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ORIGINAL ARTICLE

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Unfavorable response to cyclophosphamide in steroid-dependent nephrotic syndrome

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Abstract Development of steroid dependency represents a significant therapeutic challenge in steroid-sensitive nephrotic syndrome. Previous studies have shown conflicting results concerning the benefit of a 12-week treatment with cyclophosphamide (CPO), with 24%–67% of patients achieving long-term remission. We therefore analyzed the clinical response of 20 consecutive children with steroid-dependent nephrotic syndrome (SDNS) (12 male, median age at start of treatment 5.9 years, range 3.2–14.7 years) treated at our institution with CPO (2 mg/kg per day) for 12 weeks since 1989. Median duration of follow-up was 5.8 (range 1.1–9.25) years. Only 6 of 20 children (30%) showed a long-term remission of >2 years, while 14 of 20 (70%) developed relapses again. Of these, 12 patients (86%) again developed steroid dependency, requiring further alternative treatment. Our data show that a 12-week course of CPO leads to unfavorable results in the majority of patients with SDNS. We therefore conclude that there is a need for further optimization of therapy in SDNS.

Key words Nephrotic syndrome · Steroid dependency · Cyclophosphamide · Treatment · Steroid sensitivity

Introduction

The idiopathic nephrotic syndrome (NS) of childhood is characterized by relapsing proteinuria and steroid responsiveness in the majority of cases [1]. Initial treatment with prednisone (60 mg/m^2) leads to long-term remission in a variable proportion of patients, but up to 40%–60% of patients develop a relapsing course, with steroid dependency being a major complication in at least half of these patients [2].

The beneficial effect of cytotoxic treatment with cyclophosphamide (CPO) in steroid-sensitive NS (SSNS) has long been established and CPO is still recommended for frequently relapsing and steroid-dependent NS (SDNS) after the development of steroid toxicity [3, 4]. In an initial study of the Arbeitsgemeinschaft für Pädiatrische Nephrologie (APN) [5], there was a significant difference in the success rate of an 8-week course of CPO (2 mg/kg) between patients with frequently relapsing NS and those with SDNS. This led to a second study of a 12-week course of CPO for SDNS, resulting in long-term remission (>2 years) in 67% of patients compared with 22% of patients with SDNS who had previously been treated for 8 weeks [6]. In a prospective, controlled but unblinded study, Ueda et al. [7], however, were unable to confirm these results and patients treated for 8 and 12 weeks with 2 mg/kg had similar frequencies of long-term remission at 5 years (25% vs. 24%). To investigate the efficacy of a 12-week course of CPO for inducing long-term remission in SDNS we analyzed 20 consecutive children treated with this regimen.

Patients and methods

Twenty patients with idiopathic NS of childhood according to the criteria of the International Study of Kidney Diseases in Children [2, 8] were studied. All patients were steroid responsive at initial presentation and were treated according to the standards of the APN [9, 10].

Steroid dependency was defined by at least two relapses during alternate-day (40 mg/m^2) treatment with prednisone or within 14 days of stopping this treatment [5, 6]. In all patients steroid toxicity was present (cushingoid facies and obesity *n*=19, striae *n*=5, hypertension *n*=2, growth retardation *n*=2, psychosis *n*=1). Renal biopsy was performed in all patients prior to cytotoxic treatment and revealed minimal change disease in all cases. Median age at treatment was 5.9 (range 3.2–14.7) years and median follow-up was 5.8 (range 1.1–9.25) years. Further demographic data of the study patients and historical controls from the APN study [6] and the study of Ueda et al. [7] are presented in Table 1.

After completion of CPO, the time of the first relapse was investigated as well as the subsequent clinical course (development

Dedicated to Prof. Karl Schärer, Heidelberg, on the occasion of his 70th birthday

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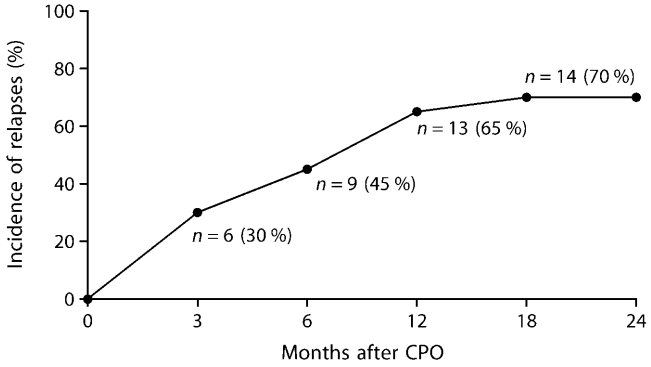

Fig. 1 Percentage of patients in relapse after cyclophosphamide (*CPO*) treatment

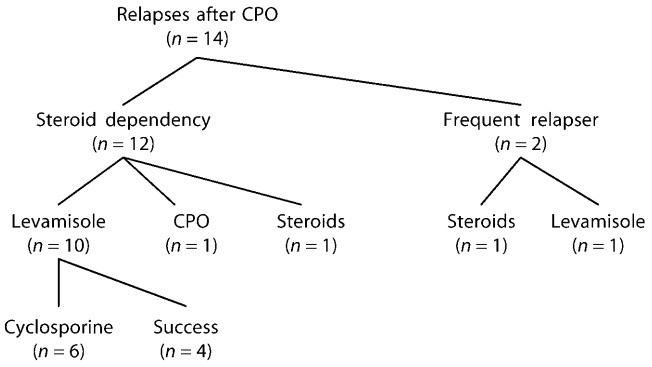

Fig. 2 Flow chart presenting clinical course of 14 patients relapsing after CPO treatment

Table 1 Baseline patient characteristics and outcome of previous and present studies. From the study of Ueda et al. [7] data for patients randomized for 12 weeks of cyclophosphamide (CPO) treatment are presented (*APN* Arbeitsgemeinschaft für Pädiatrische Nephrologie, *NS* nephrotic syndrome)

	APN [9] (*n*=18)	Ueda et al. [7] (*n*=41)	Present study (*n*=20)
Male	6/18 (38%)	67%	12/20 (60%)
Age at presentation (years)(mean ± SD)	5.8 (4.0)		3.7 (1.4)
Duration of NS (years)(mean ± SD)	2.9 (2.5)	1.6 (2.1)	3.2 (3.7)
Age at CPO treatment (years)(mean ± SD)	8.6 (4.0)	7.8 (3.7)	6.9 (3.3)
Patients in remission at 12 months			7/20 (35%)
Patients in remission ≥ 24 months	12/18 (67%)	10/41 (24%)	6/20 (30%)

Table 2 Prognostic factors in present study. There was no statistical difference between groups

	Responder	Non-responder
HLA-DR 7 positive	3/6 (50%)	11/14 (79%)
Male	3/6 (50%)	9/14 (64%)
Mean (SD) age at presentation (years)	3.9 (1.1)	3.8 (1.5)
Mean (SD) duration of NS (years)	3.2 (3.5)	2.5 (2.9)
Mean (SD) age at treatment (years)	7.1 (3.8)	6.2 (3.1)

of steroid dependency, necessity for alternative treatment). A responder to CPO treatment was defined as having a remission of at least 2 years after completion of cytotoxic treatment.

Prognostic factors (gender, age at presentation, age at treatment, presence of HLA-DR 7) were analyzed by Fisher's exact test or by the Mann-Whitney U-test as appropriate. $P<0.05$ was considered statistically significant.

Results

Of the 20 patients, 6 (30%) had a long-term remission of >2 years after a 12-week course of CPO, while 14 (70%) continued to have relapses. Figure 1 shows the incidence and the time sequence of these relapses. Of the 14 non-responders, 12 developed steroid dependency again and required extended treatment strategies (Fig. 2). Ten patients were treated with levamisole (2–2.5 mg/kg per 48 h) and 4 patients had no relapses during this treatment (success); in 3 patients remission was maintained after discontinuation of levamisole treatment. One patient with severe mental retardation due to birth asphyxia received a second course of CPO for 12 weeks (no relapse after 11 months of follow-up) and 1 received deflazacort (no relapse after 15 months of follow-up).

Two of the non-responders had a milder clinical course compared with pre CPO and could be classified as frequent relapsers; 1 of these required treatment with levamisole, while the other was managed with steroids. Both patients eventually stopped relapsing 3 and 4 years after CPO treatment. The 6 patients who responded to CPO treatment have remained in remission for a median of 6.8 (range 2.3–9.2) years at latest follow-up.

During CPO treatment, 5 patients (3 responders, 2 non-responders) developed reversible leukopenia (<4,000/mm^3), 2 acquired varicella infections (without dissemination), and 1 suffered from hemorrhagic cystitis, responding to mesna treatment. No patient developed malignant transformation of white blood cells or had clinical evidence of gonadal toxicity.

Table 1 compares demographic data and results of our study with those of previous studies. Relapse rates in the study of Ueda et al. [7] and our patients are comparable. An analysis of prognostic factors in our study is presented in Table 2. Neither demographic nor immunogenetic predictive markers could be identified.

Discussion

In this retrospective single-center analysis the majority of patients with SDNS did not benefit from a 12-week course of CPO; 70% of patients developed relapses again and almost all relapsing patients (86%) developed steroid dependency again, requiring alternative treatment. This clearly indicates that the severity of the disease course in our patients was not influenced by a 12-week course of CPO.

Despite the methodological limitations of a single-center retrospective analysis, we believe our data are valid since our study population is representative, with the inclusion of all patients treated. Although the number of treated subjects is relatively small (albeit larger than in the APN study), a beneficial effect of CPO treatment should have been evident.

Our data correspond well to the results of the randomized study of Ueda et al. [7], indicating that the response of SDNS patients to CPO treatment might be worse than previously expected from the APN study [6]. Differences in this study are probably explained by diverse patient selection. Interestingly, the cited study is characterized by a female preponderance, being rather atypical of the SDNS. Furthermore, patients were slightly older at the time of CPO treatment than in our study and that of Ueda et al. [7], indicating possible confounding variables. This suggests that children with milder disease courses might be over-represented in the APN study, leading to better results after cytotoxic treatment. Alternatively, older patients might respond better to cytotoxic treatment, since the cumulative dose per square meter of body surface area is higher, as indicated by a recent study of Vester et al. [11].

Comparisons with other studies of CPO treatment in SDNS are complicated by differences in patient selection, definition of steroid dependency, treatment response, and drug dosages. Takeda et al. [12], for instance, recently reported a sustained remission rate of 42.9% at 12 months using a CPO regimen of 2–2.5 mg/kg for 8–12 weeks, with a further decline of remission rate at 2 years. In another retrospective analysis, Neuhaus et al. [13] reported a success rate (defined as no further treatment necessary except alternate-day steroids of <0.5 mg/kg) of 57% after a first course of CPO in 181 patients (3 mg/kg for 8 weeks). These data indicate that CPO does play a substantial role in the treatment of SDNS, but also reflect the diversity of treatment schedules and definitions of steroid dependency.

We found no clinical or immunogenetic factor of value in predicting the response to cytotoxic treatment. In a study combining patients from France and Germany, Konrad et al. [14] showed that patients bearing the HLA-DR 7 haplotype responded significantly worse to CPO. However, possibly due to small sample size, HLA-DR 7 was not linked to failure of CPO treatment in our group, although HLA-DR 7 was more frequent in the cohort with treatment failure (79% vs. 50%).

In summary, in 20 consecutive patients with SDNS a 12-week course of CPO at a dose of 2 mg/kg did not result in long-term remission in the majority (70%) of patients. Because the possible long-term side effects of CPO (gonadotoxicity, oncogenicity, and bone marrow suppression) are dose related [15, 16], the risk-benefit ratio of CPO in the treatment of SDNS in our opinion needs re-evaluation. Our data indicate no benefit of a prolonged CPO treatment with higher cumulative doses, and therefore a shorter course might bear fewer long-term risks. Although CPO remains an important treatment option in SDNS [17], the poor response to CPO and the problems associated with other forms of immunosuppression in SDNS [18] indicate the need for alternative treatments.

References

1. Barratt M, Clark G (1995) Minimal change nephrotic syndrome and focal segmental glomerulosclerosis. In: Holliday MA, Barrat TM, Avner ED (eds) Pediatric nephrology, 3rd edn. Williams and Wilkins, Baltimore, pp 767–787
2. International Study of Kidney Diseases in Children (1982) Early identification of frequent relapsers among children with minimal change nephrotic syndrome. J Pediatr 101:514–518
3. Barratt TM, Bercowsky A, Osofsky SG, Soothill JF (1975) Cyclophosphamide treatment in steroid-sensitive nephrotic syndrome of childhood. Lancet I:55–58
4. Garin EH, Pryor ND, Fenell RS, Richard GA (1978) Pattern of response to prednisone in idiopathic, minimal lesion nephrotic syndrome as criterion in selecting patients for cyclophosphamide therapy. J Pediatr 92:304–308
5. Arbeitsgemeinschaft für Pädiatrische Nephrologie (1982) Effect of cytotoxic drugs in frequently relapsing nephrotic syndrome with and without steroid dependency. N Engl J Med 306:451–454
6. Report of the Arbeitsgemeinschaft für Pädiatrische Nephrologie (1987) Cyclophosphamide treatment of steroid dependent nephrotic syndrome: comparison of eight week with 12 week course. Arch Dis Child 62:1102–1106
7. Ueda N, Kuno K, Ito S (1990) Eight and 12 week course of cyclophosphamide in nephrotic syndrome. Arch Dis Child 65:1147–1150
8. International Study of Kidney Diseases in Children (1978) Nephrotic syndrome in children: prediction from histopathology from clinical and laboratory characteristics at time of diagnosis. Kidney Int 13:159–165
9. Arbeitgemeinschaft für Pädiatrische Nephrologie (1988) Short versus standard prednisone therapy for initial treatment of idiopathic nephrotic syndrome. Lancet I:380–383
10. Ehrich JHH, Brodehl J, Arbeitsgemeinschaft für Pädiatrische Nephrologie (1993) Long versus standard prednisone therapy for initial treatment of idiopathic nephrotic syndrome in children. Eur J Pediatr 152:357–361
11. Vester U, Zimmermann S, Hoyer PF (1999) Cyclophosphamide therapy in frequent relapsing and steroid dependent minimal change nephrotic syndrome: new insights from an old protocol (abstract). Pediatr Nephrol 13:C67
12. Takeda A, Ohgushi H, Niimura F, Matsutani H (1998) Long-term effects of immunosuppressants in steroid-dependent nephrotic syndrome. Pediatr Nephrol 12:746–750
13. Neuhaus TJ, Fay J, Dillon MJ, Trompeter RS, Barratt TM (1994) Alternative treatment to corticosteroids in steroid sensitive idiopathic nephrotic syndrome. Arch Dis Child 71: 522–526

14. Konrad M, Mytilineos J, Ruder H, Opelz G, Schärer K (1997) HLA-DR 7 predicts the response to alkylating agents in steroid-sensitive nephrotic syndrome. Pediatr Nephrol 11: 16–19
15. Etteldorf JN, Clark CD, Pitcock JA, Williams DL (1976) Gonadal function, testicular histology and meiosis following cyclophosphamide therapy in patients with nephrotic syndrome. J Pediatr 88:206–212
16. Lentz RD, Bergstein J, Steffes MW, Brown DR, Prem K, Michael AF, Vernier RL (1977) Postpubertal evaluation of gonadal function following cyclophosphamide therapy before or during puberty. J Pediatr 91:385–394
17. Report of a workshop by the British Association of Paediatric Nephrology and Research Unit, Royal College of Physicians (1994) Consensus statement on management and audit potential for steroid responsive nephrotic syndrome. Arch Dis Child 70:151–157
18. Hulton SA, Neuhaus TJ, Dillon MJ, Barratt TM (1994) Long-term cyclosporin A treatment of minimal-change nephrotic syndrome of childhood. Pediatr Nephrol 8:401–403

LITERATURE ABSTRACTS

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Evaluation of measured and calculated creatinine clearances as glomerular filtration markers in different stages of liver cirrhosis

Clin Nephrol (1999) 51:341-347

Background Discrepant results have been published regarding the suitability of creatinine clearance [C(Cr)] as a measure of glomerular filtration rate (GFR) in cirrhotic patients with normal renal function.
Methods In this study we evaluated the accuracy and precision of measured and calculated C(Cr) as indexes of GFR by comparing their values to those of inulin clearance [C(In)] in 10 healthy subjects and 20 patients with either Child's class A or Child's class C liver cirrhosis.
Results The accuracy and precision of GFR estimates obtained by measuring C(Cr) were good in all three study groups. The mean values of the C(Cr)/C(In) ratio were 1.05, 1.03 and 1.04, respectively, and the corresponding coefficients of variations were 2.9%, 2.9% and 3.8%. A close correlation between C(Cr) and C(In) was also found in each study group (r = 0.98, 0.99 and 0.97, respectively, with $P < 0.001$ in each case). C(Cr) calculated from serum creatinine by means of the Cockcroft-Gault formula (predicted GFR) proved to be a suitable measure of GFR in normal subjects and patients with Child's class A cirrhosis: the predicted-to-true GFR ratios were 0.93 and 0.94, respectively, CV was 12% in both cases. Moreover, a significant correlation between predicted and true GFR was observed in both groups (r = 0.73, $P < 0.02$ and r = 0.69, $P < 0.025$, respectively). On the contrary, in Child's class C cirrhotics, calculated C(Cr) significantly overestimated GFR (predicted-to-true GFR ratio 1.23, CV 20%) and no significant correlation was found between predicted and true GFR (r = 0.58, $P > 0.05$).
Conclusions In conclusion, this study shows that measured C(Cr) is a reliable index of GFR in cirrhotic patients, irrespective of the degree of liver dysfunction. Calculated C(Cr) is still an adequate marker of GFR in patients with compensated liver cirrhosis, whereas it overestimates GFR in patients with decompensated cirrhosis. A lower muscle mass, a reduced ability to convert creatine to creatinine, and the presence of ascites are most likely responsible for the overestimation of GFR by the Cockcroft-Gault formula in the latter patients.

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Collapsing glomerulopathy: clinical characteristics and follow-up

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In 1986, Weiss et al. reported a group of patients with nephrotic syndrome, progressive chronic renal failure, and the histopathologic features of glomerular capillary collapse. Similar lesions are often described in human immunodeficiency virus (HIV) nephropathy. We evaluated 893 consecutive nontransplant renal biopsies performed in our department and the follow-up of the patients at our outpatient service. Sixteen specimens were identified with the pathological features of collapsing glomerulopathy (focal segmental or global glomerular capillary collapse and visceral epithelial cell hyperplasia), with no evidence of HIV infection and/or intravenous drug abuse. Their clinical characteristics were analyzed and compared with a group of 29 patients with noncollapsing focal segmental glomerulosclerosis (FSGS). The follow-up period of both patient groups was 5 +/- 1.46 years. The Kaplan-Meier life table method was used to present survival of the patients. The age of both groups was similar, 34 +/- 4 years (mean +/- standard error of the mean) for patients with collapsing glomerulopathy and 35 +/- 3 years for those with FSGS. The serum creatinine level was greater in patients with collapsing glomerulopathy (183 +/- 31 micromol/L) compared with those with FSGS (115 +/- 18 micromol/L), but the difference was not significant (P = 0.0504). The difference in proteinuria was not significant (P = 0.7668); it was 5.83 +/- 0.74 g/d in patients with collapsing glomerulopathy and 5.42 +/- 0.84 g/d in those with focal sclerosing glomerulonephritis. The difference in systolic (P = 0.4) and diastolic blood pressure (P = 0.556) was also not significant. Survival of the patients with collapsing glomerulopathy was worse than that of patients with FSGS (P = 0.025). Renal function survived 5 years in 40% of the patients with FSGS, but patients with collapsing glomerulopathy had no renal function survival. Our data suggest that idiopathic collapsing glomerulopathy is a distinct clinicopathologic entity with similar clinical features to focal sclerosing glomerulonephritis, but a worse prognosis and a rapidly progressive course toward end-stage renal disease.