Pulse cyclophosphamide inadequately suppresses reoccurrence of minimal change nephrotic syndrome in corticoid-dependent children

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Abstract

Background. In minimal change nephrotic syndrome (MNCS), the most common primary nephrotic syndrome in children, ~95% of cases show excellent responses to steroid therapy. However, responding patients may become steroid dependent and experience serious side effects. Although oral cyclophosphamide has been recommended in these patients, long-term side effects such as gonadal toxicity are an important concern. Therefore, cyclophosphamide pulses given intravenously may provide an option that maintains remission with less-frequent side effects.

Methods. We treated 20 primary steroid-dependent MCNS patients (15 boys and five girls) with intravenous cyclophosphamide. The patients were children with ages ranging from 3 to 15 years of age. Remission was induced by steroids followed by cyclophosphamide at a dose of 500 mg/m² body surface area per month for 6 months. During this period, we attempted to completely withdraw steroids and maintain patients on cyclophosphamide alone. We monitored the patients for the occurrence of relapse and side effects during this period and for an additional 6 months after withdrawal of cyclophosphamide.

Results. At the end of the 6-month cyclophosphamide treatment period (i.e. 4 months after steroid discontinuation), nine patients (45%) were in remission on cyclophosphamide alone. However, patients that maintained treatment-free remission (cyclophosphamide responders) decreased to five (25%), two (10%) and one (5%) at 6 months, 1 year and 2 years, respectively.

Conclusion. We found that a 6-month course of pulse cyclophosphamide produced unfavourable effects in the majority of paediatric patients with steroid-dependent nephrotic syndrome.

Keywords: children; cyclophosphamide; minimal change; steroid dependent

Introduction

The development of steroid dependence in minimal change nephrotic syndrome (MCNS) patients is an important medical concern [1]. Prolonged or repeated use of corticosteroids often results in serious side effects, such as cushingoid obesity, striae, hypertension, growth failure and psychoemotional changes [2]. In MCNS patients, oral cyclophosphamide is usually recommended, especially in individuals with marked steroid side effects [3]. However, the use of daily cyclophosphamide has been associated with bone marrow depression, increased susceptibility to infections, haemorrhagic cystitis, alopecia, gonadal failure and malignancy [4]. The intravenous (i.v.) pulse administration of cyclophosphamide may lead to reductions in total dose compared to daily oral treatment and may provide favourable treatment for many diseases [5]. For example, it is well known that pulse treatment is effective for lupus nephritis and other vasculitic disorders and exerts significantly fewer side effects than oral cyclophosphamide therapy [5–7]. Nevertheless, oral cyclophosphamide remains the standard therapy for idiopathic glomerulonephritis [8].

There have been few studies on the use of i.v. cyclophosphamide pulse administration in idiopathic glomerulonephritis. Of these, only a limited number have examined the efficacy of this regimen on nephrotic syndrome patients that have minimal change lesions, that are steroid dependent, or both [9–11]. More importantly, only one of these reports was performed prospectively in a complete manner [11].

In our study, we prospectively evaluated safety and efficacy of i.v. cyclophosphamide pulse administration in steroid-dependent MCNS children. These findings are directly comparable with findings from oral
Pulse cyclophosphamide for corticoid-dependent MCNS children

...cyclophosphamide therapy, which is commonly associated with non-compliance problems.

Subjects and methods

Patients

We prospectively studied 20 children with idiopathic nephrotic syndrome selected from patients attending the outpatient clinic or admitted to the nephrology department of our centre during the period of May–December 1998. Ages ranged from 3 to 15 years, and there were 15 boys and five girls. The initial corticosteroid treatment for all patients at disease onset consisted of the International Study of Kidney Disease in Children (ISKDC) protocol (short attack treatment). All patients had a steroid-dependent pattern of response defined as the occurrence of complete remission on steroids but relapse upon withdrawal (18 patients) or within 2 weeks after withdrawal (two patients) of steroid treatment [12]. In addition, all had biopsy-proven minimal change lesions. All received more than one steroid course (median = 2.5). None had received any type of adjunctive therapy for nephrotic disease before the study. At study onset, all patients had normal creatinine values and normal complete blood counts. Parental consent was obtained before the study, which was approved by the scientific and ethics committee of the hospital.

Study design

All patients were in relapse at the start of the study and this relapse qualified the patients for recruitment into the study protocol. They were treated by increasing the prednisolone dose to 2 mg/kg/day until remission (protein-free urine on three consecutive days), followed by decreasing this to 1 mg/kg on alternate days for 14 days [14]. At that point, i.v. cyclophosphamide pulse administration was started at 500 mg/m²/month for 6 months. The calculated dose was diluted in 100 cm³ of 5% dextrose and given by i.v. infusion over a period of 1 h. We monitored patient parameters (pulse, blood pressure and temperature) as well as adverse symptoms (such as nausea and vomiting) during i.v. infusion. After infusion had been completed, 250–500 cm³ of 5% dextrose or 0.9% sodium chloride was given rapidly i.v. and the patient was asked to take ample fluids and void frequently for the rest of the day [9]. After the addition of cyclophosphamide, steroids were continued at 1 mg/kg on alternate days for an additional 14 days, and then reduced by 0.25 mg/kg every 14 days until complete withdrawal. Thus, steroids had been discontinued at 2 months following the start of cyclophosphamide. The steroid protocol used in the study was similar to that used for treatment of previous relapses prior to inclusion in the study.

Cyclophosphamide was continued for 6 months as long as remission was maintained, but it was discontinued if relapse occurred at any time during the treatment period. Relapse was defined as protein positive urine of +++ for three consecutive days [14]. This result was confirmed by a 24 h urinary protein > 50 mg/kg [15].

Patients were followed up monthly. At each visit, patients received clinical assessment, urinalysis, 24 h urinary protein, complete blood count, serum creatinine, liver function tests and serum cholesterol analysis. During the inter-visit periods, parents were instructed to monitor the reappearance of oedema, decreased urine output or any other complications. In such cases, patients were admitted for timed hospital visits. For some patients, parents also performed heat tests for urinary protein.

Responses to pulse cyclophosphamide were evaluated for occurrence and duration of remission, side effects and compliance with therapy.

Statistical analysis

Homogeneous data are expressed as means ± SD, and non-homogeneous data are expressed as medians.

Results

Baseline characteristics are shown in Table 1. Hypertension, defined as diastolic blood pressure above the 95th percentile for age, sex and height [16], was present in 35% of patients at study onset. None of our patients was obese, which was defined as body weight above the 95th percentile for age and sex [17]. Six were cushingoid at the start of the study. Eleven (55%) were either at or above the 50th percentile for height.

During the 6 month period of cyclophosphamide treatment. 10 out of 20 patients (50%) were able to successfully stop steroids for >2 weeks and thus were no longer steroid dependent.

At the end of the 6 month cyclophosphamide treatment period (4 months after steroid discontinuation), nine patients (45%) were in remission while on cyclophosphamide alone. During long-term follow-up after withdrawal of cyclophosphamide, the number of patients that maintained treatment-free remission was five (25%) at 6 months (cyclophosphamide responders), two (10%) at 1 year, and one (5%) at 2 years. Follow-up was continued for the single patient that maintained

Table 1. Baseline characteristics of patients at the start of the study

<table>
<thead>
<tr>
<th>Age (years) (mean ± SD)</th>
<th>7.38 ± 2.44</th>
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<tbody>
<tr>
<td>Female/male</td>
<td>5/15</td>
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<tr>
<td>Duration of steroid treatment (months) (mean ± SD)</td>
<td>49.8 ± 23.9</td>
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<tr>
<td>Number of steroid courses (median)</td>
<td>2.5</td>
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<tr>
<td>Maintenance every-other-day steroid dose (mg) (median)</td>
<td>10</td>
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<tr>
<td>Hypertension</td>
<td>7/20</td>
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<tr>
<td>Weight (kg) (mean ± SD)</td>
<td>28.15 ± 6</td>
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<tr>
<td>Height (cm) (mean ± SD)</td>
<td>119.7 ± 11.02</td>
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<td>Height percentile</td>
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<td>90th</td>
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</tr>
<tr>
<td>95th</td>
<td>1</td>
</tr>
<tr>
<td>Cushingoid facies</td>
<td>6/20</td>
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</tbody>
</table>
remission for 2 years after withdrawal of cyclophosphamide. At the last follow-up (46 months after withdrawal), this patient continued to maintain treatment-free remission.

Table 2 shows the side effects that occurred during cyclophosphamide therapy. The most common side effect was infection, which occurred in 60% of patients. However, all infections were mild and occurred during the period of combined corticosteroids and cyclophosphamide. All respiratory tract infections occurred in the form of mild acute bronchitis. Although asymptomatic pyuria occurred in four patients, urine culture was positive in only one, and this patient was successfully treated according to culture and sensitivity testing (Escherichia coli which was highly sensitive to sulfamethoxazole-trimethoprim). Alopecia occurred in 15% of patients but was mild, and these patients recovered rapidly and completely after withdrawal of cyclophosphamide. Hepatotoxicity occurred in only one patient and was in the form of mild and transient elevations in alanine transaminase and aspartate transaminase (65/42 IU/l; N = 8–40 IU/l). Finally, a mild and transient leukopenia occurred in one patient (white blood cell count was $3.7 \times 10^3/\text{µl}$) that was having mild acute bronchitis at that time. In summary, the overall side effects were mild and the drug was well tolerated. None of the patients discontinued therapy due to side effects. However, in patients that developed infection, hepatotoxicity or leukopenia, the dose of cyclophosphamide was delayed for 1–2 weeks until recovery from these side effects. This occurred twice in three patients and once in seven patients during the course of the cyclophosphamide pulses. Although some of the respiratory tract infection episodes occurred between cyclophosphamide pulses, these did not affect timing of the next pulse. Nevertheless, some of the cyclophosphamide pulses were delayed due to the presence of the common cold or pyuria until the results of urine cultures were available. Even though the patients did not receive mesna, none developed haemorrhagic cystitis. Furthermore, none developed nausea or vomiting during drug infusion or shortly after treatment. All patients were compliant with their treatment regimen.

Discussion

The most common variety of primary nephrotic syndrome in children is the minimal change type, and 95% of these cases show an excellent response to steroid therapy. However, responders may become steroid dependent [18–20], and such patients may experience serious side effects. To counter this, physicians have used adjunctive therapy, which commonly includes oral cyclophosphamide [1]. However, long-term side effects such as gonadal toxicity have become an important issue [5]. Intermittent cyclophosphamide pulse treatment limits the risk of these complications [6].

There are limited reports on the use of pulse cyclophosphamide in patients with nephrotic syndrome that have minimal change lesions, that are steroid dependent, or both. In 1990, Ghandi and Thomas [9] reported in a letter the use of pulse cyclophosphamide in two patients with a frequently relapsing nephrotic syndrome. A 1993 letter from Jones [10] reported similar findings. In 2001, Gulati et al. [11] reported the first prospective and complete study on the use of pulse cyclophosphamide in frequently-relapsing/steroid-dependent nephrotic syndrome patients; this well-designed study examined patients with minimal change and focal segmental glomerulonephritis.

In our centre, we have been using pulse cyclophosphamide since 1991 as standard practice for lupus nephritis and in certain cases of idiopathic nephrotic syndrome where oral cyclophosphamide therapy is indicated but where patients show non-compliance, are more vulnerable to side effects such as past history of recurrent infection episodes or show both effects. In May 1998, we conducted the present prospective trial to study the efficacy and safety of pulse cyclophosphamide in steroid-dependent MCNS children.

The initial steroid course was given to patients at 49.8 ± 23.9 months before the start of the study. At study onset, 35% of our MCNS patients were hypertensive. This incidence is far above the 13% reported by the ISKDC [18] in 1978. Such a large difference may be due to variations in the definition of hypertension (the ISKDC defined hypertension as diastolic blood pressure above the 98th percentile). This disparity may also be attributed to the use of steroid therapy in our patients, in contrast to the ISKDC report, which examined patients at the time of diagnosis of their nephrotic syndrome. Other side effects of steroid therapy in our study included cushingoid facies. Fifty-five per cent of patients were at or above the 50th percentile of height, which may reflect our policy of reducing steroid therapy to every other day as soon as remission has occurred during the treatment of relapse.

At the end of the 6 month treatment with cyclophosphamide, nine out of 20 patients (45%) were in remission despite discontinuation of steroid therapy after the first 2 months and continuation of cyclophosphamide by itself during the subsequent 4 months. This number gradually decreased after withdrawal of treatment, such that five patients (25%) were still in remission 6 months later and only one patient (5%) enjoyed remission after 2 years. Ghandi and Thomas [9] were the first to examine pulse cyclophosphamide in frequently relapsing nephrotic syndrome patients. They treated two patients with 6 monthly cyclophosphamide pulses after inducing remission by steroids. They found
that the patients continued to have a complete clinical and laboratory remission for 2 years after treatment. The lower incidence of remission among our patients may be due to the markedly greater number of subjects that we studied. It may be also attributed to the better responses to oral cyclophosphamide seen in frequently relapsing nephrotic patients compared with steroid-dependent patients [21,22]. These differences may explain the remission discrepancies between studies using pulse cyclophosphamide therapy. In their well-designed prospective study, Gulati et al. [11] examined the efficacy of pulse cyclophosphamide in 51 nephrotic children. The number of steroid-dependent patients was comparable to that in our study (29 vs 20 patients). They reported a remarkably higher incidence of sustained remission after the final cyclophosphamide dose, with 41% complete remission at the end of 27 ± 21 months follow-up vs 25 and 5% complete remission at the end of 6 months and 2 years of follow-up, respectively, in our study. These superior results were obtained despite the inclusion of histopathologic types other than MCNS (17% MCNS, 52% focal segmental glomerular sclerosis and 31% unidentified histopathology vs 100% MCNS in our study). This improved response may be attributed to differences in patient characteristics. In their study, 38% of patients had relapsed within 2 weeks after withdrawal of prednisolone and 62% had relapsed while still on prednisolone, whereas in our study these values were 10 and 90%, respectively. This superior response may also be due to genetic and racial factors that may alter the pattern of response to therapy. Furthermore, and as discussed by those authors, spontaneous remission may have slightly improved their results. In addition, the response rate of steroid-dependent nephrotic patients to oral cyclophosphamide at 1–3 years varies widely from 28 to 75% [21–26], and this difference may be extrapolated to pulse therapy. Whereas Srivastava et al. [21] reported that older age at onset of oral cyclophosphamide is a predictor of better responses, Gulati et al. [11] found higher response rates to pulse cyclophosphamide in children below 6 years of age (although this difference was not statistically significant). Thus, the lower mean age in their study (4.5 ± 0.76 vs 7.38 ± 2.44 years in our study) may have contributed to the superior results.

Our results were even poorer than those obtained with oral cyclophosphamide regimens that lead to long-term remission rates ranging from 24 to 67% after 2 years. Kemper et al. [27] studied the effects of 12 weeks of oral cyclophosphamide in 20 patients having a steroid-dependent nephrotic syndrome similar to that in our study. Although they concluded that reponses in their patients to oral cyclophosphamide were unfavourable, they observed a 30% remission for >2 years compared with the 5% remission in our study. Thus, pulse therapy seems to produce more rapid but less lasting effects than the oral protocol. These effects appear to concur with effects obtained with pulse and oral steroid therapy in steroid-dependent nephrotic patients. In our study, the overall short-term side effects of cyclophosphamide were mild. The drug was well tolerated and, in contrast with studies examining pulse cyclophosphamide in nephrotic syndrome patients, none of our patients was forced to discontinue therapy because of side effects [9,11,28]. We found a higher incidence of infection than that reported by Gulati et al. [11] (15% vs 4%). However, the infections in our study were mild (upper respiratory tract, scalp and urinary tract infections) compared with those in their study (one case of pneumonia and one case of chicken pox). The difference in incidence of infections may be due to differences in determining whether such infections were a side effect of treatment. We also observed a greater incidence of alopecia (15% vs 8%). However, in both studies, alopecia was mild and transient. The incidence of leukopenia was similar (0% vs 4%) and was mild and transient in both studies. None of our patients experienced nausea or vomiting during cyclophosphamide infusion or for the remainder of the treatment day. Even though the drug was given for 3 h in their study, compared with 1 h in our study, 5% of their patients developed nausea or vomiting during infusion. This was the only side effect reported by Elhence et al. [28].

In conclusion, and in contrast with our expectations, pulse cyclophosphamide therapy appeared to exert unfavourable effects in steroid-dependent MCNS children. Although short-term side effects of pulse cyclophosphamide were mild, the more important long-term toxicity effects were not tested. The results with pulse cyclophosphamide were poorer than the most unfavourable results obtained with the oral therapy. Thus, in steroid-dependent MCNS children, in spite of the purported but unproven lower long-term toxicity of pulse cyclophosphamide, its efficacy was proved to be inferior to the standard oral form, which itself is associated with serious side effects in this patient population.

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Conflict of interest statement. None declared.

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