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Intravenous pulse cyclophosphamide—is it effective in children with steroid-resistant nephrotic syndrome?

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Abstract Treatment of steroid-resistant nephrotic syndrome (SRNS) remains a challenge to pediatric nephrologists. Recently, intravenous cyclophosphamide (IV-CPM) infusion was shown to be effective, safe, and economical for the treatment of SRNS, particularly minimal change disease (MCD), as it results in more sustained remissions, longer periods without proteinuria, and fewer significant side effects at a lower cumulative dose. A prospective study was conducted to evaluate IV-CPM infusions in the management of children with SRNS secondary to MCD or IgM nephropathy. Five patients with SRNS (4 IgM nephropathy and 1 MCD) received six monthly IV-CPM infusions at a dose of 500 mg/m^2. No patient achieved complete or sustained remission. Three patients attained partial remission, which was not sustained for more than 1 month post therapy. One patient progressed rapidly to end-stage renal disease during treatment. Side effects included vomiting in four patients and alopecia in one patient. Conclusion: IV-CPM pulse therapy at a dose of 500 mg/m^2 is unsuccessful in obtaining complete or sustained remission in children with SRNS secondary to IGM nephropathy or MCD. Further randomized controlled studies with higher doses are required.

Keywords Intravenous cyclophosphamide · Steroid-resistant nephrotic syndrome · Minimal change disease · IgM nephropathy

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Introduction

Steroid-resistant nephrotic syndrome (SRNS) represents around 20% of primary nephrotic syndrome in children [1] and its management remains a problem for pediatric nephrologists [2]. It is mostly caused by non-minimal change histopathology [1]. The probability of having focal segmental glomerulosclerosis (FSGS) or membranoproliferative glomerulonephritis (MPGN) as the underlying cause of SRNS is higher with increasing age, whereas the risk of having minimal change disease (MCD) is more likely with younger age at presentation [3, 4]. Optimal treatment of SRNS has been hampered by a lack of prospective, controlled trials.

In the last 2 decades cyclosporin A (CsA) in combination with prednisolone has been shown to be effective in inducing complete remission in some children with idiopathic SRNS [5]. There is an increasing trend to use CsA in SRNS, particularly with FSGS [6], and its use has been recommended by many authors [7, 8]. Alkylating and antimetabolic agents have been used in SRNS since the 1960s [9], without sustained benefit. Oral cyclophosphamide (CPM) was used particularly with SRNS caused by MCD [10], with variable success. Intravenous (IV) CPM has been reported to be superior to oral CPM in inducing remission in steroid-resistant MCD [11, 12].

We report the disappointing results of a prospective pilot study of IV-CPM in children with SRNS secondary to MCD with or without diffuse mesangial hypercellularity (DMH) or IgM nephropathy.

Patients and methods

All patients presenting to our unit over the first half of 2002 with a diagnosis of SRNS were recruited. Only those with a renal biopsy showing MCD with or without DMH or IgM nephropathy were included in the study. Children with SRNS secondary to FSGS or MPGN were excluded from the study. SRNS was defined as a failure to achieve remission after 4 weeks of enteral prednisolone at a dose of 60 mg/m^2 per day, plus three intravenous doses of methylprednisolone (600 mg/m^2 per day or 30 mg/kg per day) on alter-

nate days [13]. We have seen 26 patients with nephrotic syndrome over a 6-month period, 20 patients had steroid-sensitive nephrotic syndrome (SSNS) and 1 patient with SRNS was excluded as he had FSGS. Five children fulfilled the criteria, four females and one male. The ratio of SRNS to SSNS is biased and does not reflect the actual ratio, as we represent a referal center for difficult nephrology cases. The mean±SD age at presentation was 2.2±1.2 years. All except one patient was Arab in origin. (Patient 3 was Pakistani.) Four children were primary non-responders and one was a secondary non-responder (patient 2 had steroid-dependent NS initially). None was positive for hepatitis B surface antigen or antinuclear antibody. All children had a low serum albumin at the initiation of IV-CPM pulse therapy, with mean±SD of 13.8±0.9 (range 11–16) g/l (normal 35–50). Complement components were normal, C3 1.4±0.2 g/l (normal 0.75–1.65), C4 0.3±0.04 g/l (normal 0.2–0.6), and kidney function was normal, with a mean creatinine of 21.6±7.4 µmol/l (Table 1). We used the same dose of IV-CPM as Elhence et al. [12], of 500 mg/m^2 per month for six doses. All patients were continued on oral prednisolone 40 mg/m^2 on alternate days and enalapril (0.1–0.5 mg/kg) throughout the 6-month treatment period. The response was evaluated in terms of complete remission (proteinuria <1+ on urinalysis and serum albumin >35 g/l) and non-remission (proteinuria >3+ on urinalysis and serum albumin <25 g/l). Partial remission was defined as serum albumin of 25–35 g/l. The duration of remission, serum albumin and creatinine, urinary protein, and side effects were all monitored throughout the treatment and for 2 months after. Glomerular filtration rate was calculated in all patients at the end of treatment by diethyenteriamine pentacetic acid (OTPA) scan. Unfortunately none of the cohort had a second renal biopsy, as the parents were very reluctant to give their consent.

Results

The histopathology of biopsies from two patients (3 and 5) showed a mild increase in mesangial matrix and no increase in cellularity. Light microscopy of biopsies from the other patients (1, 2, and 4) also showed a mild increase in mesangial cellularity. No sclerosis, crescents, or membrane thickening was seen in any of the specimens. Direct immunofluorescence (IF) of four biopsies showed diffuse mesangial IgM (+2) and no staining for IgG, IgA, C4, and fibrinogen. IF of the fifth biopsy (patient 3) was negative for all antibodies. Electron microscopy showed mild mesangial matrix expansion in all cases. Focal or diffuse effacement of foot processes was seen in all cases. A few small deposits in the mesangium were observed in four cases. Overall assessment indicated that four cases should be diagnosed as IgM nephropathy and one as minimal change glomerulonephritis.

No patient achieved complete remission. Three patients (1, 2, and 3) attained partial remission (Table 1), which was not sustained for more than 1 month post therapy. The other two patients remained non-responsive and one of them (patient 5) progressed rapidly to end-stage renal disease during the treatment course and needed dialysis. Side effects observed were vomiting in four patients and alopecia in one patient. None of the patients had leukopenia or hemorrhagic cystitis.

Table 1 Laboratory data before, during, and after cyclophosphamide therapy in individual patients (*TP* total protein, *GFR* glomerular filtration rate, *HBV Ag* hepatitis B virus surface antigen)

Patient number	Age at onset (years)	Sex	Pre therapy								Serum albumin (g/l) during therapy					Post therapy			
			Serum albumin (g/l)	TP (g/l)	Serum creatinine (umol/l)	HBV Ag	C3 (g/)l	C4 (g/)l	Urine protein	Urine blood	1 month	2 months	3 months	4 months	5 months	Serum albumin (g/l)	Serum creatinine (µmol/l)	Urine protein	GFR
1	1.8	M	15	40	28 -ve	1.01	0.3	3+	3+	91	7	19	23	25	28	20	-ve	117	
2	4.3	F	16	57	30 -ve	1.3	0.3	3+	3+	29	29	25	29	28	27	7	2+	175	
3	1.2	F	11	41	16 -ve	1.6	0.22	3+	–	26	22	25	26	23	17	30	3+	103	
4	1.5	F	13	42	13 -ve	1.5	0.31	3+	3+	12	29	12	12	6	11	14	3+	133	
5	1.8	F	14	40	21 -ve	1.58	0.34	3+	2+	5	6	14	15	12	14	339	3	18	

Discussion

In this pilot study we report our disappointing results using IV-CPM in five children with SRNS secondary to MCD or IgM nephropathy. None of our patients achieved a complete or sustained remission. This is at variance with the previous report by Elhence et al. [12]. All seven children who received IV-CPM in their study went into complete remission (100%), which was sustained in four patients. The remaining three patients subsequently became steroid sensitive, while one of four patients who received oral cyclophosphamide responded (25%) and the other three children continued to remain steroid resistant [12]. The poor response in our patients compared with the previous study could be explained by the difference in histopathology. Four of our cohort had IgM nephropathy, while all the patients in the previous study had MCD. Some investigators consider IgM nephropathy as a variant of MCD and they are indistinguishable clinically or in their laboratory characteristics [14, 15, 16]. Others think that, although IgM nephropathy is a variant of MCD and DMH, a significant percentage will develop impaired renal function, due to the evolution of FSGS [17]. Furthermore, it was reported that subepithelial deposits, inflammatory cells, and the percentage of interstitium IgM, IgG, and C3 deposition in MCD is univariately correlated with a poor prognosis and progression to end stage renal failure [18]. IgM nephropathy was also thought to be an entity separate from focal glomerulosclerosis or MCD [19, 20].

IV-CPM therapy was reported to be a safe, effective, and economical therapeutic modality in steroid-resistant children with idiopathic FSGS [11]. Recently, Gulati and Kher [11] from India reported complete remission in 65% of 20 children with FSGS who were treated with IV-CPM, with the mean duration of remission following last dose of IV-CPM of 12.5 months. They used monthly infusions of IV-CPM at a dose of 500–750 mg/m^2, in addition to adjunctive prednisolone [11]. Similarly, Bajpai et al. [21] reported their use of IV-CPM at a dose of 750 mg/m^2 in addition to alternate-day prednisolone in 24 patients with heterogeneous histopathology (MCD in 11, FSGS in 9, and MPGN in 4). At the end of 6 months of treatment, 7 (29.2%) patients each had complete remission and partial remission, while 10 (41.6%) patients showed no response to therapy. However, a higher proportion with MCD (45.5%) achieved complete remission compared with FSGS (22.2%) and MPGN. They concluded that therapy with IV-CPM has limited efficacy in inducing sustained remission in patients with initial corticosteroid resistance. However, sustained remission is likely to occur in a significant proportion of patients with late resistance and those with absence of significant tubulointerstitial changes on renal histology [21]. This raises the possibility of achieving remission with higher IV-CPM doses in non-MCD SRNS. All our patients received a dose of 500 mg/m^2 and we did not observe neutropenia in any patient. Another explanation for poor response or the need for a higher dose of cyclophosphamide is the ethnic and therefore the genetic background of our cohort, as all except one were Arab in origin.

We conclude that IV-CPM pulse therapy at a dose of 500 mg/m^2 was unsuccessful in achieving complete or sustained remission in children with SRNS secondary to IgM nephropathy or MCD. Further randomized controlled studies with higher doses are required.

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