Kidney graft loss in children: implications for program development

Evidence

Études

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Abstract

Background: Graft survival in children who undergo kidney transplantation is lower than that in adults. The objective of the study was to review the experience of the first 22 years of operation of the regional pediatric kidney transplantation unit for Atlantic Canada, based at the IWK–Grace Health Centre, Halifax, and to use the results to improve graft survival.

Methods: All cases of kidney transplantation performed at the centre from 1971 to 1992 were reviewed and the data compiled with the use of a predetermined database outline. Data for first transplants were analysed and compared with those in North American databases. Of the 40 graft failures, 19 (48%) occurred within the first 3 months after transplantation, a rate similar to that at other centres. The overall survival rates tended to be slightly lower than those of international databases. The introduction of cyclosporine A as an immunosuppressant, in 1985, did not provide the expected marked improvement in survival. Infection frequently accompanied acute rejection, and there was a delay in treatment of infections and rejection after discharge home. On the basis of these preliminary findings, several program changes were made: 1) a sequential immunosuppression protocol was implemented, 2) the intensity of the medical surveillance was increased for the first 3 months after transplantation, with aggressive treatment of infections and rejections, 3) a dedicated pediatric transplantation team was established as a subset of the adult team and 4) pediatric-specific selection criteria for cadaver donors were formulated. After these changes were implemented, data were collected and analysed up to June 30, 1997.

Results: Graft survival rates at 1, 2 and 5 years improved dramatically. After the beginning of 1993, there were only 2 graft losses among 22 transplants. Only one of these occurred in the first 3 months, and it was due to recurrent disease. Twenty-four rejection episodes occurred (10 in the first 3 months after transplantation), but all were reversed easily with high-dose steroid therapy.

Interpretation: Sequential immunosuppression with close medical surveillance and early aggressive treatment of infection and rejection contribute to a marked improvement in kidney graft survival in children.

Résumé

Contexte : La survie du greffon rénal est plus faible chez les enfants que chez les adultes. L'étude visait à revoir l'expérience des 22 premières années de fonctionnement de l'unité régionale des transplantations rénales pédiatriques de la région de l'Atlantique, rattachée au Centre de santé IWK–Grace de Halifax, et à utiliser les résultats pour améliorer la survie du greffon.

Méthodes : On a étudié tous les cas de transplantations de rein réalisées au Centre de 1971 à 1992 et compilé les données au moyen d'une base de données schématique prédéterminée. On a analysé les données relatives aux premières transplantations pour les comparer aux données contenues dans des bases nord-

américaines. Sur les 40 échecs, 19 (48 %) greffes ont échoué dans les trois mois qui ont suivi la transplantation, taux semblable à celui d'autres centres. Les taux généraux de survie avaient tendance à être légèrement moins élevés que ceux qu'indiquent des bases de données internationales. La mise en service de la cyclosporine A comme immunosuppresseur en 1985 n'a pas amélioré la survie autant qu'on s'y attendait. La crise de rejet était souvent conjuguée à une infection et il y a eu des retards dans le traitement des infections et des crises de rejet après la libération des patients. En se fondant sur ces constatations préliminaires, on a apporté plusieurs modifications au programme : 1) on a mis en œuvre un protocole d'immunosuppression séquentielle, 2) on a resserré l'intensité de la surveillance médicale au cours des trois premiers mois après la transplantation et traité agressivement les infections et les crises de rejet, 3) on a constitué une équipe spécialisée en transplantation pédiatrique comme sous-ensemble de l'équipe pour adultes et 4) on a élaboré des critères de sélection spécifiques pour la pédiatrie lorsque les dons provenaient de cadavres. Après avoir mis en œuvre ces changements, on a recueilli et analysé des données jusqu'au 30 juin 1997.

Résultats : Les taux de survie de la greffe à un, deux et cinq ans se sont améliorés de façon spectaculaire. Après le début de 1993, on n'a enregistré que deux échecs sur 22 transplantations. Un seul de ces échecs est survenu au cours des trois premiers mois, et il était attribuable à une maladie récurrente. Il y a eu 24 crises de rejet (10 au cours des trois premiers mois après la transplantation), mais on a pu les contrôler facilement au moyen d'une thérapie à forte dose de stéroïdes.

Interprétation : L'immunosuppression séquentielle conjuguée à une surveillance médicale rapprochée et à un traitement agressif précoce contre l'infection et le rejet contribuent à améliorer considérablement la survie des reins transplantés chez les enfants.

Kidney transplantation is the preferred treatment for children with chronic renal failure and is superior to long-term dialysis.[1] Furthermore, kidney transplantation at any age gives improved quality of life and a survival rate equal to or better than that among children receiving dialysis. If transplantation is done before skeletal growth is compromised, many children reach and maintain normal height, head circumference, motor skills and mental development. Children who survive longer than 10 years with a functioning renal graft may look forward to having an active family, social, sexual and work life.

Graft survival in children who undergo kidney transplantation is lower than that in adults.[2] There are several reasons cited: the higher incidence of postoperative renal vascular thrombosis in children,[3] the increased incidence of graft rejection with the use of immunosuppression programs developed for adult transplantation,[4] the greater incidence of congenital renal and urologic tract abnormalities seen in children with chronic renal failure, the poor performance of donor organs from children under the age of 6 years, which previously have been used as the preferred graft in children,[5] and the high rate of noncompliance with drug therapy among adolescents.[6,7]

In a pediatric transplantation program, goals for improvement should include reduced rates of illness and death, improved allograft survival, and normalization of somatic and psychologic growth and development. Between 1990 and 1992 a detailed review of our pediatric kidney transplantation program led to changes that were associated with a marked improvement in graft survival. In this paper we report our experience and describe how the results were used to improve organ survival.

Program review

The IWK–Grace Health Centre, Halifax, is the only hospital providing kidney transplantation to children in Atlantic Canada, a geographic area with about 3 million people. Pediatric transplantation has been performed here since 1971 as part of a much larger adult program based at the Queen Elizabeth II Health Sciences Centre. Children represent about 10% of the total transplant recipients. Every child in renal failure is considered a candidate for transplantation, as we have adopted inclusion criteria rather than exclusion criteria for our transplantation program.

All patients less than 18 years of age who underwent kidney transplantation at the centre between 1971 and June 30, 1997, were included in our program review. Ninety-one children (average age 10.3 years and male: female ratio 51:40) received 123 transplants over this time. Of the 123 grafts, 91 were first transplants, 27 were second

transplants and 5 were third transplants. In this review, we report and analyse data only for first transplants. A team of transplantation surgeons, based at the Queen Elizabeth II Health Sciences Centre, performed the surgical procedures at the IWK–Grace Health Centre and managed the surgical care and complications. They followed the patients after transplantation along with the medical team from the Division of Pediatric Nephrology. Each child had a preoperative assessment consisting of one or both of renal imaging and biopsy to establish the primary renal disease as well as imaging of the lower urologic tract to establish bladder integrity. All children had HLA matching, blood grouping, lymphocyte cultures, cytotoxic antibody testing and viral evaluation for cytomegalovirus (CMV), Epstein–Barr virus, human herpesvirus type 6, hepatitis viruses B and C, and HIV, as tests became available. Living related donors had a standard evaluation.

Before 1990, as in other North American centres, we followed an immunosuppressive protocol similar to adult programs, merely modifying dosages of immunosuppressants and other medications for children according to body size. In 1990 we began a review of our transplantation program with the goal of providing improved organ survival for our patients. During the period of review 2 immunosuppressive protocols were used: azathioprine (Imuran; Burroughs Wellcome Inc., Kirkland, Que.) from 1971 to 1984 and cyclosporine A from 1985 to 1992. Azathioprine was used at a dose of 1.5 to 2 mg/kg, started at the time of transplantation. All patients required prednisone therapy for an indefinite period. In 1985 cyclosporine A replaced azathioprine as the main immunosuppressant. Patients received azathioprine for 1 month and prednisone for a variable period as adjunctive therapy. Rejection episodes were treated by pulsing with glucocorticoids.

For this clinical review, we collected the historical data by reviewing the charts of all children who underwent kidney transplantation at the IWK–Grace Health Centre between 1970 and 1992. The chart reviews were performed by trained personnel not related to the patient's care, and charted information was considered as the sole correct source of historical data. The data included the patient's age, primary disease, HLA matching, surgical information, survival and, when applicable, the reason for graft failure. Graft loss was categorized as immunologic (hyperacute, acute or chronic rejection), surgical or medical (which includes renal vein thrombosis) or as due to noncompliance with drug therapy. In cases in which the patient died, we reviewed the autopsy results.

Analysis

We calculated 1-, 2- and 5-year Kaplan–Meier allograft survival estimates for the period during which azathioprine was used, the period during which cyclosporine A was used and the period after program changes were implemented (1993 to June 30, 1997). One-year estimates were plotted. We tested differences in survival over the 3 periods using a log-rank test (Mantel–Cox). Survival time was censored if the graft was functioning at the time of death or at the end of the study period, or if the patient was lost to follow-up after transfer to the adult service (3 cases). A test for linear trend in survival estimates over the 3 periods was also done.[8] We made informal comparisons with survival estimates from the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS)[4] and the Canadian Organ Replacement Registry (CORR)[9] using confidence intervals for Kaplan–Meier estimates of survival at 1, 2 and 5 years. Using "exact" logistic regression for stratified 2×2 tables, we tested the association between the presence of HLA mismatching and failure of cadaver donor grafts in the azathioprine and cyclosporine A periods. We used an exact test for an $n \times 2$ contingency table (i.e., a test of independence of rows and columns) to compare the frequencies of causes of organ loss in these 2 periods[10,11] (LogXact-Turbo, Cytel Software Corporation, Cambridge, Mass., 1993).

Results

There were 34 patients who received first transplants during the azathioprine period and 35 in the cyclosporine A period. The proportions of living related donors were 29.4% and 37.1% respectively. Of the cadaver donor organs, 44 matched at least one HLA antigen, and 10 were complete mismatches.

There were 23 graft losses in the azathioprine period and 17 in the cyclosporine A period. Comparisons with CORR and NAPRTCS data from the time of the beginning of their data collection (1981 and 1987 respectively) to the end of our cyclosporine A period (end of 1992) showed that, for cadaver donor grafts, our survival rates appeared to be slightly lower. The 95% confidence intervals overlapped between the 3 studies, but formal testing of significance of these differences was not possible because of insufficient information in the published data. In the azathioprine period 2 patients died from infection (*Cryptococcus neoformans meningitis* and *Candida albicans sepsis*), and 1 patient died from a heparin-induced hypocoagulative state complicated by subarachnoid and gastrointestinal hemorrhage. In the cyclosporine A period 2 patients died from septicemia (due to *Escherichia coli* and *C. albicans*), and another died 6 weeks after transplantation from a complication of unrelated elective surgery.

Rejection accounted for most of the 40 organ graft losses during the 2 periods. There were 5 hyperacute rejection episodes; in each case the organ matched at one or

more HLA loci. For cadaver donor grafts, at the end of 1 year the (exact) estimated odds of loss from acute or chronic rejection with no HLA loci matches was 6.2 times the odds of loss with one or more matches (exact test, one-tailed $p = 0.005$). Only one unmatched graft survived longer than 1 year. A total of 19 (28%) of the 69 transplants (including the 5 cases of hyperacute rejection) failed within the first 3 months. This represents 48% of all losses, a figure comparable to that observed in the NAPRTCS, 51.2%.[4] Of the 19 early graft losses 13 were due to hyperacute or acute rejection, 5 were medical or surgical losses, and 1 was due to recurrent disease. An exact test of independence between the various causes of graft loss and the 2 periods showed no evidence of association (exact test, $p = 0.306$).

Noncompliance with drug therapy complicates treatment in any chronic disease. It accounted for 5 (12%) of the 40 graft losses, compared with 2.0% in the NAPRTCS.[4] All of our noncompliant patients were adolescent girls. Teenagers receiving cyclosporine A have vocalized unhappiness with the dysmorphic and hirsute changes secondary to their medication.

Surgical complications resulting in graft loss occurred twice, both in the azathioprine period. In one case there was a stricture of the renal artery anastomosis, and in the other there was wound dehiscence resulting in graft loss.

Our patients' rate of graft loss from vascular thrombosis, 12%, was the same as that observed in the NAPRTCS[12] and was higher than that in the CORR (3.75%).[13] From the beginning of our program, a hematologist completed a detailed coagulation profile for all patients before transplantation. Any patient thought to be at risk for vascular thrombosis underwent hypocoagulation with low-dose heparin during and after surgery. Three patients in the azathioprine period lost their graft secondary to renal vein thrombosis, and one patient in the cyclosporine A period had graft loss due to renal vein thrombosis following an anaphylactic reaction to a bee sting.

Program changes

Our program review showed that 48% of all graft losses occurred within the first 3 months after transplantation; cyclosporine A did not provide the degree of improvement in graft survival that was expected based on the adult experience; infections were common and were frequently associated with rejection; children preferentially received kidneys from young donors; there were delays in therapy for both rejection and infection; and we did not have a serious problem with surgical complications or graft thrombosis.

On the basis of this review, we made the following changes to our program:

- Patients were monitored closely for signs of infection, rejection and complications during the first 3 months after transplantation, such that patients were seen almost daily by a transplantation physician during this period.
- Sequential immunosuppressive therapy replaced previous protocols.
- Pediatric-specific selection criteria for cadaver donors were formulated.
- A dedicated pediatric surgical and medical team was formed.
- The hypocoagulation program was continued.

Because almost half of the graft losses occurred within the first 3 months after transplantation, we felt that an improvement in organ survival could be made by focusing attention on this period. Children who had been discharged home often returned, within the first 3 months, in crisis with acute rejection, infection or sepsis. Aggressive management saved lives, but sometimes, because of delays in starting appropriate therapy, the transplanted organ was lost. Geographic limitations of access to our centre played a large role in the delay of treatment, and frequently there was a delay in parental and local medical recognition of the crisis. Administrative pressures to shorten discharge times did not allow an appreciation that these losses were potentially preventable, and it was felt that increased medical surveillance could possibly avert these problems. Consequently, children remained in hospital or in close proximity for 90 days after transplantation. They were examined and assessed daily for at least 2 months, with this schedule diminishing slowly to twice weekly before their discharge home. An aggressive program of monitoring for viral and bacterial infection and rejection was conducted during this period.

A review of the NAPRTCS data showed that the addition of antilymphocyte globulin (ALG), antithymocyte globulin (ATG) or OKT3 to the immunosuppression regimen improves graft survival significantly.[4] We adopted the sequential immunosuppression protocol used at the University of Minnesota Hospitals, Minneapolis.[1] The initial (induction) immunosuppressant is ATG or ALG antibody, with overlapping introduction of cyclosporine A between days 10 and 14, which is continued as the primary immunosuppressant (we initially used ALG [Sangstat, Mississippi] derived from horses but then switched to ATG [Sangstat] from rabbits because of fewer side effects). Patients also receive azathioprine from the time of transplantation for at least the first year, with the vast majority of children continuing the drug along with cyclosporine A indefinitely. They also receive prednisone as adjunctive therapy, with an attempt to discontinue this

drug after 1 year. Rejection episodes are treated by pulsing with glucocorticoids.

In our program review it was noted that the Atlantic provinces organ-matching computer system tended to give a higher score to adults because of the sense of urgency imparted by their coexisting medical conditions. The necessity for early transplantation in developing children was not fully recognized by the matching system. It was also clear from the literature that the use in children of kidneys from young donors results in a worse outcome than the use of kidneys from adult donors.[5] Hence, the issue of children receiving kidney transplants within a larger adult program was reconsidered. Although this arrangement had many advantages, we felt that children required special or different consideration. To this end, with the cooperation of the entire transplantation team, the cadaver donor selection criteria were changed in 1994 to include the following:

- Children have been placed on an equal footing with adults in the organ matching program.
- Kidneys from donors less than 6 years of age are not to be used for children.
- A match with at least one HLA-DR locus is mandatory for the first transplant (one HLA-DR and one HLA-B antigen match for second and subsequent transplants).
- The length of cold storage of organs is always less than 24 hours.
- No blood group incompatibility is permitted.
- CMV-positive kidneys are accepted, but if a CMV-positive organ is to be used in a CMV-negative child, a passive immunization program using high-CMV-titre gamma globulin is begun and ganciclovir therapy is started.

A dedicated pediatric transplantation team was formed. Its members include the transplantation surgeons, pediatric nephrologists, an anesthetist, an intensivist, a microbiologist as needed and a nephrology research nurse. The team meets regularly to devise changes in the treatment guidelines and to address issues common to the team.

The hypocoagulation program was continued. Most children undergo hypocoagulation for 7 days with heparin (10 U/kg per hour) to maintain their partial thromboplastin time between 30 and 35 seconds.

Evolution after program changes

Data were collected prospectively after the program changes were implemented. From Jan. 20, 1993, to June 30, 1997, 22 children received first transplants. The proportion of living related donors was 63.3%. The incidence of transplantation (number of procedures per 100 000 population per year), the sex ratio and the mean age at transplantation were the same as in the azathioprine and cyclosporine A periods.

There were 2 graft losses, 1 due to chronic rejection at 959 days and 1 due to recurrent disease (hemolytic uremic syndrome) at 7 days after transplantation. There was a significant increase in the 1-, 2- and 5-year Kaplan–Meier graft survival estimates compared with the 2 previous immunosuppression periods (Table 1). Fig. 1 shows the differences in the 1-year Kaplan–Meier survival estimates over the 3 periods.

There were no losses from rejection in the first 3 months and no losses due to medical or surgical complications (Table 2). There were 24 acute rejection episodes in 14 patients, but all reversed easily with high-dose corticosteroid treatment. Half of the acute rejection episodes were associated with an infection, mainly due to human herpesvirus type 6 or Epstein–Barr virus, as reflected by the presence of IgM antibody. Since November 1994 we have used antiviral agents along with antirejection therapy for rejection episodes associated with a viral infection. Three children died with a functioning graft (2 because of gram-negative sepsis and 1 following bowel obstruction and perforation). As of June 30, 1997, all the other grafts were functioning.

Table 1: Kaplan–Meier survival rates of kidney grafts in children who received 1 of 3 immunosuppression protocols, by type of graft

Immunosuppression protocol	Time since transplantation; proportion surviving (and standard error of estimate)		
	1 yr	2 yr	5 yr
Graft from living related donor			
Azathioprine	0.600 (0.155)	0.500 (0.158)	0.400 (0.155)
Cyclosporine A	0.839 (0.104)	0.839 (0.104)	0.671 (0.135)
Sequential	0.928 (0.069)	0.928 (0.069)	0.928 (0.069)
Graft from cadaver donor			
Azathioprine	0.508 (0.106)	0.457 (0.107)	0.343 (0.107)
Cyclosporine A	0.724 (0.096)	0.673 (0.102)	0.517 (0.111)
Sequential	1	1	0.800 (0.179)

Interpretation

As in other North American centres,[4] there has been a steady improvement in kidney graft survival at our institution over the past 25 years. Since the introduction of sequential immunosuppression the improvement has been marked. This is not unlike the experience of the NAPRTCS,[4] although our graft survival rates appear to be somewhat better. Unlike other centres, we have experienced no graft losses due to acute rejection and only one loss due to chronic rejection.

There are several reasons for the improvement in graft survival. In addition to our 4 major program changes, there have been continuing improvements in laboratory, medical and surgical techniques during the review period; hence, it is impossible to isolate the individual contributions of the various factors. However, we feel that 3 changes have had an important effect: the change to sequential immunosuppression, which has been noted in other studies to improve long-term graft survival;[4] the improved medical surveillance during the first 3 months after transplantation, in which rejection-associated graft loss has essentially been eliminated; and the formation of a dedicated pediatric transplantation team (so far there have been no losses due to medical or surgical complications).

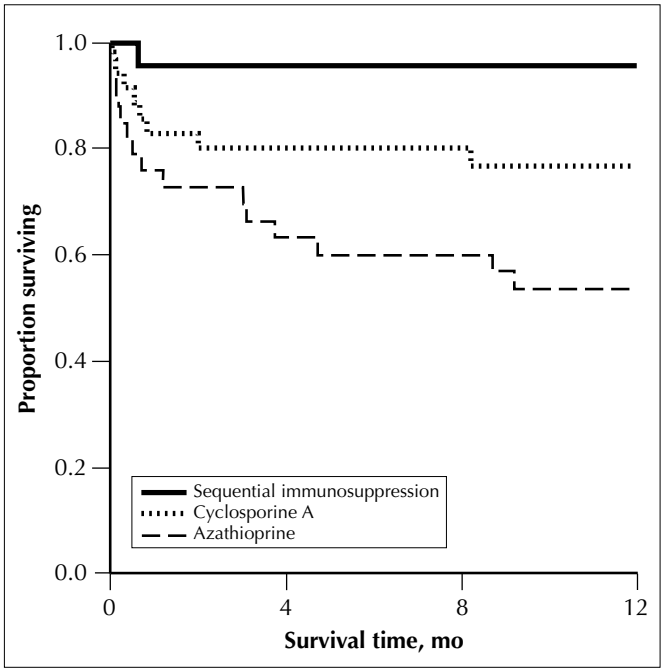

Fig. 1: Kaplan–Meier estimates of graft survival for 3 immunosuppression protocols: azathioprine (Imuran) (1971–1984), cyclosporine A (1985–1992) and sequential immunosuppression (1993 to June 30, 1997). Log-rank tests showed statistically significant difference between protocols (χ^2 = 11.072, 2 degrees of freedom [df], p = 0.004). A one-tailed test of linear trend[8] over the 3 periods was significant (χ^2 = 10.935, 1 df, p < 0.001). Note the marked rate of graft failure during the first 3 months after transplantation with the azathioprine and cyclosporine A protocols.

In the first 4 ½ years after our program changes were implemented, there were 10 rejection episodes during the first 3 months after transplantation (of 24 episodes overall), but they were easily reversed. There was only one graft loss, due to recurrent disease. International data show that half of all losses occur within the first 3 months.[14] Our experience suggests that many such losses can be averted by changes in patient management. Among the patients who received the azathioprine or cyclosporine A protocol, many of the losses within the first 100 days were related to delays in starting appropriate therapy, but such delays no longer occur. The aggressive investigation and treatment of viral and bacterial infections have likely contributed to the improved results as well. Infection has been a coincident or, possibly, a triggering event in many rejection episodes, and treatment of the infection as well as of the rejection may explain why the episodes were easily reversed during the early post-transplantation period. The literature shows that sequential immunosuppression alone does not change the rate of chronic rejection, but patients in whom early lengthy rejection episodes are averted have a lower incidence of chronic rejection.[4]

The importance of HLA matching in cadaver donor transplantation continues to be controversial.[14,15] In the azathioprine and cyclosporine A periods of our program almost all of the unmatched organs eventually failed within the first year. The use of mismatched organs was seen as a way of shortening the transplantation waiting time.

Death rates remained the same in all 3 review periods. This is one area that requires more scrutiny in pediatric transplantation. Most of the deaths in this series were due to infections and occurred while the child was at home. The families often did not recognize the problem and

Table 2: Reasons for graft loss

Reason	Immunosuppression protocol; no. of cases		
	Azathioprine *n = 34*	Cyclosporine A *n = 35*	Sequential *n = 22*
Rejection			
Hyperacute	4	1	0
Acute	5	4	1
Chronic	4	7	0
Noncompliance with drug therapy	3	2	0
Surgical	2	0	0
Medical*	2	3	0
Recurrent disease	3	0	1
Total†	23	17	2

*All due to renal vascular thrombosis.
†These numbers do not include 3 cases during each protocol period in which the patient died but the graft was functioning at the time of death.

sought medical care too late. Resolution of this issue will require education of families and primary health care givers, easy access to a transplantation physician, minimization of immunosuppressive therapy, prophylactic treatment of recurrent urinary tract infections, active vaccination programs (e.g., against *Streptococcus pneumoniae*) and aggressive management of infection. Other problems have yet to be properly addressed, the most urgent being infections in the early post-transplantation period and their relation to acute rejection.

The program changes we instituted come with an initial high price (e.g., the initial lengthy hospital stay). In a climate in which fiscal considerations sometimes supersede medical sanity, it is difficult to address important issues unique to pediatric transplantation: the higher death rates, the high rates of noncompliance, the preferential use of donor organs from children, the rates of cancer, and fertility problems due to long-term immunosuppression. Our study shows that increasing medical care is at least part of the answer to these problems.

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