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Original Article

Comparison of oral and intravenous cyclophosphamide in children with steroid-resistant nephrotic syndrome

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Abstract

Background There are variations in remission rates following treatment of steroid-resistant nephrotic syndrome (SRNS) with cyclophosphamide.

Objective To compare the efficacy of oral versus intravenous cyclophosphamide (CPA) in the management of pediatric SRNS.

Methods This was a prospective study of 41 children with SRNS treated with CPA. One group received oral CPA at a dose of 2 mg/kg body weight/day for 8-12 weeks, while the other group received intravenous CPA at a dose of 500mg/m^2 body surface area (BSA) monthly for 6 months. All patients were concomitantly treated with prednisone on alternate days. The primary outcome was the number of patients attaining remission.

Results The study was comprised of 20 children receiving oral CPA and 21 children receiving intravenous CPA. There were 29 boys and 12 girls. The mean age of children at the onset of nephrotic syndrome (NS) was 47 ± 40 months old (range 12 months – 13 years), and the mean duration of NS before initiation of CPA therapy was 15 ± 28 months (range 1 – 129 months). Remission was achieved in 29 (70.7%) patients, with no difference between oral and intravenous route of CPA administration. The mean time to achieve remission was 22.7 weeks (about 5 months). The oral route group required less time in achieving remission than the intravenous route group. No association was found between remission and other factors, such as onset of steroid resistance, route of CPA, hypertension and hematuria. Side-effects included infection, anemia, nausea/vomiting, and alopecia. None of the patients required discontinuation of the medication.

Conclusion Oral CPA was as effective as intravenous CPA for children with steroid-resistant nephrotic syndrome. **[Paediatr Indones. 2011;51:266-71].**

Keywords: steroid-resistant nephrotic syndrome, cyclophosphamide

Nephrotic syndrome (NS) is the most frequent glomerular disease in childhood. Most pediatric patients respond to corticosteroid therapy, but 10% of them fail to respond to this treatment. Resistance to corticosteroids has been shown to be a risk for extra-renal complications of NS, with half progressing to end-stage renal disease (ESRD) within 5 years, constituting about 10% of ESRD in children.[1] Thus, in SRNS, the need for an alternative immunosuppressive treatment is mandatory.

Various therapeutic options are available, including cyclophosphamide (CPA), cyclosporine, intravenous methylprednisolone, angiotensin-converting enzyme inhibitors (ACE-I) and mycophenolate mofetil.[2,3] Most studies have reported a success rate of 50–60%. There are, however, considerable differences in treatment modes, combinations and dosage regimens among these agents.[2] A suitable combination with the least toxicity remains to be determined.

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Among these options, we extensively use CPA as the treatment of choice for SRNS in Indonesia. CPA has been shown to prevent progressive scarring within the kidney, preserve renal function, induce remission, and reduce the risk of end-stage renal failure. But CPA may cause lymphopenia, decrease immunoglobulin secretion, suppress some T-cell functions and enhance immune response by inhibiting suppressor T cells. CPA is an alkylating agent, widely used in steroid-dependent nephrotic syndrome, either orally or intravenously.[4,5]

Intravenous CPA has had a beneficial role in steroid-resistant minimal change disease (MCD), with few side effects. Intravenous CPA has also been used for lupus nephritis and various vasculitides disorders.[6] It has been shown to be an effective form of therapy with significantly fewer side effects than oral CPA.[7] Compared to newer drugs, such as cyclosporine A (CSA), CPA is considered safer for the kidney, less expensive and does not require routine monitoring of plasma levels. Both CPA and CSA are efficacious second-line treatments, following steroid monotherapy. CPA has also been associated with lower relapse rates and longer relapse-free periods.[8,9]

This study aimed to compare the efficacy of oral versus intravenous CPA, for treating SRNS.

Methods

This prospective study was done in the Department of Child Health, Cipto Mangunkusumo Hospital, Jakarta, between 2003 and 2010. Subjects were children with idiopathic SRNS who were subsequently treated with CPA. Patients were enrolled if their SRNS onset was between the age of 1 and 18 years, they were resistant to corticosteroids, and had no other systemic disease that shared pathogenic relation to NS, such as Henoch-Schonlein nephritis and systemic lupus erythematosus. Children with congenital NS were not included. Steroid resistance was defined by the persistence of NS despite prednisone therapy at a dose of 2 mg/kg/day for more than 4 weeks. Patients who responded (negative to trace urine protein for 3 consecutive days) to such therapy during the initial episode, but failed to respond to daily oral prednisolone in a subsequent relapse, were labeled as late steroid resistance. Informed consent was obtained for all subjects.

The following data were obtained for all subjects: demographic characteristics, clinical data (blood pressure, body weight, edema, hematuria, and renal function), time elapsed since the diagnosis of NS, and previous immunosuppressive treatments. Immunosuppressive and other modes of treatment at the time of CPA administration and thereafter were also carefully recorded. An analysis of family history of renal diseases was performed in every case. The data reviewed were age at disease onset, age at the start of CPA treatment, gender, disease duration, response to CPA therapy and discontinuation, and the occurrence of CPA-related side effects. We also examined the peripheral blood and biochemical data of the study population before and at regular intervals after the initiation of CPA, including serum urea, creatinine and albumin. Estimation of GFR was calculated using plasma creatinine concentration according to the Schwartz formula.

The response to CPA was evaluated in terms of remission and time to achieve remission. We defined remission as either complete or partial, because in daily clinical care, both types of remission seem to improve long-term renal survival.[10]

At the initial onset of the disease, all children were given prednisone, 60 mg/m^2/day orally for 4 weeks (FD = full dose), followed by 40 mg/m^2 on alternate days for another 4 weeks (AD = alternate dose). The criteria of SRNS were fulfilled if remission did not occur after FD therapy. None of the children had been treated previously with other immunosuppressive agents. A kidney biopsy was suggested prior to CPA therapy, but most patients did not consent. However, this was not a prerequisite for enrollment in the study.

Oral CPA was given at a dose of 2-3 mg/kg body weight/day for 8-12 weeks, while intravenous CPA was administered at a dose of 500mg/m^2 BSA monthly for 6 months. Intravenous CPA was administered in 100 mL normal saline and infused over 2-3 hours in the one-day care ward. Patients were not given mesna. Treatment was deferred if the total leukocyte count was less than 3,000/mm^3 or the absolute neutrophil count was less than 1,000/mm^3.

All patients also received treatment with oral prednisone at a dose of 1.5 mg/kg on alternate days for the first month, tapered down 0.25 mg/kg per month, and held at a dose of 1 mg/kg until the end

of CPA administration. After completion of CPA treatment, prednisone was again tapered down 0.25 mg/kg every 2 weeks over the next 3 months, then stopped. Angiotensin-converting enzyme (ACE) inhibitor (captopril 0.3-0.6 mg/kg, 3 times a day) and angiotensin receptor blocker (ARB) (losartan 1 mg/kg once a day) were given to patients who started treatment in 2006 and afterwards.

Patients were followed-up every 2 weeks in the first and second months, and every month thereafter. At each visit, they were clinically evaluated and subjected to laboratory assessment, including evaluation of peripheral blood count, plasma urea, creatinine, and spot urine for semi-quantitative proteinuria. Remission was defined by a negative to trace protein on urine dipstick for three consecutive days.

Response to therapy was categorized as complete remission (negative or trace proteinuria), partial remission (1+ proteinuria), and no response (≥ 2+ proteinuria). Renal impairment was defined when (1) serum creatinine increased by 30% or more of its baseline level, even if absolute values were still in the normal range for age, or (2) GFR decreased by 30% or more.

Data were presented as mean ± standard deviation for normally distributed data and median and range for skewed data. Comparison of treatment efficacy between oral and intravenous CPA was analyzed by Kaplan-Meier method and logrank test. Mean comparison between groups was analyzed by Student's t-test, while proportion difference between groups was analyzed by chi-square or Fisher's exact tests. Events were defined as any remission occurring during or after CPA therapy. Time-to-event was defined as the time duration (in months) between the first CPA therapy and remission. A P value of less than 0.05 was considered significant. All tests were two-sided. Statistical analyses were performed with SPSS for Windows PC version 13.0 (SPSS Inc., Chicago, Illinois, USA).

Results

A total of 41 children with SRNS were treated with CPA therapy at our center between 2003 and 2010. There were three times more boys than girls. The mean age of subjects was 47 ± 40 months (range 12 months to 13 years), and the mean duration of NS before initiation of CPA therapy was 15 months (range 1 – 129 months). No subjects had a family history of NS. More than half of the children had primary onset SRNS. Other demographic characteristics are shown in **Table 1**.

At presentation, hypertension was noted in 9 (21.9%) subjects, and microscopic hematuria in 14 (34.1%). Five patients had reduced creatinine clearance with eGFR < 60 mL/min/1.73m^2 due to hypovolemic status caused by hypoalbuminemia. All were normalized by initiation of CPA treatment continuing that way to the end of therapy. Four children developed hypertension on full dose prednisone therapy. Hypertension was well controlled and no patients had hypertension at the time of CPA discontinuation.

Aside from CPA and alternate dose prednisone, ACE inhibitor (captopril) was given to 33 patients, 23 of whom used captopril in combination with ARB (losartan 1 mg/kg once a day). There was no association between remission and the administration of ACE inhibitor and ARB. Twenty-one children received intravenous CPA while the remainder received oral CPA. Twenty-nine (70.7%) children achieved remission after CPA therapy, either orally or intravenously. The mean time to achieve remission was 22.7 weeks, or about 5 months. More rapid remission was achieved through the oral route than

Table 1. Characteristics of the study subjects (n=41)

Characteristic	n = 41
Sex	
• Male, n (%)	29 (70.7)
• Female, n (%)	12 (29.3)
Age Group, n (%)	
• <2 years	9 (22.0)
• 2-6 years	20 (48.8)
• 6-12 years	8 (19.5)
• >12 years	4 (9.8)
Nutritional status, n (%)	
• Obese	4 (9.8)
• Good	33 (80.5)
• Poor	4 (9.8)
Type of SRNS, n (%)	
• Primary resistance	23 (56.1)
• Late resistance	18 (43.9)
Mean hemoglobin, g/dL (SD)	12.6 (2.1)
Mean albumin, mg/dL (SD)	1.9 (0.8)
Mean urea, mg/dL (SD)	28.4 (21.5)
Mean creatinine, mg/dL (SD)	0.7 (0.7)
Mean eGFR, ml/min/1.73m^2 (SD)	110.1 (50.3)

the intravenous but it did not statistically significant route (**Table 2**). Kaplan-Meier analysis also revealed the same conclusion (**Figure 1**).

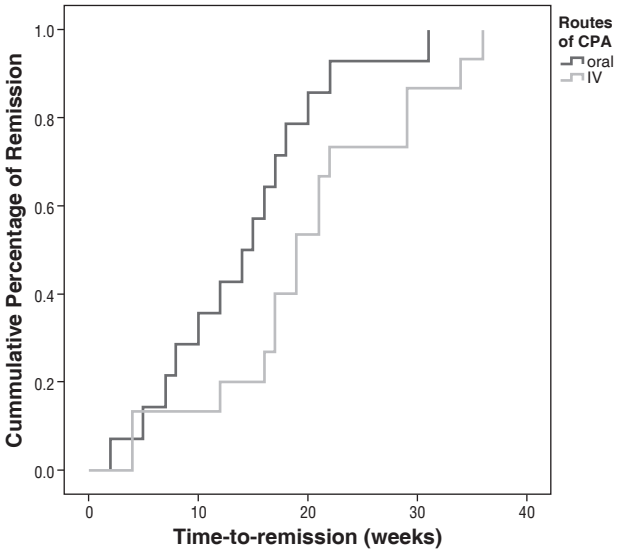

Figure 1. Kaplan-Meier estimation curve for cumulative percentage of remission in patients treated with oral CPA vs intravenous CPA; P=0.047 (log-rank test).

Subjects whose onset of NS was between the ages of 2-6 years were more likely to achieve remission compared to children whose onset was above the age of 6. No association was found between remission and other factors, including onset of steroid resistance, route of CPA treatment, and the presence of hypertension and hematuria (**Table 3**).

During CPA treatment, 7 out of 41 children (17.1%) developed recurrent infections, including diarhea, acute respiratory infection, stomatitis and varicella (after varicella infection this boy went into remission). Other side effects noted were anemia in 4 (9.8%) patients, nausea and vomiting within 24 hours of initiating CPA infusion in 5 (12.2%) patients and reversible alopecia in 1 (2.4%). These side effects were considered mild and did not necessitate discontinuation of the medication.

Discussion

Several controlled therapeutic intervention studies have confirmed that persistence of proteinuria is associated with a higher risk of ESRD.[1,11] Thus,

Table 2. Remission after CPA treatment in children with SRNS

	All patients	oral CPA	intravenous CPA	P value
Duration of treatment, mean ± SD (weeks)	22.7 ± 7.09	18.0 ± 6.21	27.2 ± 4.49	0.004*
Mean time-to-remission, weeks (SD)	17.1 (8.94)	14.1 (7.59)	20.0 (9.38)	0.064§

* Student *t* test; §Mann-Whitney U test

Table 3. Relationships among clinical factors and remission after CPA treatment in children with steroid-resistant nephrotic syndrome (SRNS)

Variables	Remission		P value *Chi-square test*
	Yes, n (%)	No, n (%)	
Onset of NS			
• 1-6 years, (n=29)	24 (82.8)	5 (17.2)	0.020*
• >6 years (n=12)	5 (41.7)	7 (58.3)	
Onset of SRNS			
• Primary resistance	16 (69.6)	7 (30.4)	0.853
• Late resistance	13 (72.2)	5 (27.8)	
Route of CPA treatment			
• Oral	14 (70.0)	6 (30.0)	0.920
• Intravenous	15 (71.4)	6 (28.6)	
Presence of hypertension			
• Yes	10 (76.9)	3 (23.1)	0.719*
• No	19 (67.9)	9 (32.1)	
Presence of hematuria			
• Yes	8 (57.1)	6 (42.9)	0.278*
• No	21 (77.8)	6 (22.2)	

* *Fisher's exact test*

it is necessary to aggressively and safely control proteinuria to prevent progressive renal damage. The available data on the CPA efficacy for NS is scant and contradictory. In our study, 29 (70.7%) patients achieved remission with CPA therapy, either orally or intravenously. This remission rate was better than the average remission rate of 60–65% that has been reported for other immunosuppressive agents in SRNS.[2] Tune *et al*. demonstrated beneficial results in 65% of patients treated with multiple IV pulses of methylprednisolone, oral CPA for 8–12 weeks, and tapering doses of prednisone over 30 months.[12,13]

A study of 13 children was conducted to compare intravenous to oral CPA in minimal change NS patients. All patients in the IV group had remission (100%), compared to 25% remission in the oral group, however, due to small numbers there was no significant difference between therapies.[14] Results from a randomized, controlled study suggested that there was no beneficial effect of oral CPA therapy compared to prednisone in SRNS patients with histopathological characteristics of focal segmental glomerulosclerosis (FSGS).[15] Another prospective study on the efficacy of intravenous CPA reported complete or partial remission in 58% of patients.[16] Mantan *et al*. showed that intravenous CPA combined with oral, alternate dose prednisolone and high, intravenous doses of corticosteroids combined with oral CPA were comparable in inducing remission of SRNS. Complete or partial remissions were achieved in 61.5% of patients receiving intravenous CPA and 56% of patients receiving intravenous dexamethasone with oral CPA.[17] Characteristics of patients in this study were similar to ours in terms of treatment before enrollment. No patients had previously been treated with immunosuppressive drugs other than oral steroids. Similar to our study, other reports have shown the proportion of remissions in initially steroid-resistant patients to be lower than that of patients with late steroid resistance.[16-18]

Randomized, controlled trials in children with SRNS have demonstrated that cyclosporin was more effective than intravenous CPA, suggesting that cyclosporine should be regarded as first line therapy.[19] CPA was used for the majority of patients with steroid-dependent nephrotic syndrome (SDNS).[4,7,9] However, prolonged therapy with oral cyclosporin may be expensive and the need for detailed follow-up limits its use in Indonesia.

In addition, two randomized, controlled trials demonstrated significant reductions in proteinuria with ACE inhibitors in childhood NS.[20,21] A previous study in our hospital revealed the benefits of ACE inhibitors, together with ARB to decrease proteinuria in children with SRNS.[22]

The results of our study suggest that CPA, both orally and intravenously, may be effective for patients with SRNS. The time to achieve remission was more rapid with the oral route than the intravenous route. Therapy was tolerated in most patients with low incidence of side effects. However, it is not possible to make recommendations from this uncontrolled study, with a small number of patients. Further prospective, controlled trials are needed to determine therapeutic guidelines and combined drug protocols for SRNS patients.

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