Eur J Pediatr (1988) 147:239–241

European Journal of
Pediatrics

Cyclophosphamide in treatment of minimal change nephrotic syndrome

I. Shohet[1], J. Meyerovitch[2], M. Aladjem[2], and H. Boichis[2]

[1]Department of Clinical Epidemiology and [2]Department of Paediatrics "C", The Chaim Sheba Medical Centre, Sackler School of Medicine, Tel Aviv University, Tel Hashomer, 52621, Israel

Abstract. Nineteen children with the minimal change form of nephrotic syndrome were divided according to their pattern of response to prednisone: steroid-dependent and frequent relapsers. All patients received cyclophosphamide for 56 days in a single daily dose of 2.5 mg/kg (total 140 mg/kg), in order to prolong the length of remission. The percentage of patients who continued in remission at the end of the 1st, 2nd and 5th years was greater in the frequent-relapser group. This retrospective analysis confirms that the pattern of response to prednisone may be an important criterion for the selection of patients who will benefit from cyclophosphamide therapy.

Key words: Nephrotic syndrome – Corticosteroid – Cyclophosphamide

Introduction

The minimal change form of nephrotic syndrome is the most frequent type of nephrotic syndrome in children [20]. It is characterized by normal kidney function, responsiveness to corticosteroid therapy in most instances, minimal or no findings on light microscopy, and fusion of the epithelial foot processes seen on electron microscopy [6].

The goal of therapy is the cessation of urinary protein excretion. Treatment with a standard initial prednisone regimen (60 mg/m^2 per 24 hours in divided doses for 4 weeks and 40 mg/m^2 per 24 hours three times weekly for 4 weeks) was found to be satisfactory in terms of the subsequent course and lack of toxicity in approximately 20% of over 380 children with minimal change histology, treated between 1967 and 1976 [14]. These patients either did not relapse or relapsed so infrequently that additional short courses of prednisone therapy were effective and produced no discernible toxicity. However, this treatment regimen was not satisfactory for the 40% or more who did respond, but then relapsed frequently [13].

Cyclophosphamide has been known to be effective in reducing the proportion of patients who relapse frequently and in increasing the length of subsequent remissions in those who nevertheless do relapse. When cyclophosphamide is used concomitantly with prednisone, it is more effective than intermittent prednisone alone in inducing a prolonged remission [12]. Because of the potential risk of sterility, as well as side-effects such as haemorrhagic cystitis, alopecia, leucopenia and infections, it has been recommended that cyclophosphamide be used only in carefully selected patients and under close supervision [7, 8, 18].

The purpose of our retrospective study was to define the characteristics of those patients who benefitted most from cyclophosphamide therapy. The pattern of response to prednisone in idiopathic minimal lesion nephrotic syndrome can serve as a guideline in selecting patients for cyclophosphamide therapy.

Offprint requests to: I. Shohet

Materials and methods

Twenty-one children between 1 and 18 years of age with steroid-dependent and frequent-relapsing nephrotic syndrome, presenting between 1968 and 1982, were treated with a combination of prednisone and cyclophosphamide. Two children did not fulfill the study criteria regarding cyclophosphamide dosage and duration of therapy because of low compliance, and therefore were not included in the study. None had macroscopic haematuria, hypertension, hypocomplementaemia, or decreased glomerular filtration rate.

A bout of nephrotic syndrome was defined (International Study of Kidney Disease in Children) as proteinuria greater than 40 mg/m^2 per hour which responded to treatment with a return of protein excretion to normal values (proteinuria less than 4 mg/m^2 per hour [14]).

Eleven children were defined as frequent relapsers (group A) (ISKDC), with two or more relapses within 6 months of an initial response, or five or more relapses within any 1 year, with remission periods longer than 10 days [2]. Eight children were defined as steroid dependent (group B), in whom two consecutive relapses occurred after the amount of prednisone given had been reduced to an alternate-day schedule, or within 10 days after the end of a course of steroid therapy [2].

Corticosteroid treatment was given with 60 mg prednisone/m^2 body surface area per day in three to four divided doses for 4 weeks in the first bout, and until the urine was protein free for 3 consecutive days in relapses [3]. This was followed by alternate-day therapy with 40 mg/m^2 per 24 hours as a single morning dose for 4 weeks [14].

Cyclophosphamide was given in a dosage of 2.5 mg/kg per day for 56 days (total 140 mg/kg) combined with prednisone at a dosage of 60 mg/m^2 per 24 hours for 2 weeks, or after induction remission by steroid therapy. The prednisone was gradually tapered off within 2 additional weeks [5, 15, 17]. Acute side-effects were recorded and cyclophosphamide was temporarily discontinued if the total white cell count fell below 2000/nm, and was restarted when it rose above 4000/nm.

Table 1. The number of children with remission periods of 1, 2, and 5 years who were treated with cyclophosphamide for frequent-relapsing and steroid-dependent nephrotic syndrome

	Remission periods			No remission	Total
	1 year	2 years	5 years		
Frequent relapser	1	2	4	4	11
Steroid dependent	1	0	0	7	8

Renal biopsies were performed before cyclophosphamide treatment in seven patients in group A and four patients in group B, in order to exclude children with disorders other than minimal change disease. Semi-quantitative measurements of protein in the urine were performed by the parents of patients throughout the entire period of observation. Proteinuria was detected in urine by Albustix and was graded 0–4+ according to the manufacturer's scale.

Results

Nineteen children were found to meet the study criteria. The two groups were comparable with regard to mean age at the time of the initial attack, mean duration of nephrotic syndrome prior to therapy, and mean follow-up period.

All children responded well to the combination of prednisone and cyclophosphamide and were still in remission at the end of the combined therapy. The time of discontinuation of cyclophosphamide was taken as the start of the remission period. No correlation was found between the patient's age and the remission period.

In children with frequent relapses, treatment with cyclophosphamide induced long-lasting remission in the majority of cases, in contrast to children with steroid-dependent nephrotic syndrome (Table 1). Seven out of 11 children in group A and 1 of 8 in group B were still in remission at the end of the 1st year. Five children in group A and none in group B were in remission at the end of the 2nd year. After 5 years of follow-up, four children in group A and none in group B were still in remission. The difference in relapse rate between the two groups was found to be statistically significant ($P = 0.025$, Fisher exact probability test). This indicates a clear superiority of the use of cyclophosphamide for frequent relapsers over its use for steroid-dependent nephrotic syndrome patients.

Acute side-effects attributed to cyclophosphamide were encountered in nine patients: six patients needed temporary cessation of therapy because of neutropenia which appeared at some time between the 1st and the 8th week after initiation of cyclophosphamide. Moderate hair loss was noted in one child, while two others suffered from mild hair loss. In all instances the hair grew back after cessation of treatment. None of our patients complained of dysuria and weekly urinalyses gave negative results. No significant viral, bacterial or fungal infections were observed.

Discussion

Steroid dependence and frequent relapses are known variants of minimal change nephrotic syndrome [9]. Although toxic effects of prolonged corticosteroid therapy have been reduced by the use of alternate-day schedules, the uncertainty of the long-term results justifies new approaches to the treatment of minimal change nephrotic syndrome [5, 10, 19]. About 25% of the patients are steroid dependent or frequent relapsers and are candidates for such cytotoxic therapy [1, 12].

Several authors have previously reported the efficacy of cyclophosphamide in treatment of the minimal change form of the nephrotic syndrome [1, 11, 12]. Comparative studies have demonstrated that the administration of steroids together with cyclophosphamide resulted in longer average remissions than trials in which cyclophosphamide was given alone [4]. Recent reports of infertility, azospermia, amenorrhoea,, and ovarian fibrosis following cyclophosphamide treatment stress the need for careful selection of patients for this type of treatment and for the limited duration of drug administration [7, 16, 18].

The results of this retrospective study confirm the conclusions drawn by Garin et al. [9] in their retrospective analysis and by the controlled prospective study of the Arbeitsgemeinschaft für Pädiatrische Nephrologie [2]. Both had concluded that children with minimal change nephrotic syndrome with frequent relapses will respond favourably to cyclophosphamide therapy, while children with steroid dependency will not benefit from this treatment. The dose of cyclophosphamide used by them was 2 mg/kg given for 8 weeks. They suggested primary resistance to cyclophosphamide in the steroid-dependent patients, or a too low cumulative dosage of cyclophosphamide, as possible explanations.

Our patients were treated with cyclophosphamide in a dosage of 2.5 mg/kg given for 56 days with a total cumulative dosage of 140 mg/kg. The total dose of cyclophosphamide we used was significantly higher than that used by Garin et al. and the Arbeitsgemeinschaft für Pädiatrische Nephrologie. Analysis of the remission periods and relapse rates shows a clear advantage of cyclophosphamide therapy for frequent relapsers over its use with steroid-dependent nephrotic syndrome patients.

These results suggest that the pattern of response to prednisone in idiopathic minimal lesion nephrotic syndrome can serve as a criterion in selecting patients for cyclophosphamide therapy. Further study is necessary to confirm these findings and to explore the possible reasons for this difference.

References

1. Abramowicz M, Edelmann CM, Spitzer A (1970) Dogma disputed: Alternate-day steroid therapy in the nephrotic syndrome of childhood. J Pediatr 76:336–338
2. Arbeitsgemeinschaft für pädiatraiche Nephrologie (1982) Effect of cytotoxic drugs in frequently relapsing nephrotic syndrome with and without steroid dependence. N Engl J Med 306:451–454
3. Arnell GC, Lam CN (1966) Long term assessment of steroid therapy in childhood rephrosis. Lancet II:819–821
4. Barratt TM, Soothill JF (1970) Controlled trial of cyclophosphamide in steroid-sensitive relapsing nephrotic syndrome of childhood. Lancet II:479–482
5. Barratt TM, Bercowsky A, Osofsky SG, Soothill JF (1975) Cyclophosphamide treatment in steroid-sensitive nephrotic syndrome of childhood. Lancet I:55–58
6. Churg J, Habib R, White RHR (1970) Pathology of the nephrotic syndrome in children. A report of the International Study of Kidney Disease in Children. Lancet I:1299–1302
7. Etteldorf JN, West CL, Pitcock JA, Williams DL (1976) Gonodal function, testicular histology and meiasis following cyclophos-

phamide therapy in patients with nephrotic syndrome. J Pediatr 88:206–212
8. Fairly KF, Barrie JU, Johnson W (1972) Sterility and testicular atrophy related to cyclophosphamide therapy. Lancet I:568–569
9. Garin KF, Pryor ND, Fennell RS, Richard GA (1978) Pattern of response to prednisone in idiopathic, minimal lesion nephrotic syndrome as a criterion in selecting patients for cyclophosphamide therapy. J Pediatr 92:304–308
10. Harter JG, Reddy WJ, Thorn GW (1963) Studies on intermittent corticosteroid dosage regimen. N Engl J Med 269:591
11. Herin P, Eriksson M (1980) Cytotoxic treatment in children with idiopathic nephrotic syndrome. Acta Paediatr Scand 69:315–320
12. International Study of Kidney Diseases in Children (1974) Prospective, controlled trials of cyclophosphamide therapy in children with the nephrotic syndrome: report of the Lancet II:423–427
13. International Study of Kidney Diseases in Children (1979) Nephrotic syndrome in children: a randomized trial comparing two prednisone regiments in steroid-responsive patients who relapse early. J Pediatr 95:239–243
14. International Study of Kidney Diseases in Children (1981) Primary nephrotic syndrome in children: clinical significance of histopathologic varients of minimal change and of diffuse mesangial hypercellularity. Kidney Int 20:765–771
15. McCrory WW, Shibuya M, Wen-Hsiung L, Levy JE (1973) Therapeutic and toxic effects observed with different dosage programs of cyclophosphamide in treatment of steroid-responsive, but frequently relapsing nephrotic syndrome. J Pediatr 82:614–618
16. Parra A, Santon D, Cervantes C, Sojo I, Carranco A, Cortes-Gallegos V (1978) Plasma gonadotrophins and gonadal steroids in children treated with cyclophosphamide. J Pediatr 92:117–124
17. Pennisi AJ, Grushkin CU, Lieberman E (1976) Cyclophosphamide in the treatment of idiopathic nephrotic syndrome. Pediatrics 57:948–951
18. Penso J, Lipde B, Ehrlich R, Smith FG (1974) Testicular function in prepubertal and pubertal male patients treated with cyclophosphamide for nephrotic syndrome. J Pediatr 84:831–836
19. Soyka LF (1967) Treatment of the nephrotic syndrome in childhood. Am J Dis Child 113:693–701
20. White RHR, Glasgow EF, Mills RJ (1970) Clinicopathological study of nephrotic syndrome in children. Lancet I:1353–1359

Received June 9, 1987 / Accepted September 22, 1987