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Treatment with Cyclophosphamide for steroid-resistant nephrotic syndrome in children

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ABSTRACT

The management of patients with steroid-resistant nephrotic syndrome remains difficult. We repport our experience with Cyclophosphamide therapy, in an attempt to compare the results between an oral protocol and two i.v. protocols. The complete and sustained general remission rate was 43.1%, which confirms the efficacy of the treatment, especially for children with minimal change nephrotic syndrome. For the i.v. administration we recommend only 6 month of therapy, due to severe side-effects in longer courses.

Key words: nephrotic syndrome, Cyclophosphamide, steroid – resistancy

INTRODUCTION

The management of children with steroid-resistant nephrotic syndrome (SRNS) is a serious problem, as many of these children have difficult problems such as intractable oedema, hyperlipidemia, thrombosis, as well as risk for severe infections.

Cyclophosphamide (CP) has been introduced in 1967 in the nephrotic syndrome protocoles, as the first cytotoxic drug effective in reducing steroid requirement in children with this diagnosis (1). Since then, various protocols have been published, with a variety of cummulative drug exposure, ranging from 84 to more than 300 mg/kg. However, the long-term success of CP treatment is rather disappointing,

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due to a poor remission rate after 5 years and to well known adverse effects, including the oncological risk (2).

We report our experience on the effectiveness of CP in children with SRNS. ❑

METHODS

We performed a retrospective study in 51 children with idiopathic SRNS who have been treated with CP in the IVth Clinic of Pediatrics from Iasi, beginning from 1994 to the end of 2009. We included 45 patients with primary steroid-resistance and 6 patients with secondary steroid-resistance. Only patients who received at least 2 months of oral CP or 3 pulses of i.v. CP and those followed for at least 1 year were included.

The treatment with CP was introduced after 4 weeks of Prednisone course 2 mg/kg/day and 3 alternative boluses of Methilprednisolone 30 mg/kg/day.

We considered the next parameters:

1. age at onset of nephrotic syndrome
2. the hystopathological spectrum of renal biopsies
3. the treatment duration and the cumulative dose per kilogram of body weight, in case of oral and intravenous treatment
4. the evolution after therapy for those patients followed for at least one year.

We used CP in a dose of 2 mg/kg/day, daily, for oral treatment (protocol I), 400 mg/m2/dose, i.v. in monthly boluses, 6 months (protocol II), and 400 mg/m2/dose, i.v. in monthly boluses, 6 months, followed by 3 boluses at 3 months interval (protocol III).

Associated medication during CP consisted of alternate-day Prednisone, in a tapered dosage.

We considered as a good response – remission – the absence of proteinuria for 3 consecutive days and, as persistent remission, at least 6 months of survey with absent proteinuria from the end of therapy with CP.

Statistical analysis was performed using the SPSS 16.0 for Windows. A p value of less then 0.05 was defined to indicate a significant difference. ❑

RESULTS

The age at the onset of nephrotic syndrome varied between 13 and 192 months, with a mean of 99.14 months, and 2 frequency picks at 84 and 168 months.

Renal biopsies were performed only in 47 cases before initiation of oral or i.v. treatment with CP. The hystological findings included:

- mesangioproliferative glomerulonephritis (MesPGN) – 22 patients (43,1%),
- minimal change nephrotic syndrome (MCNS) – 9 patients (17.6%),
- membranous nephropathy (MN) – 8 patients (15.7%),
- focal segmental glomerulosclerosis (FSGS) – 4 patients (7.8%),
- membranoproliferative glomerulonephritis (MPGN) – 4 patients (7.8%).

Patients and treatment characteristics, according to the hystopathological spectrum and response to the therapy with CP, are shown in Table I.

The cumulative dose of CP varied between 26.6 and 490.9 mg/kg, with a mean of 104.59 mg/kg. The duration of treatment with CP varied according to the protocol type. We treated 9 children with protocol I (17.6%), 24 children with protocol II (47.1%), and 18 children with protocol III (35.3%).

There is significant correlation between the age of children at the onset of nephrotic syndrome and the protocol we used ($p=0.027$). Also, there is a strong correlation between the protocol type and the cumulative dose of CP ($p=0.001$), the cumulative dose being higher for the patients treated with protocol I. Twenty-two patients (43.1%) experienced a sustained remission while on CP therapy and one year after the onset of treatment, whereas 29 children (56.9%) had only clinical or no remission. There is no correlation between the histological type and remission of the SRNS ($p=0.258$).

Complete remission was noted in 11.8% of patients under protocol I, in 17.6% of patients under protocol II, and in 13.7% of patients under protocol III.

The adverse effects noted in our cases were: leukopenia (1 patient), acute chemical cystitis (1 patient), allopecia (1 patient) and two cases with severe infections (tuberculous serositis – 1 patient, primary peritonitis – 1 patient). ❑

DISCUSSION

Only a small percentage of the children with nephrotic syndrome fail to enter in remission with Prednisone, the question being about what is the treatment of choice for that specific cases.

	Protocol I	Protocol II	Protocol III	Total
Number of patients	9	24	18	51
Histopathological findings				
-MCNS	1	6	2	9
-MesPGN	3	9	12	24
-MN	2	4	0	6
-FSGS	0	3	1	4
-MPGN	0	1	3	4
- no biopsy	3	1	0	4
Complete remission	6 (11.8%)	9 (17.6%)	7 (13.7%)	22 (43.1%)

TABLE 1. Distribution of patients in our study, according to CP protocol, histology and remission rate

The actual protocols range from alkylating agents, such as CP or Chlorambucil, to Azathioprine, or the newer ones as Mycophenolate mophetil and the calcineurine inhibitors to clasic i.v. therapies like Methilprednisolone, with or without other alkylating agents (i.v. CP). Some case series have pondered on the use of ACE inhibitors such as Lisinopril or Captopril, and on plasmapheresis (3, 4).

CP is the drug which has been mostly used in SRNS in our clinic, still remaining the drug of choice for the moment, due to socio-economic reasons.

We reviewed several case series from international repports and noticed that, because of the small number of patients involved different protocols, it is difficult to conclude weather there is, or there isn't any real advantage of one protocol over another. For instance, for the use of oral CP and Prednisolone, we found only studies that looked at the outcome at the end at the therapy course, about 78% of the children having experienced some improvement, of which 70% achieved complete remission (5). The majority (about 60%) of children went into relapse, actually, after cessation of treatment.

Ehrich had reported complete remission in 25% of SRNS cases, with a combination of oral CP and Prednisone, administered for 90 days (6). In our study there was a poor improvement rate after oral CP, of only 11.8% complete remission (protocol I).

The oral administration of CP was used in our clinic between 1994 and 1998, after that period being choosed other protocols with i.v. CP (7-9). The use of i.v. CP was also due to the absence of the oral drug during that period of time. In our study there was a good response to CP in children less than 7 years old with minimal change nephrotic syndrome, when the cumulative dose was over 200 mg/kg.

The efficiency of the i.v. administration of CP varied between different studies, repported from 40 to 100% of remission (10, 11) after 6 months of therapy. Our remission rate with both oral and i.v. protocols is 43.1%, which is at the lower limit comparative to the international studies. This could be explained by different hystopathological aspects and also by genetic features that we were not able to analyse.

There is concern regarding the long-term effects of alkylating agents. Sterility has been reported in patients treated as children, particularly with prolonged or repeated courses. Therapy with alkylating agents has been also associated with an increased risk of neoplasms (12). For these reasons we advise only 6 months of treatment with i.v. CP.

The duration of follow-up between 12 and 36 months did not allow us to study the long-term effects of treatment with CP. On short-term we noted adverse effects only in 5/51 children. ❑

CONCLUSION

Treatment with CP can still be of an option for the treatment of SRNS, leading to complete and sustained remission in 43.1% of the cases included in our study.

The i.v. administration of CP has significantly better efficiency, when compared with the oral course (31.3% over 11.8%).

For those children, who do not enter into remission after 6 months of CP therapy, we strongly recommend to evaluate another therapeutic option, due to the risk of long-term side effects of CP.

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