRA +; 2 HLA MM, PRA +; 0–1 MM, PRA–; 2–4 HLA MM, PRA–); within each level, selection takes into account waiting time and age difference from donor age. The evaluation of 731 transplants allocated in 19 months with the new algorithm, as against 698 transplants allocated in the preceding 19 months according to the previous algorithm, showed a significantly higher proportion of recipients who had been on the waiting list for more than 3 years (33.2% versus 22.6%). The use of the new algorithm was also associated with a significantly increased number of transplanted alloimmunized patients (18.8% versus 9.2% with the previous algorithm) and recipients with 0–1 HLA mismatches (22% versus 14.3%). Furthermore, the number of kidneys used locally has steadily increased. Differences in 6-month graft survival and percentage of patients with excellent function at 6 months were not statistically significant in recipients transplanted with the new versus the previous algorithm. Survivals were 93.7% versus 91.8%. Percentages of patients with excellent renal function were 69.9% and 71.8%, respectively. These preliminary data suggest that the new algorithm improves HLA match and reduces the number of patients on the waiting

list for 3 or more years without determining significant modifications of 6-month graft survival and function. Moreover, it facilitates the achievement of a fair local balance between organs retrieved and transplanted, the compliance of operators with objective allocation rules and the documentation of the whole allocation process.

Key words HLA-matching · Allocation criteria · Kidney transplantation

Introduction

The large imbalance between supply and demand for cadaver kidneys has triggered a revision of the criteria used so far for cadaver kidney allocation within our transplant program, with the aim of implementing a more equitable and effective kidney allocation system [3, 4, 8, 10, 11]. We based the critical revision of the North Italy Transplant program (NITp) [6] cadaver kidney allocation algorithm on an analysis of the relative impact of a number of immunological, clinical, social and administrative factors on transplant outcome in patients who had received transplants within the NITp from 1 January 1990 to 30 September 1997 [7]. On the basis of the results of this analysis, we implemented a new cadaver kidney allocation algorithm, which was named NITK3 to indicate that it is the third kidney allocation algorithm used in the NITp.

Here we report the results obtained in the 19 months after the implementation of NITK3 and compare them with those collected in the 19 months, immediately before, when the previous algorithm (NITK2) was still in use.

Materials and methods

The North Italy Transplant program

The NITp [6] is a transplant organization established in 1972, which serves n area with 18 million inhabitants, 48 procuring hospitals, 37 transplant centers located in 15 hospitals (12 adult kidney, 3 pediatric kidney, 5 kidney and pancreas, 7 liver, 6 heart and 4 lung transplant centers), and 119 dialysis centers. NITp serves a defined territory on the basis of official contracts issued by the Regional Health Authorities in collaboration with the Reference Center. This implies that patients resident in the NITp regions have free access to the waiting list, whereas nonresidents cannot exceed a predetermined proportion of the waiting list. Although operating under common immunological evaluation and organ allocation policies, centers enter patients on the waiting list according to slightly different criteria.

The NITp has a Reference Center in Milan, which manages the waiting lists, performs immunological evaluation of recipients and donors, allocates organs, organizes transports, collects data from transplant candidates, donors and grafted patients, sets up protocols with the operative units, develops information campaigns, provides psychological support to donor families, and promotes research and development related to organ procurement and transplantation.

Management of the waiting list

Patients with end-stage renal failure who are suitable for kidney transplantation are admitted to the NITp waiting list with no age limit. Before 1998, every transplant center could enroll any NITp resident plus a quota of nonresidents not exceeding 25% of its own list, while since 1998 every transplant center has been allowed to enroll up to 250 patients, with priority given to residents.

NITK3 description and validation

NITK3 works in two steps and on four levels.

In step 1 the first kidney is offered to the patients belonging to the local pool. The local pool includes all patients resident in the NITp area who are on the waiting list of the Transplant Center responsible for organ retrieval and transplantation in the specific NITp retrieval zone where the donor has been procured.

Level 1 identifies ABO-identical or -compatible patients with PRA > 30% (auto-antibodies excluded) or re-transplants, with 0–1 HLA-A, B, DRB1 mismatches with the donor.

Level 2 identifies the same categories of recipients with 2–4 HLA mismatches, divided into 2 sublevels: 2 and 3–4 mismatches. This level considers only sensitized patients with lymphocytotoxic antibodies of clearly identified specificity and the forecast of negative cross-match. The software gives an indication if the screening of the patient sera has identified antibodies specifically directed against donor's antigens and, for re-transplants, the presence of the same incompatibilities of previous grafts to exclude these patients.

Level 3 identifies nonsensitized patients and first transplants with 0–1 HLA-A, B, DRB1 mismatches with the donor.

Level 4 selects the same categories of possible recipients with 2–4 HLA-A, B, DRB1 mismatches. In each level, patients are ranked according to waiting time, with priority for those on the waiting list for more than 3 years, which was the median time on the NITp list in September 1997. Within the group of possible recipients with the same waiting time class, priority is given to the patients closest to the donor's age; this is aimed at limiting the allocation of kidneys from older donors to young recipients and vice versa. When no patient from the local pool is found in these four levels, instead of allocating a kidney to patients with 5 or 6 mismatches, the transplant center is invited not to transplant the kidney concerned, and it is put at the disposal of the entire waiting list. In such cases a payback is assigned to the transplant center giving up the available kidney.

In step 2, the second kidney is allocated following the rules adopted for the first kidney, the entire waiting list, including the local being considered. However, if there is a negative balance between transplants performed and organs retrieved by a specific transplant center, the duty officer can select only from the patients registered in that center and they are listed according to the rules above.

The NITp duty officer proposes the two best possible recipients.

To perform a validation of NITK3, we compared some features and outcomes in the first series of 731 consecutive transplants per-

Table 1 Demographic characteristics of grafts and Kaplan-Meier analysis of 12-month graft survival during 19 months before[a] and after[b] the implementation of NITK3

Time	Before	After	*P*-value
Algorithm	NITK2	NITK3	–
Number of transplants	698	731	–
Kaplan-Meier analysis of 12-month graft survival (%)	91.8	93.7	n.s.
Percentage of patients with grade A renal function at 6 months	71.8	69.9	n.s.
Percentage of patients on waiting list for > 36 months before transplant	22.6	33.2	0.001
Percentage of kidneys used locally	33.0	48.9	0.001
Percentage of patients with 0-1 HLA-A, B, BRB1 mismatches	14.3	22.0	0.003
Percentage of retransplanted patients	6.0	7.2	n.s.
Percentage of transplanted patients with panel reactive antibodies	9.2	18.8	0.001

[a] February 1996 to September 1997
[b] October 1997 to April 1999

formed during October 1997 to April 1999 with those of 698 consecutive transplants allocated with NITK2 during March 1996 to September 1997. Variables considered included: graft survival and grade A function at 6 months, proportions of recipients with waiting time > 3 years, of recipients with PRA > 30% and re-grafts, of recipients with 0–1 HLA mismatches, and of kidneys that were used locally.

Data analysis

Graft survival according to the covariates was calculated by the Kaplan-Meier method. The significance of the associations was tested by the log-rank test. The Chi-square test was used to compare the percentages of patients transplanted according to NITK02 and to NITK03 with respect to different parameters. The data were analyzed with the Statistical Analysis System package (SAS Institute, Cary, N.C.).

Results

A preliminary evaluation of 731 transplants allocated in 19 months with the new algorithm compared with 698 transplants allocated in the preceding 19 months according to the previous algorithm showed a significantly higher proportion of recipients who had been on the waiting list for more than 3 years (33.2% versus 22.6%). The use of the new algorithm was also associated with a significantly increased number of transplanted alloimmunized patients (18.8% versus 9.2% with the previous algorithm) and recipients with 0–1 HLA mismatches (22% versus 14.3%).

With NITK3, the proportion of kidneys locally used increased to 48.9%, as against 33% with NITK2.

Differences in 6-month graft survival and percentage of patients with excellent function at 6 months were not statistically significant in recipients transplanted according to the new versus the previous algorithm. Survivals were 93.7% versus 91.8%. Percentages of patients with excellent renal function were 69.9% and 71.8%, respectively (Table 1).

Discussion

In a previous study [7], we evaluated the impact of a number of immunological, clinical, social and administrative factors on cadaver kidney graft survival and function in the setting of the North Italy Transplant program, with the ultimate aim of improving the effectiveness, equity and transparency of our allocation policy. All patients who received transplants during 1990–1997 were investigated. The investigations were triggered by the concern that factors showing important effects in the past might have lost their importance owing to recent changes in immunosuppressive protocols and in HLA-typing techniques [5] and to the adoption of extended criteria for patient admission to the waiting lists and for donor acceptance.

Of the factors considered [7], donor age, HLA matching and the administration of transfusions had major impacts on transplant outcome. These findings were used to revise the cadaver kidney allocation algorithm for adult patients, which was named NITK3. This was set up by a specific working group. This group started its activity with retrospective testing of an allocation algorithm based on a scoring system [11]. However, it was found that in several instances the results did not reflect the major principles the group wanted to promote, the system being too rigid [9].

Therefore, the group considered an allocation system based on a sequence of levels identifying suitable prospective recipients meeting the principal requirements who were subsequently ranked for secondary variables. Besides the general condition of donor and patient at the time of transplantation, the ABO and HLA matches, the cross-match result, and the presence of lymphocytotoxic antibodies in the patient's sera [1] were taken into account. Other factors, which were relevant for ethical reasons, such as donor/recipient age matching and time on the waiting list, were also considered [2, 4, 8, 11]. Finally, the balance between organs procured and transplanted within each community was ascertained,

to gather support and participation in organ procurement.

The results obtained with NITK3 in the first 19 months after its implementation indicate that the main goals of performing transplants in better HLA-matched cases and in difficult patients has been achieved. In fact, significantly higher proportions of patients with a waiting time longer than 3 years, of sensitized recipients and of patients in the best HLA-matching level have been transplanted than in the preceding year. Furthermore, the number of kidneys used locally has steadily increased.

We were concerned about the fact that transplanting kidneys to "difficult" patients could worsen the results. On the contrary, the results are satisfactory. Under this new allocation policy, there is less place for the clinical choice of the candidates at transplantation. This imposes waiting list management with special attention to the patients with long waiting times, as was suggested by the ad hoc Council of Europe Expert Group (draft, 1998).

We believe that NITK3 has improved the equity and transparency of our system and the quality of the results, with due respect for HLA matching and the promotion of organ retrieval.

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