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ORIGINAL ARTICLE

Pre-emptive rituximab and plasma exchange does not prevent disease recurrence following living donor renal transplantation in high-risk idiopathic SRNS

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Abstract

Background Children with non-genetic steroid-resistant nephrotic syndrome (SRNS) are at high risk of disease recurrence (DR) and graft loss following renal transplant (RT). Although pre-emptive plasma exchange (PE) and rituximab have been suggested to prevent DR, there is insufficient published data to support this practice. The aim is to study the role of pre-emptive PE and rituximab in the prevention of DR in children with non-genetic SRNS undergoing living donor (LD) RT.

Methods Prospective single-centre study of four consecutive children (age 6–17 years) with non-genetic SRNS (including two with previous graft loss due to DR) who underwent LD RT between July 2014 and September 2016. All patients received a single dose of rituximab 375 mg/m^2 2–4 weeks prior to the RT and four sessions of PE in the week prior to RT. All patients had previously undergone bilateral native nephrectomies.

Results All children had early DR (2–26 days) following LD RT. Following early initiation of PE, three children achieved partial remission (PR) or complete remission (CR) 5–22 days after commencing treatment. One child continued to have heavy proteinuria along with graft dysfunction despite 52 sessions of PE and lost the graft 5 months after RT. At the latest follow-up of 36–60 months following RT, one child remains in CR and two are in PR. The latest eGFR was 45–104 ml/min/1.73m^2.

Conclusions Pre-emptive rituximab and PE does not prevent DR in high-risk non-genetic SRNS. Prompt initiation of PE following DR appears to achieve PR or CR in the majority of patients.

Keywords SRNS · Renal transplant · Disease recurrence · Rituximab · Plasma exchange

Introduction

Disease recurrence (DR) following renal transplantation (RT) can occur in up to 50% of patients with steroid-resistant nephrotic syndrome (SRNS), with many progressing to graft loss, despite intensive treatment [1]. The risk of DR is over 80% in those with previous graft loss. Over the last two decades, advances in genetics have helped to identify patients who are at high risk of DR following RT [2, 3]. Patients with monogenic cause of SRNS are far less likely to develop DR compared to those where no pathogenic mutation associated with SRNS has been detected. Younger age at presentation, initial steroid sensitivity, minimal change disease in the native kidney and rapid progression to end-stage kidney disease (ESKD) are the other risk factors for DR following RT [4–6].

A number of treatment options have been considered to prevent DR following RT. Because of the rapid recurrence of the disease following RT and also because of the salutary response to plasma exchange (PE) in a number of patients, an as yet unidentified circulating factor has been implicated in the causation of DR. There are a number of case reports of pre-emptive PE to prevent DR in patients with SRNS [7–9] which suggest that the treatment may prevent DR in about 50% of the patients. However, many of these reports are from the time when genotyping was not widely available and, therefore, do not accurately predict efficacy. Rituximab on its own and also along with PE has also been used to prevent DR [10–12].

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Chikamoto et al. reported a single child who did not have DR in the second transplant following pre-emptive treatment with rituximab and PE [12].

In this study, we aimed to determine whether pre-emptive rituximab and PE prevents DR in high-risk children with non-genetic SRNS undergoing LD RT.

Methods

We prospectively studied 4 consecutive children with SRNS (including 2 with previous graft loss due to DR) who underwent LD RT at the Royal Manchester Children's Hospital between July 2014 and September 2016. All patients received a single dose of rituximab 375 mg/m^2 2–4 weeks prior to the RT and were also treated with 4 sessions of PE in the week prior to RT (Table 1). The substitution fluid for PE was 4.5% human albumin solution, apart from the last session, where the children received 25%of the replacement fluid as fresh frozen plasma in order to minimise the risk of perioperative bleeding. The age at initial presentation with SRNS ranged from 1.7 to 12.2 years. The children progressed to ESKD 7–14 months following the initial presentation. All patients underwent bilateral native nephrectomies (BNN) prior to LD RT because of ongoing proteinuria. Whole exome sequencing with a focus on the 53 genes known to be associated with SRNS at the time of testing [13] did not identify any known pathogenic genes. The age range at RT was 6.5 to 18.0 years. Two of the children (Patients 1 and 2) had previous graft loss from DR, 11 and 6 years prior to the second RT. Immunosuppression was as per the TWIST study protocol [14] – Basiliximab/Tacrolimus/Mycophenolate mofetil and early steroid withdrawal – apart from Patient 2 who also received maintenance prednisolone as the living donor was HLA incompatible. Estimated GFR was calculated using the modified Haycock-Schwartz formula using a k factor of 40 for all ages [15].

We defined DR as urine protein:creatinine ratio (UPCR) > 200 mg/mmol and rising on two consecutive days. Complete remission (CR) was UPCR < 20 mg/mmol and partial remission (PR) as UPCR 21–200 mg/mmol.

Results

All patients had good primary graft function but early DR (Table 2) between day 3 and day 26 following RT. PE exchange was commenced promptly once a diagnosis of DR was made. All patients received daily 1.5 times the plasma volume PE for 5 sessions and then 2–3 sessions per week depending upon the clinical response. In Patients 1, 2 and 4, there was a good response to PE with reduction in proteinuria, and PE was discontinued after 5–28 sessions. Patient 3 continued to have heavy proteinuria along with graft dysfunction and progressed to ESKD by 5 months following RT despite intensive PE (total 52 sessions). All but Patient 2 had one or more graft biopsies in order to exclude alternative pathology in the first 3 months following RT. At the latest follow-up 36–60 months following RT, the remaining three patients are doing well with estimated GFR 45–104 ml/min/1.73m^2. Patient 2 is in CR, while Patients 1 and 4 have persistent proteinuria despite anti-proteinuric therapy.

Discussion

This prospective case series clearly demonstrates that pre-emptive rituximab, and PE does not prevent DR in high-risk non-genetic SRNS following LD RT. However, following prompt initiation of PE following diagnosis of DR, three children achieved PR or CR, and one lost their graft after a mean follow-up period of 3.5 years.

Although a number of case series have reported the role of pre-emptive PE with or without rituximab, we report, for the first time, a clearly defined group of children with non-genetic FSGS who were at high risk of DR, all of whom underwent BNN prior to LD RT and received identical pre-emptive treatment with rituximab and PE [7–12]. The rationale for the pre-emptive treatment with rituximab and PE was to stop the

Table 1 Patient characteristics

Patient no.	1	2	3	4
Age at presentation (y)	6.0	1.7	12.2	4.2
Sex	M	F	F	M
Time to ESKD (y)	0.7	0.6	1.2	1.4
Previous graft loss	Y	N	N	Y
Interval between graft loss and 2nd transplant	11 years	6 years	–	–
Age at transplant (y)	18	12.5	14.6	6.5
HLA mismatch (A:B:DR)	1:1:0	0:0:1	0:1:0	1:1:1

ESKD end-stage kidney disease

Table 2 Outcome

Patient no	1	2	3	4
Time to DR (days)	3	3	4	26
Peak UPCR (mg/mmol)	729	718	609	695
No of PE sessions	28	5	52	20
Time since RT (months)	60	38	Graft loss at 5 months	36
Anti-proteinuric treatment	Irbesartan 75 mg daily	No	No	Losartan 50 mg daily
Current UPCR (mg/mmol)	81	12	Anuric	72
Current eGFR (ml/min/1.73m^2)	45	104	< 15	65

DR disease recurrence, *UPCR* urine protein:creatinine ratio, *PE* plasma exchange, *RT* renal transplant

production of, and also remove, any circulating factor, which might be involved in DR [16]. All of our patients had evidence of B cell depletion following rituximab. All patients received four 1.5 times plasma volume PE immediately prior to the RT which would have removed almost 90% of any remaining circulating factor in the plasma. While the early DR seen in all the children would be against the presence of a circulating factor causing DR in the plasma, the prompt response of the disease to early institution of PE in three of our four children would be supportive of this hypothesis. It might be possible that the transplant kidney acts as an immediate trigger to generate an as yet unidentified circulating factor, and pre-emptive treatment to stop its production, or remove this factor, prior to RT may not be an effective treatment in this condition. This is supported by one of the largest retrospective reports by Verghese et al., who reported no difference in the DR rate in the 26 children who received prophylactic PE and the 31 who did not [17, 18].

Two of the four children in this series had previous graft loss due to DR, and both of them have done very well in 3 and 5 years since LD RT. Their DR on this occasion has not been as aggressive as with the first transplant, and in addition, the disease responded promptly to PE. The better prognosis for the second transplant could be due to the long-time interval (6 and 11 years) between the two procedures [9–12]. Chikamoto et al. reported a single child who did not have DR in the second transplant following pre-emptive treatment with rituximab and PE. It is of note that the second transplant was performed 5 years after the first one (12). Pre-emptive treatment with rituximab and PE might have also attenuated the DR, although we have no way of proving or disproving this. One could hypothesise that the disease becomes less aggressive with time. It would perhaps not be unreasonable to delay the second transplant in patients who have rapidly lost a graft due to aggressive DR; however, how long this time interval ought to be is not clear at present. This decision must also be balanced with the risk and benefits of maintaining dialysis access and the quality of life factors associated with long-term renal replacement therapy.

There is also a debate whether children with ESKD due to SRNS and high risk of DR ought to undergo LD RT. Some centres would only list these children for deceased donor RT. Our data and also other reports demonstrate that LD RT can be undertaken in this challenging group of patients [11, 12, 17, 18]. This allows for careful planning of management if DR were to occur. However, it is important that families are counselled about the increased risk of DR and also graft loss in this condition.

Unfortunately, there appears to be no good treatment option to prevent DR in children with high-risk SRNS. Prompt institution of PE as soon as there is evidence of heavy proteinuria following RT appears to be important.

In conclusion, pre-emptive rituximab and PE does not prevent DR in high-risk children with non-genetic SRNS; however, 3 out of 4 children in this series had CR or PR and have preserved kidney function at 3–5 years post-transplant following the immediate institution of PE rescue therapy.

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