Transpl Int (2002) 15: 660–663
DOI 10.1007/s00147-002-0471-4

BRIEF REPORT

Clemens Gerstenkorn
David Deardon
C. Geoffrey Koffman
Vassilios E. Papalois
Peter A. Andrews

Outcome of renal allografts from non-heart-beating donors with delayed graft function

Received: 8 October 2001
Revised: 2 July 2002
Accepted: 12 July 2002
Published online: 19 October 2002

C. Gerstenkorn (✉)
39 Arragon Gardens, Streatham,
London, SW16 5LY, UK
E-mail: clemensgerstenkorn@hotmail.com
Tel.: +44-208-4886982

C. Gerstenkorn
Department of Renal Medicine
and Transplantation,
St. George's Hospital, London, UK

D. Deardon · C.G. Koffman
Renal and Transplant Unit,
Guy's Hospital, London, UK

V.E. Papalois
Renal and Transplant Unit,
St. Mary's Hospital, London, UK

P.A. Andrews
Renal and Transplant Unit,
St. Helier Hospital,
Carshalton, Surrey, UK

Abstract Delayed graft function (DGF) in renal transplantation using non-heart-beating donors (NHBDs) usually exceeds 80%. There is debate whether DGF in this subgroup is associated with poor long-term outcome. Between 1 January1988 and 31 January 2000, 130 of 158 (82.3%) NHBD graft recipients with functioning grafts transplanted within our regional NHBD programme developed DGF. Overall graft survival and graft survival censored for recipient death was 113/130 (86.9%) versus 113/121 (93.4%) at year 1, 55/84 (65.5%) versus 55/64 (85.9%) at year 5 and 18/40 (45.0%) versus 18/28 (64.3%) at year 10 after transplantation. Seventeen grafts (13.1%) were lost due to rejection or graft nephropathy. Nine of these kidneys failed during the 1st year. Twenty-seven patients (20.8%) died with functioning grafts, eight within the 1st year after transplantation. In those patients who survived, DGF was associated with excellent long-term outcome in this study. The number of grafts lost due to recipient death exceeded those lost due to rejection or graft nephropathy.

Keywords Non-heart-beating donor · Kidney transplantation · Delayed graft function · Long-term outcome

Introduction

Delayed graft function (DGF), donor age and acute rejection have been associated with reduced renal allograft survival in heart-beating cadaveric donor transplantation [4, 8, 15, 17]. Some studies have shown these to have an interactive effect [12, 15]. There is no reason to believe that the detrimental influence of increasing donor age and frequent rejection episodes should differ in this donor group. In contrast, it is important for non-heart-beating donor (NHBD) programmes to analyse the relative impact of DGF on both short- and long-term survival, since its rate exceeds that in heart-beating donor (HBD) programmes by 30%–70% and the nature of this renal insult may be very different [5]. Unavoidable DGF in NHBD programmes is usually caused by the additional primary warm ischaemia time in this setting [14]. Therefore, it has to be interpreted differently from DGF within HBD programmes. DGF in most of the uncontrolled NHBDs (categories I and II according to the Maastricht classification) usually lasts for up to 4 weeks and is characterised by selective severe acute tubular necrosis, which has been shown to be reversible in this donor group [4, 6, 11]. When more detailed analyses regarding DGF in HBD programmes were performed, it was found that the detrimental effect of DGF might be

confined mainly to the 1st year after transplantation and is associated with increased incidence of rejection [15, 18]. Thereafter, no significant differences in graft survival have been observed, as measured by the half-life of grafts functioning at 1 year with DGF alone, compared with grafts with immediate function [12]. This study therefore analyses the long-term outcome of renal allografts from NHBDs with DGF to determine whether they have impaired long-term graft outcome.

Patients and methods

Between 1 January 1988 and 31 January 2000, 202 kidneys from NHBDs were transplanted into patients within the South Thames Region (Guy's Hospital, St. George's Hospital, Dulwich Hospital, Brighton Sussex Hospital and St. Helier Hospital). NHBDs were from category II (A& E), IIIA (hospital, mainly ITU) and IIIB (hospice) according to the Maastricht classification and its London modification regarding hospice donors [7, 11]. Transplants were divided into three subgroups: immediate or primary function (PF), DGF and permanent non-function (PNF). DGF was defined as a requirement for dialysis for 3 days or longer after transplantation. Overall and observed graft survival within the DGF group was retrospectively estimated by the bivariate Kaplan-Meier method. Graft survival was recorded at 1, 3, 5 and 10 years after transplantation. The cause of graft loss was analysed, and the annual graft loss rate calculated. Graft nephropathy was defined as graft impairment after transplantation due to chronic rejection or reperfusion injury, disease recurrence, medication toxicity, etc. All patients received triple immunosuppression with cyclosporine, azathioprine and prednisolone up to 1995; after 1995, 22 of 40 patients received tacrolimus instead of cyclosporine.

Results

Of 202 NHB renal allografts, 158 (78.2%) had immediate (PF) or DGF. Forty-four (21.8%) kidney transplant recipients had PNF. The rate of DGF within the group of functioning grafts was 82.3% (130/158), and the median postoperative dialysis requirement in the subgroup with DGF was 22 days (range: 3–61days).

In the subgroup of transplant recipients with DGF, patient survival was 121/130 (93.1%) at year 1, 87/102 (85.3%) at year 3, 64/84 (76.2%) at year 5 and 28/40 (70.0%) at year 10 after transplantation (Table 1). The overall graft survival and observed graft survival censored for recipient death in the subgroup were 113/130 (86.9%) and 113/121 (93.4%) at year 1, 77/102 (75.5%) and 77/87 (88.5%) at year 3, 55/84 (65.5%) and 55/64 (85.9%) at year 5 and 18/40 (45.0%) versus 18/28 (64.3%) at year 10 after transplantation (Table 1). Seventeen grafts (13.1%) of the study group with DGF were lost due to rejection or graft nephropathy (Fig. 1). Nine of these kidneys failed during the 1st year, resulting in an initial annual graft loss of 6.9% (Fig. 2). During subsequent years, a further eight grafts were lost as follows: year 2 ($n=1$), year 3 ($n=2$), year 4 ($n=2$), year 6 ($n=2$) and year 10 ($n=1$) (Fig. 2). Twenty-seven patients (20.8%) died with functioning grafts, eight within the 1st year after transplantation (Figs. 1 and 2).

Discussion

Besides the legal and logistic issues, there are two main medical concerns regarding the use of NHBD kidneys for renal transplantation: the incidence of PNF and the high rate of DGF [5, 13]. In an attempt to address the latter, this retrospective study of a large NHBD programme investigated the long-term outcome of NHBD kidney transplant recipients with DGF.

DGF in renal NHBD programmes using category I and II donors according to the Maastricht classification usually exceeds 80% and has not been reduced even by use of different preservation techniques such as pulsatile machine perfusion [3, 7]. Knowledge of its effect on long-term graft outcome in the recipient is important, to measure the quality of such donor organs and to give appropriate recommendations to potential transplant recipients. In addition, PNF rates have to be kept as low as possible – ideally under 5% – and are still a major concern regarding NHBD programmes [1, 20]. The observed 5-year graft survival of kidneys from NHBDs with DGF in this study was 55/84 (65.5%) and was similar to that of the total group of cadaveric kidneys, including those with PF, transplanted within the UK and the Republic of Ireland during the same period from 1988 to 1993 (2220/3399, 65.3%) (Table 1) [6]. In addition, there was no increase in the annual rate of graft loss between 5 and 10 years after transplantation. The majority of grafts lost was due to recipient death ($n=27$; 61.4%), particularly in the 1st year after transplantation;

Table 1 South Thames NHBD programme 1988–2000 ($n=202$). Recipients with DGF for more than 3 days ($n=130$)

Time after transplantation (years)	Transplants at risk (n) with follow-up	Recipients alive (n), patient survival (%)	Recipients with functioning grafts (n)	Graft survival of recipients with DGF≥3 days (%)	Survival of grafts with DGF censored for recipient death (%)
0	130	130 (100)			
1	130	121 (93.1)	113	86.9	93.4
3	102	87 (85.3)	77	75.5	88.5
5	84	64 (76.2)	55	65.5	85.9
10	40	28 (70.0)	18	45.0	64.3

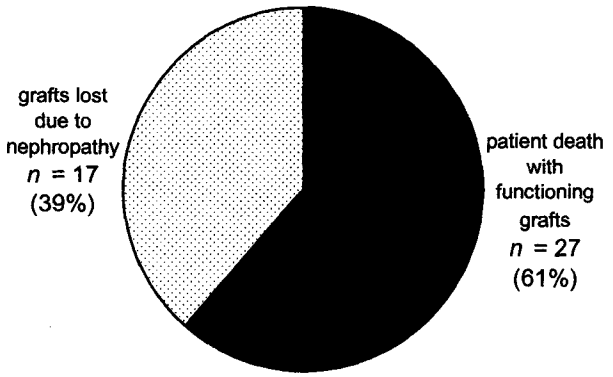

Fig. 1 Distribution of renal graft loss

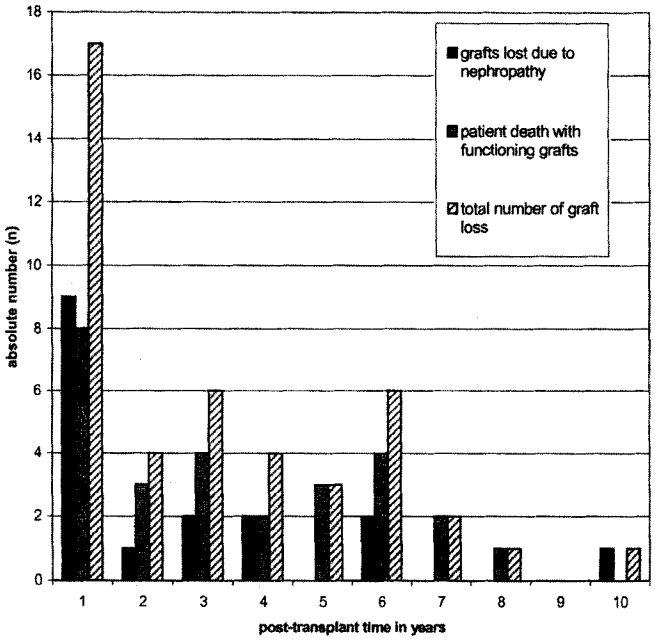

Fig. 2 Cause and time of renal graft loss

only 17 grafts (38.6%) were lost due to rejection or graft nephropathy over a follow-up period of up to 12 years (Fig. 1). The high incidence of patient death with functioning graft during the 1st year indicates that patient selection or pre-transplantation treatment of co-morbidities was not ideal and may be improvable.

The data suggest that the outcome of kidney transplants from NHBDs who develop DGF is not inferior if they are correctly managed. The management of recipients with DGF is more complex than those with PF. Early rejection within the period of DGF needs to be excluded by biopsy or treated to avoid impaired long-term graft function and survival [9]. To lower DGF in HBD programmes, sequential immunosuppressive regimens with delayed use of calcineurin inhibitors have been developed, and pulsatile perfusion during the storage time is performed in some centres [4, 16].

DGF in uncontrolled NHBDs is usually unavoidable even with improved preservation techniques [7, 9]. In this study, it lasted on average, for 22 days. The underlying cause is severe acute tubular necrosis (ATN) due to the prolonged primary warm ischaemia time. The proximal tubules, which are most sensitive to ischaemia, cannot survive without damage in this setting. If no additional detrimental effect is added, such as impaired donor-organ quality, advanced donor age or immunological damage due to rejection, this form of ATN in NHBDs has been shown to be completely reversible with no long-term side effects [7, 10]. In some HBD programmes this and other donor- and recipient-related problems (increasing donor age, incomplete perfusion, prolonged cooling, co-morbidities such as atherosclerosis, diabetes and hypertension, etc.) have led to impaired long-term graft survival [4, 19].

If it is accepted that the incidence of DGF in NHBD programmes is high, and efforts are made to incorporate this factor into post-transplant management, as was done within the South Thames region, DGF will not be associated with impaired graft function in such programmes. Lowering of permanent non-function rates in NHBD kidneys, and reliable viability tests for kidneys prior to transplantation still remain challenging issues for a successful NHBD programme [2].

Acknowledgements We thank Marie Cummins, Helen Mandefield, Helen Gregson, Diana Osborne and Rene Chang for help regarding follow-up data of some of the transplant patients.

References

1. Andrews PA, Compton F, Koffman CG, Chang RWS (2001) Prediction of outcome in non-heart-beating kidney transplantation. Transplant Proc 33:1121–1124
2. Balupuri S, Abusin K, Gerstenkorn C, Manas DM, Talbot D (1999) Expansion of donor pool: lack of function predictors. Transpl Int 12:158
3. Balupuri S, Buckley P, Mohamed M, Chidambaram V, Gerstenkorn C, Sen B, Kirby J, Manas DM, Talbot D (2000) Early results of a non-heart-beating donor (NHBD) programme with machine perfusion. Transpl Int 13 [Suppl 1]:S255–S258
4. Barber WH, Hudson SL, Deierhoi MH, Laskow DA, Diethelm AG (1990) Pulsatile perfusion preservation: early post-transplant dialysis requirement predicts rapid graft loss. Transplant Proc 22:446–447

5. Gerstenkorn C, Oliveira D, MacPhee I, Chang R (2000) Non-heart-beating donors for renal transplantation. Lancet 356:1854
6. Gerstenkorn C, Robertson H, Bell A, Shenton B, Talbot D (2001) CMV infection as a contributory factor for renal allograft injury and loss. Transplant Proc 33:2461–2462
7. Gerstenkorn C (2002) Non-heart-beating-donors (NHBDs): a renewed source of organs for renal transplantation in the 21st century. World J Surg (in press)
8. Gjertson DW (2000) Impact of delayed graft function and acute rejection on kidney graft survival. Clin Transpl 467–480
9. Jain S, Curwood V, White SA, Furness PN, Nicholson ML (2000) Sub-clinical acute rejection detected using protocol biopsies in patients with delayed graft function. Transpl Int 13 [Suppl 1]:S52–S55
10. Koffman CG, Bewick M, Chang RWS, Compton F (1993) Comparative study of the use of systolic and asystolic kidney donors between 1988 and 1991. Transplant Proc 25:1527–1529
11. Kootstra G, Daemen JHC, Oomen APA (1995) Categories of non-heart-beating donors. Transplant Proc 27:2893–2894
12. Kyllönen LE, Salmela KT, Eklund BH, Halme LE, Höckerstedt KA, Isoniemi HM, Mäkisalo HJ, Ahonen J (2000) Long-term results of 1047 cadaveric kidney transplantations with special emphasis on initial graft function and rejection. Transpl Int 13:122–128
13. Laskowski IA, Pratschke J, Wilhelm MJ, Paz D, Tilney NL (1999) Non-heart-beating kidney donors. Clin Transplant 13:281–286
14. Light JA, Barhyte DY, Gage FA, Sasaki TM, Aquino AO (1999) Long-term graft survival after transplantation with kidneys from uncontrolled non-heart-beating donors. Transplantation 68:1910–1914
15. McLaren AJ, Jassem W, Gray DW, Fuggle SV, Welsh KI, Morris PJ (1999) Delayed graft function: risk factors and the relative effects of early function and acute rejection on long-term survival in cadaveric renal transplantation. Clin Transplant 13:266–272
16. Muller T, Ruffingshofer D, Bidman B, Arbeiter K, Balzar F, Aufricht C (2001) Reduction of delayed allograft function using sequential immunosuppression. Pediatr Nephrol 16:613–617
17. Nankivell BJ, Fenton-Lee CA, Kuypers DR, Cheung E, Allen RD, O'Connell PJ, Chapman JR (2001) Effect of histological damage on long-term kidney transplant outcome. Transplantation 71:515–523
18. Rosenthal JT, Danovitch GM, Wilkinson A, Ettenger RB (1991) The high cost of delayed graft function in cadaveric renal transplantation. Transplantation 51:1115–1139
19. Shoskes DA, Shahed AR, Kim S (2001) Delayed graft function. Influence on outcome and strategies for prevention. Urol Clin North Am 28:721–732
20. Vanrenterghem Y (2000) Cautious approach to use of non-heart-beating donors. Lancet 356:528