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Original Article

Cyclophosphamide in frequent-relapsing or steroid-dependent nephrotic syndrome: Review of 38 patients

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ABSTRACT

Background Steroid-sensitive nephrotic syndrome (SSNS) in children is characterized by relapsing courses in a substantial proportion of affected individuals. Children with frequent-relapsing nephrotic syndrome (FRNS) or steroid-dependent nephrotic syndrome (SDNS) are at risk of severe steroid toxicity and need individualized treatment. Previous studies have elucidated that cyclophosphamide (CPA) reduced the risk of relapses and increased the length of subsequent remissions in children with relapsing SSNS.

Methods This retrospective study evaluated 38 patients (26 FRNS and 12 SDNS) after cyclophosphamide therapy to elucidate the efficacy of CPA in FRNS or SDNS in the Department of Child Health, Cipto Mangunkusumo Hospital. All patients were treated with CPA (2 mg/kg per day) for 8 weeks, in combination with prednisone.

Results The median (range) duration of follow up was 45 months (24-140 months) for FRNS and 29 months (24-63 months) for SDNS. The mean relapse rate one year prior to CPA therapy in FRNS and SDNS were 3.8 relapses/year (95%CI 3.4; 4.2) and 4.0 relapses/year (95%CI 3.3; 4.7), which were reduced to 1.6 relapses/year (95% CI 1.1; 2.1) and 2.3 relapses/year (95%CI 1.5;3.2), respectively. The overall rate of cumulative sustained good response (complete remission or infrequent relapses) was 65% after 36 months. Frequent relapsing versus steroid-dependent status was significantly correlated with rate of sustained good response after 36 months (85% versus 15%) with OR=23 (95%CI 3.1;225.2).

Conclusion The efficacy of cyclophosphamide therapy in the management of FRNS is better than in SDNS **[Paediatr Indones 2005;45:18-23].**

Keywords: *nephrotic syndrome, frequent relapse, steroid dependent, cyclophosphamide*

Nephrotic syndrome (NS) is the most frequent glomerular disease encountered during childhood[1] with minimal change disease being the underlying histopathology in more than 85% of cases.[2] Overall, approximately 80-90% children respond to initial corticosteroid therapy, but 76-93% relapse. Approximately half of the relapse children experienced frequent relapses or became steroid dependent that impaired their quality of life.[3,4] Patients with frequent relapsing nephrotic syndrome (FRNS) or steroid-dependent nephrotic syndrome (SDNS) are at risk of severe steroid toxicity, mainly because of the frequency with which they are exposed to continuous, high-dose prednisone to induce remission.[5] A substantial number of frequent-relapsing or steroid-dependent nephrotic children require additional administration of an immunosuppressant, such as cyclophosphamide.[6,7]

Cyclophosphamide (CPA) has been used in the treatment of childhood nephrotic syndrome since 1963. It was initially shown to be effective in prolonging remission but the potential carcinogenic and infertility side effects have limited its use to only one or two courses of 8 to 12 weeks.[5] The usage of CPA has been evaluated in cases of steroid-resistant NS at the Department of Child Health, Cipto Mangunkusumo Hospital in the year 1975,[8] it was

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routinely used as a second line immunosuppresive agent following a steroid regimen.[8,9] To evaluate the efficacy of cyclophosphamide for inducing longterm remission in FRNS or SDNS, we analyzed children treated with this regimen.

Methods

We reviewed children aged 1 to 18 years suffering from primary steroid-responsive NS who relapsed frequently or developed steroid dependence and had been treated with CPA as the second-line immunosuppresive therapy. All children received initial prednisone therapy for NS in the Department of Child Health, Cipto Mangunkusumo Hospital between January 1985 and August 2000.

The definition and criteria for nephrotic syndrome, remission, and relapse were the same as those used by the International Study of Kidney Disease in Children (ISKDC).[10] Nephrotic syndrome was characterized by heavy proteinuria (>40 mg/m^2/h) and hypoalbuminemia (<2.5 g/dl), also often associated with edema and hypercholesterolemia (>250 mg/dl). Steroid-dependent patients were defined as those in whom two consecutive relapses occurred during the alternate-day prednisone treatment regimen given for an earlier relapse; or within 14 days after the end of an alternate-day prednisone regimen. Relapse was defined by the appearance of proteinuria >4 mg/m^2/h (2+ protein or more by Albustix) on three consecutive days, after a known period of remission. A patient was classified as a frequent relapser if he/she experienced more than 1 relapse during any 6-month period or more than 3 relapses during any 12-month period. Steroid resistance was defined as no remission after a minimum of 8 consecutive weeks of prednisone therapy. Complete remission was defined as a reduction in urinary excretion of protein to ≤4 mg /m^2/h for 3 consecutive days.[10,11]

In children who were diagnosed as FRNS or SDNS, all relapses were treated with prednisone 60 mg/m^2 per day initially for two weeks. After remission had been induced, CPA (2 mg/kg per day) were given for 8-12 weeks in combination with prednisone (2/3 of initial dose). Prednisone therapy was discontinued at the same time of stopping CPA. This was the standard cyclophosphamide therapy for FRNS and SDNS in our unit.

Statistical analysis was performed using SPSS 11.5 for Windows and Epi Info. The relapse rate (relapses per year) during 1 year prior to and after CPA was expressed as mean and 95% confidence interval (CI). Kaplan-Meier analysis was performed to calculate the proportion of patients in complete remission and infrequent relapse (good response). The difference between the survival curves of FRNS and SDNS was analyzed with generalized Wilcoxon's test. A P value of less than 0.05 was defined to indicate a significant difference.

Results

There were 190 NS patients traced from clinical records who received initial prednisone therapy in our unit between January 1985 - August 2000. The number of NS patients during that time was actually larger but some patients who had received initial prednisone treatment at other hospitals or who were monitored less than 2 years were not included as the subjects of this study. Among 171 steroid responders, 64 patients became frequent relapsers or steroid dependent and only 59% of them (26 frequent relapsers and 12 steroid dependent patients) were treated with CPA and matched the inclusion criteria.

Tables 1 and **2** show patient characteristics and baseline clinical characteristics at the beginning of CPA therapy. Patients were grouped as SDNS and FRNS. None had hematuria. Hypertension which had occurred in 5 patients was controlled with captropril and/or furosemide.

Median duration of follow up was 45 months (range 24 -140 months) for FRNS and 29 months (range 24 - 63 months) for SDNS, and all were followed up for at least two years. All patients had an eight-week course of CPA at a dosage of 2 mg/kg per day.

Following the CPA therapy, five patients in FRNS group remained in complete remission without any relapse for two years; in contrast, none in the SDNS group was in remission. The number of relapses in one year after initial remission to CPA therapy was significantly reduced in both groups (**Table 3**).

The association between the response to CPA therapy and to initial prednisone at the end of observation period can be seen in **Table 4**. Patients with FRNS showed a better response than those with SDNS.

TABLE 1. DISTRIBUTION OF PATIENT CHARACTERISTICS AT THE BEGINNING OF CPA THERAPY

Patient characteristics	SNRS N = 12	FRNS N = 26	Statistics
Characteristics			
Gender: Male	6	16	NS
Female	6	10	
Age at initial NS manifestation *: ≤ 6 years	10	9	x^2=5.97; p=0.015; OR=9.4
> 6 years	2	17	(95%CI 1.4;81.2)
Age at start of CPA**: ≤ 6 years	10	7	x^2=8.41; p0.004; OR=13.6
> 6 years	2	19	(95%CI 1.9;122.1)
Clinical manifestations			
Hipertension: Positive	1	3	NS
Negative	11	23	
Edema: Generalized	8	10	NS
Non generalized	4	16	
Nutritional status: Good - over nutrition	9	19	NS
Under nutrition	2	5	
Malnutrition	1	2	
Laboratory findings			
Proteinuria: > +1	12	21	NS
+1	0	5	
Albumin: < 2 g/dL	3	8	NS
≥ 2 g/dL	9	18	
Cholesterol: < 350 mg/dL	5	10	NS
≥ 350 mg/dL	7	16	
GFR: 30-49 ml/minute/1.73 m^2	1	1	NS
50-79 ml/minute/1.73 m^2	3	1	
≥ 80 ml/minute/1.73 m^2	8	24	
Renal biopsy: MCNS	-	2	-
Not representative	-	2	

NS = not significant

TABLE 2. DISTRIBUTION OF BASELINE CLINICAL CHARACTERISTICS

Variable	Steroid-dependent		Frequent- relapsing	
	Mean	95% CI	Mean	95% CI
Age at onset of NS (years)	3.76	2.28; 5.25	7.36	5.86; 8.86
Age at start of CPA (years)	4.63	3.22; 6.04	9.07	8.48; 10.56
Cumulative CPA dose (mg/m^2 BSA)	2739	2323; 31556	3023	2840; 3206
Duration of NS before CPA (months)	12.8	7.9; 17.7	16.6	10.2; 23.1
Follow up after CPA (months)	37.8	27.6; 47.9	55.0	41.6; 68.4

TABLE 3. RELAPSE RATE IN PATIENTS WITH SDNS AND FRNS AFTER CPA THERAPY

Number of relapses per year	Steroid-dependent		Frequent-relapsing	
	Mean	95% CI	Mean	95% CI
One year before CPA therapy	4.0	3.3; 4.7	3.8	3.4; 4.2
One year after initial remission after CPA therapy	2.3	1.5; 3.2	1.6	1.1; 2.1

TABLE 4. RESPONSE TO CPA IN FRNS AND SDNS

Initial response to prednisone	Response to CPA until the end of follow-up		
	Good response	Poor response	Statistics
Frequent-relapsing NS	9	3	*Yates corrected* x^2=12.51; P=0.000; OR=23.00l (95%CI 3.02; 229.25)
Steroid-dependent NS	3	23	

The cumulative rate of sustained good response was analyzed in all patients, SDNS and FRNS patients, using the life table analysis method (**Figure 1**). The overall rate of cumulative sustained good response was 65% after 36 months. Patients with FRNS had a significantly higher cumulative rate of sustained good response than those with SDNS (85% versus 15% after 36 months, P=0.0001)

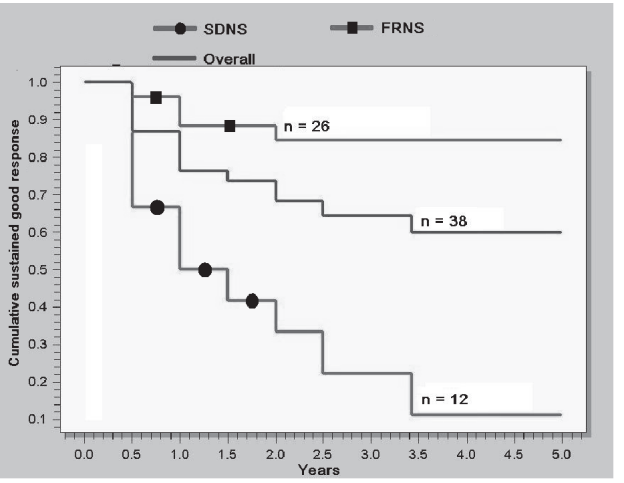

FIGURE 1. SUSTAINED GOOD RESPONSE OVER A PERIOD OF 5 YEARS

During CPA therapy, reversible leukopenia occurred in 5 patients and anemia in one patient. Two patients suffered from hypertension. None developed thrombocytopenia or suffered from hemorrhagic cystitis or severe infection during either the treatment or the following observation. Only one patient needed specific treatment for excessive vomiting. Four patients developed renal failure (3 SDNS and 1 FRNS). The first patient developed renal failure 70 days after remission to CPA therapy, the second patient after 270 days, the rest had suffered from hypertension at the beginning of the CPA therapy. Two patients died at the end of the observation period due to the complications of chronic renal failure, one of them had uncontrolled hypertension.

Discussion

Despite of methodological limitations of a retrospective analysis, we believe our data were valid since we included all patients treated with CPA which made our study population representative. Despite the relatively small number of treated patients, the calculated power of this study is sufficient (90%).

The proportions of FRNS and SDNS in this study were higher than reported by Pulungan[12] (16.5% and 7.9%, respectively) and Wilawirya[13] (18.9% and 1.6%, respectively). This was probably caused by the longer observation period in this study, covering the new NS patients. In 1976, ISKDC reported a higher proportion of FRNS (39%).[2] Not all FRNS and SDNS patients were treated with CPA due to financial constraint, bad compliance and no parental consent.

Steroid dependent nephrotic syndrome patients were younger at the onset of NS compared to FRNS. This result is in agreement with the study of Pennisi *et al.*[14] and Kemper *et al.*[15] (age of 3.1 and 3.7 years, respectively). However, in contrast with our result, there are studies revealing that SDNS patients were older at the time when CPA therapy was started.[14-16] This difference may be due to diversity of treatment schedules.

It has been a common practice to perform renal biopsy prior to the administration of alkylating agent, but Mattoo found that renal biopsy prior to the administration of CPA is not essential in patients who respond to initial corticosteroid therapy.[17] In this study, renal biopsy was only performed in four patients, two of them with minimal change NS and the other two could not be histopathologically typed as the sample were not representative.

Several factors were significantly correlated with the favorable outcome i.e., duration of treatment,[16,18,19] a cumulative dosage per body surface area (BSA) $\leq$ 5040 mg/m^2, leukopenia during CPA therapy, frequent relapsing versus steroid-dependent status, age at onset of the disease, and age when CPA therapy was started.[20] *Arbeitsgemeinschaft für Pädiatrische Nephrologie*[16] (APN) concluded that response to 12-week course of CPA therapy was better than 8-week course, but Ueda *et al.*[18] found no difference between 8-week and 12-week course of CPA therapy. All of our study patients had 8-week course of CPA therapy. The influence of leukopenia in this study could not be analyzed because only 3 patients developed leukopenia during CPA therapy.

Among the patients who got relapses after CPA treatment, some had a marked reduction number of

relapses during one year after remission (**Table 2**). However, patients with FRNS had a significantly better response than patients with SDNS (**Table 3**). A similar result was obtained by *Arbeitsgemeinschaft für Pädiatrische Nephrologie*.[16,21] Kemper *et al*. found that 70% SDNS relapsed and 86% of them became steroid dependent again after 2 years.[15] This study revealed 2 patients became steroid dependent after 2 years. Difference in this study is probably explained by diverse patient selection, different treatment duration and small sample size.

Patients with FRNS had a significantly higher good response than patients with SDNS (85% versus 15% after 36 months, **Figure 2**). This result (in FRNS group) was higher than the studies of Vester *et al*.[20] (54%) and of Latta *et al*.[22] (72%). On the contrary, the result in SDNS group was relatively lower than other studies that used 12-week course of CPA therapy i,e., the study of APN[18] (67%), Kemper[15] (30%), and Ueda[16] (24%). Since our cumulative dosage for BSA was lower than the threshold given by Vester *et al*,[20] we suggest to increase the cumulative dose for SDNS which can be achieved with a longer duration of CPA therapy.

None of the patients in this study developed any serious side effect. Two patients died because of complications of chronic renal failure, one case with uncontrolled hypertension.

In conclusion, our study shows that the efficacy of cyclophosphamide is better in the management of patients with frequent realpsing nephrotic syndrome compared to those with steroid-dependent nephrotic syndrome.

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