

Intravenous cyclophosphamide pulse therapy in Japanese children with lupus nephritis

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Abstract

In order to better understand the effectiveness of intravenous cyclophosphamide pulse therapy (IVCY) in Japanese children with systemic lupus erythematosus (SLE), we investigated the laboratory data and clinical courses in 4 patients retrospectively. None of the patients had serious side effects, and the dosage of prednisolone was reduced in all cases. Hematuria and proteinuria disappeared during treatment. Their laboratory data improved except for one case with low levels of complement.

Introduction

Applications of intravenous cyclophosphamide pulse therapy (IVCY) for collagen disease started from the latter half of the 1980's, and its effectiveness on lupus nephritis and a vasculitis has been established. Compared with treatment only by steroids the effectiveness is high, and it has become a standard therapy for the diffuse proliferative type of lupus nephritis in adults. IVCY has significantly better effects on preventing renal failure than that of conventional oral cyclophosphamide therapy. Although there are many ethnic and age differences in patients with systemic lupus erythematosus (SLE), there has been no report about the effectiveness of this treatment in Japanese children with SLE.

Material and methods

Four patients (2 males and 2 females) with SLE were enrolled in this study (Table 1). They were between 13 to 15 years old, and all had lupus nephritis (WHO class II, IVb, Vb). Their SLEDAI scores before treatment

were 5 to 13. Cyclophosphamide was administered intravenously monthly for 6 months then maintained every 3 months for 18 additional months. The initial dose of cyclophosphamide was 500 to 750 mg/m². Mesna was also used. Prednisolone was given in doses ranging from 5-20 mg per day, adjusted according to their data and clinical symptoms.

Results

One boy complained of mild digestive symptoms of nausea and vomiting temporally. All patients reduced the dosage of prednisolone during the treatment (Figure 1), and the titers of anti-nuclear antibodies and anti-DNA antibodies decreased in all cases (Figure 2). In all children, hematuria and proteinuria disappeared during the treatment. These changes were accompanied by a marked reduction in SLEDAI score.

Low complement titer continued in only one case after 1 year from the start (Figure 3). Hemorrhagic inflammation of the gallbladder occurred once in one case. Their levels of creatinin clearance were within the normal range. One patient showed no hematuria, but

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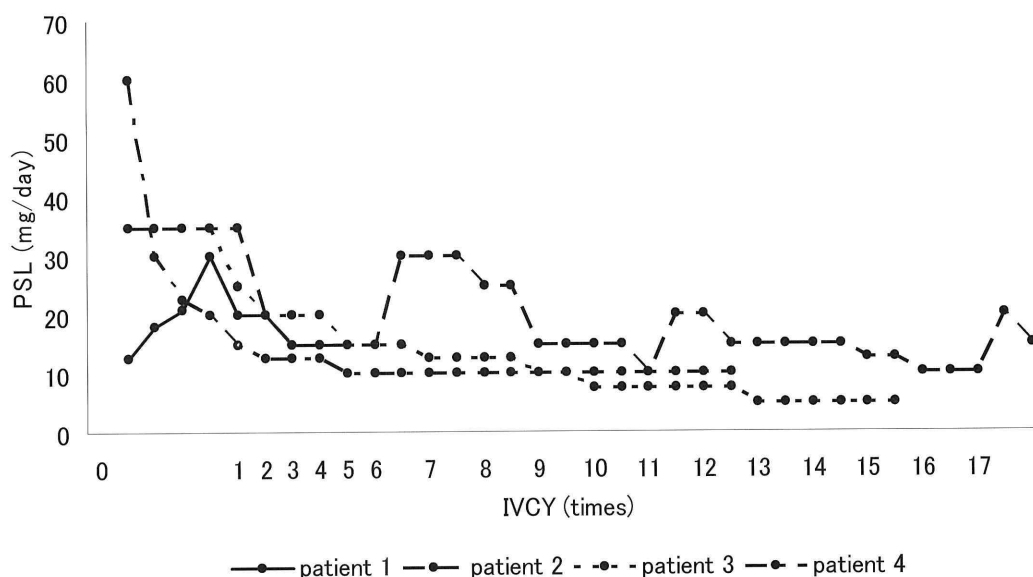
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Table 1 Profile of patients in this study

	1 (KM)	2 (MN)	3 (SI)	4 (SH)
Onset age (year)	8	7	10	11
Sex	female	female	male	male
BP (mmHg)	141/98	140/90	120/68	120/64
Duration	8 years	6 years	6 months	3 months
SLEDAI	12	12	5	13
ESR	35	57	67	12
ANA	320	640	<40	320
Anti-dsDNA	640	320	0	17
C3	54	43	173	70
C4	5	9	44	15
Cr clearance	112	150	263	78
U-Protein/Cr ratio	1,750/27.6	230/97.1	5/113.6	8/35.1
hematuria	3+	3+	2+	—
WHO class	IVa	IV	Vb	II
others	brain anomaly epilepsy	Sjs		APS thrombocytopenia

SJs : Sjögren's syndrome, APS : Anti-phospholipid antibody Syndrome

**Fig. 1** the fluctuations of dose of prednisolone in four cases

had Sjögren's syndrome for 4 years. One boy showed no symptoms and no abnormal laboratory data without any prednisolone treatment for 2 years. Another patient who showed fever and arthralgia with no hematuria was positive for antiphospholipid antibodies when the dosage of prednisolone was decreased to 10 mg. One girl had low complement but no hematuria, and needed 15 mg of prednisolone, but had no other symptoms.

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. The immunosuppression is thought to be caused mainly by B cell death. Side effects such as digestive symptoms, bone marrow suppression, infection, hemorrhagic cystitis, gonadal function and secondary cancer are known.

Childhood onset of SLE accounts for approximately 20% of all cases. The incidence of SLE is high in African-American, Oriental, and Hispanic populations¹⁾²⁾. Onset varies considerably according the countries due to ethnic differences. Moreover childhood SLE is more aggressive in children than in adults. Here we report Japanese children with lupus nephritis who

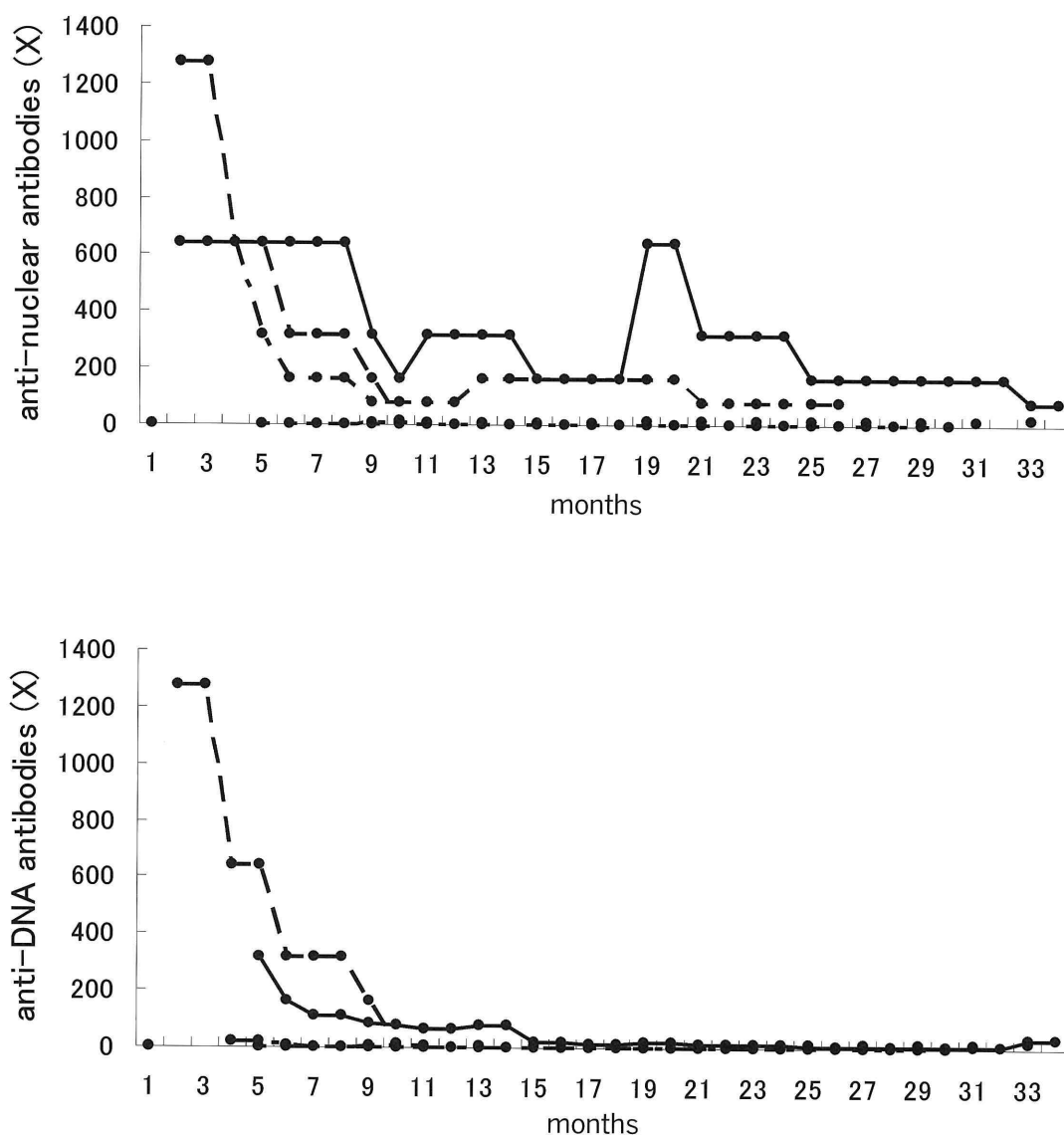


Fig. 2 the fluctuations of anti-nuclear antibodies and anti-DNA antibodies in four cases during IVCY treatment

were treated with IVCY. There were 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 the indication of IVCY should be decided based on the symptoms and laboratory data. The effect is obvious in all treated cases. During treatment no patient needed additionally therapy including prednisolone, despite the fact that childhood SLE is more aggressive than in adults.

Martinelli R et al. reported the clinical effectiveness of IVCY in 20 patients with SLE. They found good responses in 6 out of 10 cases with renal involvement and 4 out of 5 cases with severe extrarenal SLE, and recommended IVCY for severe, steroid refractory SLE in adults³⁾. In childhood SLE, according to a retrospective study by Dixit et al.⁴⁾, of 14 patients, 3 (21%) achieved systemic remission but all relapsed subsequent-

ly; 7 of 14 achieved renal remission, although 6 relapsed. They also reported adverse outcomes in 6 (42%). They reported a poor response to standard therapeutic protocols of IVCY with higher relapse rates, as well as significant adverse outcomes in childhood SLE⁴⁾. Concerning the side effects, Malaviya et al reported the safety of the treatment in 50 patients aged 4 to 37 years having severe/refractory lupus nephritis, vasculitis or neuropsychiatric manifestations who were treated with IVCY. The treatment was found to be associated with significant and sustained improvement during a 2 year follow up with respect to the mean renal activity score, individual renal parameters, focal neurological manifestations, vasculitic lesions, antinuclear antibody titers, complement component C3, anti-dsDNA antibodies levels and ESR. They also reported that the adverse reactions were mild, self limiting and reversible⁵⁾. Our study of 4 Japanese cases showed dramatically improve-

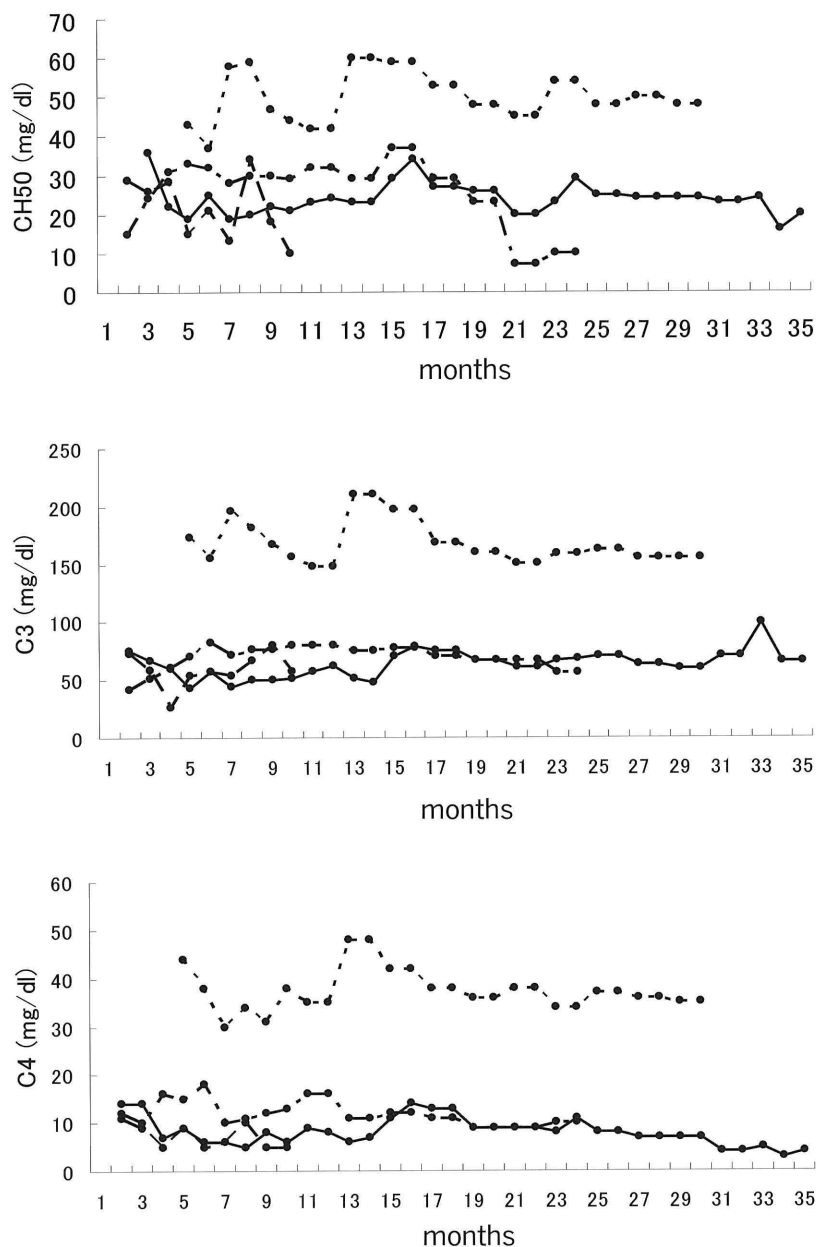


Fig. 3 the fluctuations of complements in four cases during IVCY treatment

ment without any serious adverse reactions. The differences in effectiveness might be due to the ethnic differences or the duration of follow up.

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日本人小児 4 例のループス腎炎に対する シクロフォスファミドパルス療法の検討

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全身性エリテマトーデス (SLE) に伴うループス腎炎は、小児の SLE の中で最も多い症状の 1 つであり、難治性の疾患としてステロイド剤を始め免疫抑制剤など種々の治療法が試みられてきた。そして現在、強力な免疫抑制剤を使用することによって、小児 SLE 患者の予後は劇的に改善されてきている。シクロフォスファミド (IVCY) パルス療法の膠原病への応用は 1980 年代後半より試みられ、ループス腎炎や血管炎に対する有効性が確立してきている。ステロイド薬単独に比べ、腎機能の低下を有意に抑えること、従来の経口シクロフォスファミド療法より有効性が高く、副作用が少ないことより、特に末期腎不全へと進行するリスクの高いびまん性増殖性ループス腎炎の基本的治療法となっている。今回我々は、全身性エリテマトーデス (SLE) におけるループス腎炎に対し、シクロフォスファミド (IVCY) パルス療法を小児 4 例に施行、血液検査・臨床経過を後方視的に調査し有効性と安全性について検討を行った。症例は 13 歳から 15 歳の男女各 2 名ずつ、腎組織 WHO 分類はそれぞれ II、IVb、Vb、治療前 SLEDAI は 5 から 13 点であった。シクロフォスファミド 1 回量 500 から 750 mg/m² を始めの 6 ケ月間は各月、以降 18 ケ月間は 3 ケ月に 1 回投与した。結果、シクロフォスファミドパルス療法の間、全例に血尿および蛋白尿は認められず、抗核抗体・抗 DNA 抗体は全例、補体に関しては一例を除き改善を認めた。結果として SLE の活動性を示す SLEDAI を改善させた。2 例に軽度の消化器症状・1 例に出血性膀胱炎を認めたものの、重篤な副作用を認めたものはなく、臨床症状の悪化無くプレドニゾロンの減量を可能とした。

〈キーワード〉 シクロフォスファミドパルス療法、小児、全身性エリテマトーデス、ループス腎炎
