—Case Reports—

Intravenous Cyclophosphamide Pulse Therapy in Japanese Children with Systemic Lupus Erythematosus

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Abstract

Background: Intravenous cyclophosphamide (IVCY) pulse therapy has been used for lupus nephritis since the latter half of the 1980s; it has been shown to be effective for lupus nephritis and vasculitis and has become a standard therapy for the diffuse proliferative type of lupus nephritis in adults. IVCY therapy has also come to be used in children. This paper reports the long-term outcomes of IVCY therapy in children.

Methods: Six female patients (age range, 13 to 18 years) with systemic lupus erythematosus (SLE) were enrolled in this retrospective study. Three patients had lupus nephritis (World Health Organization class IIb, IVa, IVc), 2 had central nervous system (CNS) lupus, and 1 had neither lupus nephritis nor CNS lupus. The mean pretreatment SLE disease activity index (SLEDAI) score was 18.8 ± 4.6. Cyclophosphamide (initial dose, 500 mg/m^2) was administered intravenously each month for 6 months and then given every 3 months for maintenance. Prednisolone was given in dosages ranging from 5 to 60 mg/day, adjusted according to laboratory data and clinical symptoms. Levels of C3, C4, CH50, and creatinine; the SLEDAI score; and the SLE responder index were monitored and evaluated. The SLE responder index was considered to have improved if the SLEDAI score had decreased by 4 points or more after 52 weeks.

Results: Prednisolone doses were reduced in all patients. Because methylprednisolone pulse therapy was administered before IVCY therapy, some patients had low titers of immunoglobin G antibodies against double-stranded DNA at the start of IVCY therapy. All patients had low serum creatinine levels. Proteinuria resolved in 1 of the 3 patients with lupus nephritis. The SLEDAI scores improved after 52 weeks in 5 of 6 patients (mean, 5.2 ± 2.6). No patients had severe bone marrow suppression or hemorrhagic cystitis during IVCY pulse therapy.

Conclusions: IVCY pulse therapy for SLE in children achieved good long-term outcomes with no serious adverse effects, such as digestive symptoms, bone marrow suppression, infection, and hemorrhagic cystitis. IVCY pulse therapy for children with SLE has recently been approved by the Ministry of Health, Labour and Welfare. Accordingly, this paper might become a guideline for this treatment.
(J Nippon Med Sch 2013; 80: 396–400)

Key words: intravenous cyclophosphamide pulse therapy, lupus nephritis, pediatric, systemic lupus erythematosus disease activity index, systemic lupus erythematosus responder index

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Introduction

Intravenous cyclophosphamide pulse therapy (IVCY) pulse therapy has been used to treat lupus nephritis in children since the latter half of the 1980s[1], and its effectiveness for lupus nephritis and vasculitis has been established. Compared with treatment with corticosteroids alone, IVCY pulse therapy is highly effective and has become a standard therapy for the diffuse proliferative type of lupus nephritis in adults. IVCY pulse therapy is significantly better for preventing renal failure than is conventional oral cyclophosphamide therapy.

As IVCY pulse therapy has come to be used for children, the number of cases of long-term use has increased. In this paper, we report on our experience with the long-term use of IVCY pulse therapy.

Case Report

Six female patients aged 13 to 18 years with SLE were enrolled in this retrospective study (**Table 1**). Three of the patients had lupus nephritis (World Health Organization class IIb, IVa, IVc), and 2 had central nervous system (CNS) lupus. One patient had no lupus nephritis or CNS lupus. Patient 1 required long-term treatment with prednisolone. Because of side effects, such as obesity, moonface, and hirsutism, she decided to discontinue treatment with high-dose prednisolone and to undergo IVCY pulse

Table 1

(a)	Patients who underwent IVCY treatment					
Patient no.	1	2	3	4	5	6
Age (years)	24	17	30	23	20	37
Sex	F	F	F	F	F	F
Onset age (years)	6	6	9	10	5	18
Complication	SLE	CNS lupus	lupus nephritis	CNS lupus	lupus nephritis	lupus nephritis
World Health Organization class			IVc		IIb	IVa
SLEDAI	7	12	16	12	6	18
(b)	Findings at initial IVCY treatment					
Patient no.	1	2	3	4	5	6
Age at first IVCY treatment (years)	14	13	13	15	16	18
Antinuclear antibodies	1 : 640	1 : 80	1 : 20	1 : 640	1 : 640	1 : 20
anti-dsDNA antibodies (IU/mL)	5.6	<5	3	32.6	142	1
C3 (mg/dL)	12	53	89	115	63	45
C4 (mg/dL)	17	2	42	8	10	12
CH50 (U/mL)	38.6	14.3	45.8	28.1	29.7	20
Creatinine (mg/dL)	0.71	0.45	0.5	0.54	0.42	1.27
Urine protein	(−)	(−)	(2+)	(−)	(2+)	(3+)
(c)	Findings at final IVCY treatment					
Patient no.	1	2	3	4	5	6
Therapy duration (months)	81	56	157	60	23	87
Therapy duration (times)	32	20	21	19	12	18
SLEDAI	4	10	6	4	14	4
anti-dsDNA antibodies (IU/mL)	400<	6	15	49	400<	<5
C3 (mg/dL)	65	42	78	80	79	128
C4 (mg/dL)	5	4	13	8	16	21
CH50 (U/mL)	21.6	15.4	32	32.8	38.4	42.9
Creatinine (mg/dL)	0.4	0.38	0.41	0.44	0.37	0.73
Urine protein	(−)	(−)	(3+)	(−)	(−)	(+)

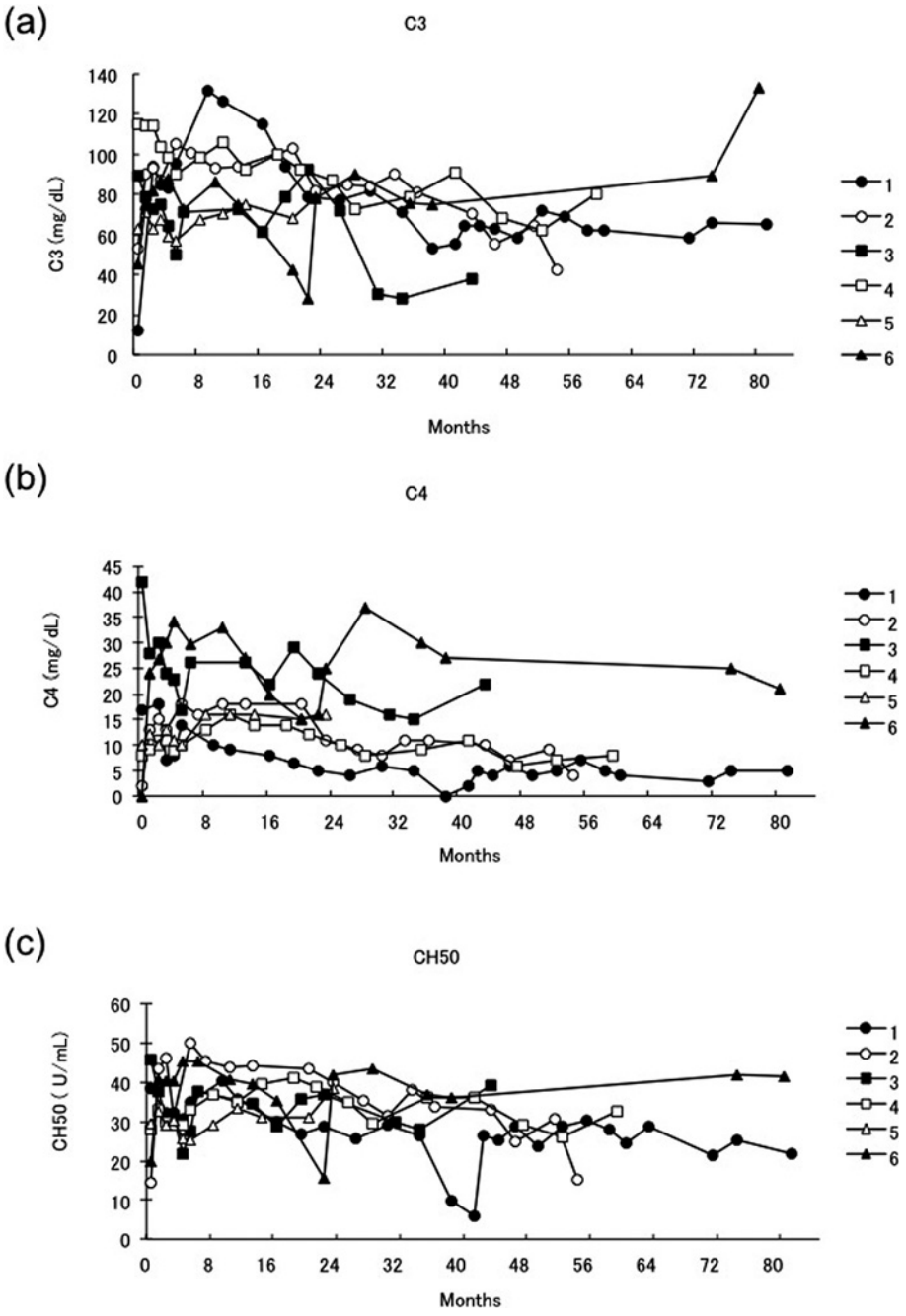

Fig. 1 (a) Changes in serum C3 levels during IVCY treatment in 6 patients with SLE. (b) Changes in serum C4 levels during IVCY treatment in 6 patients with SLE. (c) Changes in serum CH50 levels during IVCY treatment in 6 patients with SLE.

therapy with low doses of prednisolone. The mean pretreatment SLE disease activity index (SLEDAI) score was 18.8 ± 4.6. Cyclophosphamide was administered intravenously each month for 6 months and then given every 3 months for maintenance according to a previous study[2]. The initial dose of cyclophosphamide was 750 mg/m^2. Prednisolone was given in dosages ranging from 5 to 60 mg/day, adjusted according to laboratory data and clinical symptoms. All patients received glucocorticoid therapy together with tacrolimus or mizoribine orally. However, when these immunosuppressants were used differed for each patient.

Levels of C3, C4, CH50, and creatinine; the SLEDAI score; and the SLE responder index (SRI) were monitored and evaluated **(Fig. 1)**. The SRI was

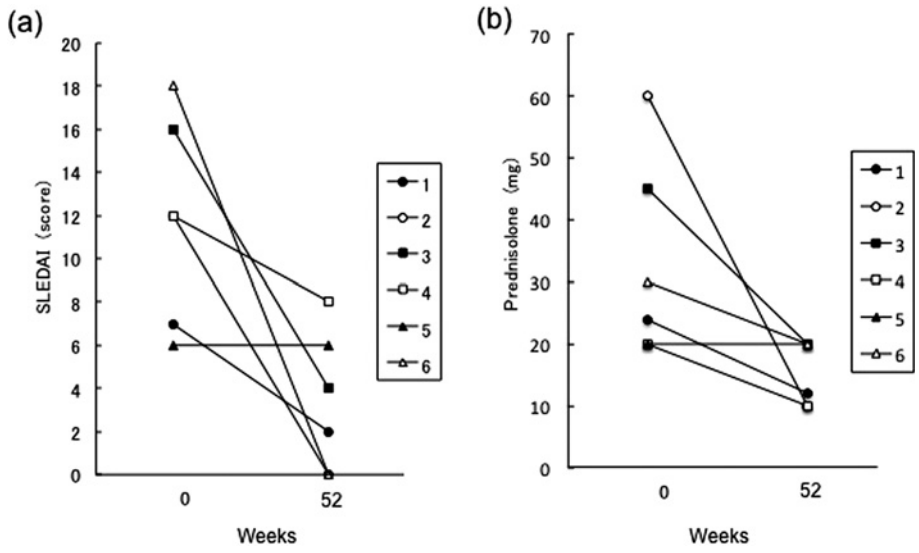

Fig. 2 (a) Changes in the SLEDAI score after IVCY therapy in 6 patients with SLE. The mean ± standard deviation (SD) score was 11.8 ± 4.8 before IVCY therapy and was significantly lower ($p<0.05$; Wilcoxon test), at 3.3 ± 3.2, at 52 weeks. (b) Changes in prednisolone after IVCY therapy in 6 patients with SLE. The mean ± SD score was 33.3 ± 16.1 before IVCY therapy and was significantly ($p<0.05$; *t*-test) lower, at 15.3 ± 5.1, at 52 weeks.

considered to have improved if the SLEDAI score had decreased by 4 or more points after 52 weeks[3].

The corticosteroid (prednisolone) doses could be reduced in all patients (**Fig. 2b**). Because methylprednisolone pulse therapy was administered before IVCY pulse therapy was started, some patients showed low titers of immunoglobin G antibodies against double-stranded (ds) DNA at the start of IVCY pulse therapy (**Table 1b**). Serum levels of creatinine were low in all patients (**Table 1 c**). Proteinuria resolved in 1 of the 3 patients who had lupus nephritis (**Table 1c**). The SLEDAI scores improved after 52 weeks in 5 of 6 patients (mean, 5.2 ± 2.6) (**Fig. 2a**). Neither severe bone marrow suppression nor hemorrhagic cystitis was evident during IVCY pulse therapy.

Discussion

Cyclophosphamide, which is a representative alkylating agent, induces DNA interstrand cross-links, prevents the separation of the strands of the DNA helix, and thus inhibits DNA replication[4]. Its immunosuppressive effect is thought to be caused mainly by B-cell death. Reported side effects include digestive symptoms, bone marrow suppression, infection, hemorrhagic cystitis, gonadal dysfunction, and secondary cancer. Childhood onset of SLE accounts for approximately 14% of all cases. The incidence of SLE is high in African-American, Asian, and Hispanic populations[5,6]. Onset varies considerably by country due to ethnic differences. In general, IVCY pulse therapy is extremely effective in adults and is recommended for severe, steroid-refractory SLE[7]. However, in children with SLE, results have been mixed. Dixit et al. have reported a poor response to standard protocols of IVCY pulse therapy, with higher relapse rates and significant adverse outcomes, in children with SLE[8]. On the other hand, Lehman et al. have reported found that 36 months of IVCY pulse therapy leads to decreased renal biopsy activity without progression to chronicity, with excellent disease control and a reduction in the mean corticosteroid dose of greater than 50%[2]. A previous Japanese study showed improvement with no serious adverse reactions[9].

The present data also showed no serious adverse effects, including digestive symptoms, bone marrow suppression, infection, and hemorrhagic cystitis. However, the risk of gonadal dysfunction or secondary cancer is still unclear. Therefore, whether to administer IVCY pulse therapy should be decided

on the basis of symptoms and laboratory data. Beneficial effects were obvious in all treated cases. In all patients the prednisolone dosages during IVCY pulse therapy (mean, 15.3 ± 5.1 mg/day) were lower than those before (mean, 33.3 ± 16.1 mg/day; $p<0.05$ by *t*-test). Serum complement levels decreased approximately 3 months after the end of IVCY pulse therapy. Although IVCY pulse therapy increased serum complement levels, the effect was temporary. The complement levels in this study (**Table 1c**) were low because they were measured in blood samples obtained on days when IVCY pulse therapy was being given. However, even when complement levels were low on days of treatment, they were higher in tests performed 4 weeks after the end of therapy (data not shown). The SLEDAI scores improved as a result of IVCY therapy (before, 11.8 ± 4.8 before treatment and 3.3 ± 3.2 after treatment; $p<0.05$ by Wilcoxon test), and the SRI improved in 5 of 6 patients but showed no change in 1 patient. Therefore, we conclude that IVCY pulse therapy is effective for maintaining remission.

IVCY therapy can maintain remission not only in lupus nephritis but also in CNS lupus, meaning that it can be beneficial in cases of SLE in children requiring large doses of prednisolone. No severe adverse reactions occurred during therapy, and patient satisfaction was high. Gonadal suppression is more frequent in boys than in girls, and it may have more of an effect in older patients. Infertility develops at an unacceptable frequency only in those patients who have received a lifetime cumulative dose of cyclophosphamide of more than 17 g/m^2[4]. SLE is more common in girls, and switching to an alternative therapy must be considered in light of gonadal suppression[10]. Combinations of immunosuppressants and antibodies targeting B cells, such as anti-CD22 antibodies and LJP-934, are possible future treatments for SLE.

Conflict of Interest: No competing financial interests exist.

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(Received, October 2, 2012)
(Accepted, November 27, 2012)