Medicine in the Tropics

Ten Tanzanian transplants: problems and perspectives

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Summary: A strategy of live related donor kidney transplantation coupled to the briefest possible preparatory period of haemodialysis was adopted as the most cost effective treatment for a selected group of 9 Tanzanian patients who received a total of 10 grafts. Patient and donor selection and preparation were carried out at Muhimbuli Medical Centre, Dar es Salaam, and the transplant procedure and first few months of follow-up were done at St. Thomas' Hospital, London. There was a high incidence of complications which drew attention to particular risk factors in the group treated. The high cost of treating these individuals emphasizes the need for research into chronic communicable and non-communicable diseases in Africa and highlights the dilemma of appropriate use of resources in serving the world's medical needs.

Introduction

End stage renal failure (ESRF), because of a high incidence of glomerulonephritis¹ and the potential of Africans to develop renal damage due to hypertension,² is a common clinical problem in developing African countries. Not infrequently it causes the death of people in the prime of life where loss to their families and their country represents a particularly tragic occurrence.

Treatment of ESRF by dialysis and transplantation, now routine in developed Western countries,³ is too expensive to be made available to more than a limited number of Tanzanian patients. The most cost effective strategy is the minimum time on dialysis and early transplantation. Because of limited supply of cadaver organs, the most readily available organs are those given by live (usually related) donors. The purpose of this paper is to report the experience of a small programme of renal transplantation carried out jointly between Muhimbuli Medical Centre (MMC) in Dar es Salaam and St. Thomas' Hospital (STH) in London.

Patients and donors

Ten live donor kidney transplants have been carried out in nine patients between September 1981 and February 1987. The first patient was regrafted 32 months after the first transplant. Table I summar-

izes the characteristics of the patients who have been treated in chronological order of grafting.

Most of the patients presented with advanced renal failure usually complicated by severe hypertension. In one patient (no. 6) hypertension was diagnosed 2 years and in another (no. 3) 6 months prior to ESRF, but other patients, were diagnosed too late for effective treatment of hypertension to preserve renal function.

Ultrasound or intravenous urography was done to exclude obstruction and to measure renal size. All patients had small contracted kidneys without scars or cysts. One only (no. 9) had had a nephrotic syndrome in childhood (not biopsied), another had probable nephrotic syndrome in adult life (no. 5) and the one patient (no. 6) who had been biopsied (at CMC, Vellore, India) had renal histological appearances compatible with ischaemic damage due to hypertension. None had glycosuria prior to grafting.

The donors were all male relatives of the patients whose motivation and medical suitability were assessed at the MMC. None was paid or under coercion except that due to personal concern to help the dying patients for whom no other long-term treatment was available. General medical examination at MMC ensured that donors were fit, had two kidneys and a compatible blood group. Remote tissue typing and cross-match tests on blood sent from MMC to STH helped to select from a short list of potential donors but because of problems in arranging couriers proved time-consuming. The donors for patients nos. 1 and 2

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Table I The patients

Patient (no.)	Date of graft	Sex	Age	Cause of ESRF	Hypertension
1 (1)	07.09.81	F	32	'End stage' kidneys	Moderate
(2)	23.05.84	F	35		
2	31.03.82	M	45	'End stage' kidneys	Severe
3	04.07.84	M	44	'End stage' kidneys	Very severe
4	26.06.85	M	44	'End stage' kidneys	Very severe
5	22.11.85	M	29	GN (nephrotic syndrome)	Mild
6	25.04.86	M	31	Ischaemic nephrosclerosis (biopsied)	Severe
7	06.05.86	M	61	'End stage' kidneys	Severe
8	28.10.86	F	31	Probable GN	Severe
9	03.02.87	F	17	GN (nephrotic syndrome)	Moderate

GN = glomerulonephritis.

were HL-A and -B identical to their recipients, those for patients nos. 4, 5, 7, 8 and 9, shared one haplotype with their recipients, the donor for patient no. 6 had three mismatches and the donor for patient no. 3 four mismatches. Routine workup included search for malarial parasites, and vascular anatomy of the kidneys was demonstrated by digital subtraction angiography. Donor nephrectomy was performed through a subcostal incision.

Results

Haemodialysis facilities at MMC are limited and are usually reserved for patients suffering from acute reversible renal failure such as that following

obstetric accidents. Two of the nine patients (nos. 7 and 9) received some haemodialysis while awaiting transfer to London. All arrived in London in advanced uraemia, two patients exhibiting among the highest serum creatinines recorded at STH in recent years – 4,302 $\mu\text{mol/l}$ (no. 5) and 1,980 $\mu\text{mol/l}$ (no. 6).

Emergency haemodialysis was required for all except no. 1 and no. 8. Access was achieved by leg shunts or by double lumen or pairs of venous catheters inserted into the internal jugular, subclavian and occasionally femoral veins. The total number of haemodialyses (Table II) was dictated by the medical state of the recipient and the preparation of the donor. Immediate graft reduction occurred in all ten transplants.

Table II Results and complications of transplants

Patient (no.)	Number of haemodialyses	Complications	Creatinine ($\mu\text{mol/l}$)	
			3 months after graft	April 1987
1 (1)	0	U. leak, malaria, DM	80	
(2)	0	TOP hypert.	93	148
2	44 (19 in USA)	DM, hypert, obesity	132	137
3	5	U. leak, acute LVF, malaria	215	Died 6 months post graft
		Severe rejection		
4	27	U. leak, malaria, DM	141	603
5	12	Acute LVF	132	105
6	31	Acute LVF, psychosis	137	125
7	17 (4 at MMC)	U. leak, DM	103	Died 7 months post graft
8	1	U. leak, wound infection	105	155
		herpes, lymphocoele		
9	13 (6 at MMC)	U. leak	126	126

U. leak = ureteric leak; hypert = hypertension; TOP = termination of pregnancy; DM = diabetes mellitus; LVF = left ventricular failure.

Postoperative complications (Table II) were dominated on the surgical side by a high incidence of urinary leaks (60%) due to breakdown of the ureteric anastomosis to the bladder, usually the consequence of ischaemic necrosis. Bacteraemia and septicaemia accompanied some of these leaks. Definitive surgical management in four cases was achieved by pelvi-ureterostomy using the recipients ipsilateral ureter and splinting the anastomosis with a T tube into the bladder.

Initial immunosuppression was by azathioprine and steroids for the first graft of patient no. 1 and for patient no. 2, thereafter cyclosporin and low dose steroids were used. Cyclosporin (4 mg/kg) was given by slow (6 hours) i.v. infusion on each of the first 3 days and then replaced by oral cyclosporin 13 mg/kg/day reducing by 2 mg/kg/day weekly.

Prednisolone 20 mg/day was given in conjunction with the cyclosporin. After 6 to 8 weeks azathioprine was introduced and its dose progressively increased to 100 and 150 mg/day while cyclosporin was gradually withdrawn. Several patients had rejection episodes during the switch of therapy or immediately after it and oral steroid dose was often increased to cover the switch. All patients had rejection episodes at some time and these were managed in in-patients by i.v. bolus injections of methylprednisolone 0.5 g on 2 to 3 consecutive days and in out-patients by oral high dose prednisolone, increased to 100 mg/day for 3 days, thereafter tapered by 25 mg/day every third day.

Malaria occurred in the first three cases during the first few weeks after transplant and one of these was associated with a rejection episode. Malaria in Tanzania is often chloroquine resistant⁴ and all donors and patients have since been given a course of quinine and pyrimethamine (Fansidar) as a precautionary measure, even if blood films were negative.

Hypertension was a medical complication, to all the cases. Severe hypertension with left ventricular failure developed acutely during the first 48 hours in three patients, each of whom required either venesection or a nitroprusside infusion to prevent pulmonary oedema and death.

Heart failure occurred in the presence of dramatic polyuria (often exceeding 10 litres per 24 hours) and without overall weight gain and appeared to be due to a severe increment in peripheral vascular resistance. All patients required powerful long-term oral hypotensive agents. Minoxidil was found particularly useful in conjunction with beta-blockade and usually diuretics and was even preferred by one female patient despite the side effect of hirsutism necessitating regular facial shaving.

The steroids used for immunosuppression

induced non-ketotic diabetes in four of the patients. All four required insulin during the early months but the dose required was eventually diminished and in one patient management by diet alone proved satisfactory.

All patients returned to Tanzania with functioning grafts having spent between 3 and 6 months in London for early post-transplant follow-up and the switch of immunosuppressive drugs. However, several patients had hearts which had been severely damaged by long-standing hypertension and two of these (no. 3 and no. 7) died quite suddenly 3 weeks after reaching their homes. Seven out of the ten grafts were functioning in April 1987, but the graft of patient no. 4 which suffered repeated rejection episodes in earlier months, two years after transplantation showed declining renal function.

The first graft in patient no. 1 was lost after 2 years and it seems likely that poor control of hypertension was the major factor. The transplant from a second brother continues with stable function and she is reconciled to the use of minoxidil to control her hypertension which she monitors with her own sphygmomanometer.

Rehabilitation of the patients has been of variable quality. One has been able to continue a full academic life as a university professor and another, a trained pilot and the only patient to discontinue hypotensive drugs so far, has been restored to flying duties. Two of the female patients have young children to care for and one is a young girl whose earlier illnesses interrupted her education and would have cut her life short on the threshold of adulthood. One of the survivors (no. 6) married after return to Tanzania but subsequently lost his job and became confused and psychotic, requiring psychiatric care.

Discussion

A strategy of LRD transplantation was adopted as the most cost effective. However, the average cost of each patient's treatment, including accommodation and living allowances in London and drugs for one year, amounted to the equivalent of almost 2 million Tanzanian shillings (roughly equivalent to £20,000 sterling at present rates of exchange, although this has altered during the years covered by this programme). This must be placed in the context of a total government health expenditure of less than one hundred Tanzanian shillings per subject per year. Despite this stark comparison it is the firm view of the clinicians at MMC that patients should not be totally debarred from transplantation. The productive lives to which several of these patients have been restored underlines the

dilemma confronting developing countries when such expensive high technology medicine has been shown to be so effective. The true cost of transplantation can be judged properly only when compared to the cost of training a pilot or to the value of an internationally active university professor. Cost in London was primarily dependent on the length of hospitalization in STH and in the period of preparatory dialysis and it is therefore pertinent to consider all factors which delay transplantation. Only three of the transplants were planned electively, both grafts in patient no. 1 and that of patient no. 8. All other patients were desperately ill on arrival in London, their transfer sometimes delayed by administrative hold-ups and this necessitated urgent haemodialysis and made it impossible to carry out the LRD transplant until the patient had been restored to a satisfactory state with relief of advanced uraemia and control of blood pressure. The two most recent patients arrived in reasonable clinical condition with satisfactory donors and therefore very little delay occurred before transplantation.

It is an unenviable task to select some patients for this treatment out of very large numbers who die each year from ESRF in Tanzania. Inevitably, criteria for choice have not been entirely medical and therefore, some patients have possessed risk factors which made them far from ideal candidates for treatment.

The complications encountered illustrate particular surgical and medical problems which we have now come to anticipate and which make us regard many of these patients as 'high risk' candidates for dialysis and transplantation. The high incidence of urinary leaks has not been matched by a similar experience in our UK or other foreign patients.

Chloroquine-resistant malaria must be considered ubiquitous⁴ and it is a particular hazard in immunosuppressed patients. It appears capable of triggering rejection and we have now adopted a policy of giving a course of treatment, irrespective of blood smear results, to both recipient and donor, and of advising chemoprophylaxis on return to Tanzania. All patients had a past history of hypertension, in most cases severe with clinical, radiographic and electrocardiographic evidence of left ventricular damage.

Many African subjects have a dramatic potential to develop hypertension² and fulminating hypertensive crises within the first 48 hours after transplant almost caused the death of two patients despite profuse urinary outputs. It is possible that

the cyclosporin infusion given at this stage was a factor in causing hypertension. Long term treatment of hypertension is of great importance in maintaining these grafts as illustrated by the fate of the first transplant in patient no. 1. Good blood pressure control has resulted in regression of the features of left ventricular damage in the long-term patients.

Four patients developed diabetes with the moderate doses of steroids used. Three continued on insulin (nos. 1, 4 and 7) and one is now controlled by dietary care only (no. 2).

Despite complications all patients have reached Tanzania with functioning grafts. However, the high incidence of complications, particularly the urinary leaks, have added to the duration of hospitalization and therefore to the total cost of the procedure. The high cost of private medical beds in London has constrained many clinical decisions during the first 3 to 6 months while the patients remained in London. Many severe rejection episodes (not a few accompanied the switch in immunosuppressive drugs) have been managed without readmission to hospital as have infective complications of wounds, urinary tract and respiratory system.

After return to Tanzania immunosuppression was continued with azathioprine and low dose steroids. Azathioprine was chosen for long-term immunosuppression because of the high cost of cyclosporin, even in low doses currently employed. The risks of switching these drugs after three months is well documented.⁷ Successful switching is possibly even more difficult to achieve during the first 3 months, but our objective was probably helped by using related donors and no grafts were lost during this process despite severe rejection episodes which were encountered.

The small programme reported in this paper establishes that successful renal transplantation can be offered to subjects of a country which does not yet envisage the inception of an autonomous programme of dialysis and transplantation for ESRF. Collaboration between clinicians at MMC and STH now obviates any necessity for patients to return to London for routine follow-up. It is also improving the efficiency of transfer arrangements to diminish risks to the patient and overall costs. Finally, by highlighting the ultimate costs of glomerulonephritis and hypertension we draw attention to widespread and chronic medical problems in the population which call for research, prevention and treatment.

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