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ORIGINAL ARTICLE

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Intermittent intravenous cyclophosphamide pulse therapy for the treatment of active interstitial lung disease associated with collagen vascular diseases

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Abstract The availability of intravenous cyclophosphamide (CYC) pulse therapy for collagen vascular diseases (CVD)-associated interstitial lung disease (ILD) has been indicated. However, the standard protocol concerning the dosage and the interval of CYC infusion has not yet been established. The aim of this study is to elucidate the efficacy and the safety of our "divided administration" protocol of CYC for the treatment of CVD-ILD. The treatment protocol consists of two steps: step 1, CYC 400–500 mg at 10-day intervals for at least 30 days, and step 2, CYC 500 mg at 14-day intervals for at least 4 weeks. The ILD activities were monitored by respiratory symptoms, serum levels of KL-6 (a serological marker of IP), chest computed tomography (CT), and pulmonary function tests. Seventeen patients [nonspecific interstitial pneumonia (NSIP), 12 patients; usual interstitial pneumonia (UIP), 4; lymphocytic interstitial pneumonia (LIP), 1] accomplished the study protocol. The sessions of CYC infusion ranged from 5 to 20 (mean, 8.3). In all patients, respiratory symptoms were improved and the serum levels of KL-6 were decreased (from 1572 ± 904 to 978 ± 392 U/ml; $P < 0.01$). Chest CT findings were improved in 4 patients (23.5%): they were all classified as NSIP; not deteriorated, 13 patients (76.5%). An improvement in the vital capacity percentage (%VC) was recognized in 10 patients (78.6%) and in diffusing capacity of carbon monoxide (%DLco) in 8 patients (61.5%). Nevertheless, mean %VC and mean %DLco did not change significantly. No major adverse event(s) occurred. The efficacy and safety of our "divided administration" protocol of CYC for CVD-ILD was demonstrated.

Key words Computed tomography · KL-6 · Pulmonary functioning test

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Introduction

Interstitial lung disease (ILD) is a pulmonary manifestation recognized in collagen vascular diseases (CVD), such as rheumatoid arthritis (RA), systemic sclerosis (SSc), polymyositis (PM)/dermatomyositis (DM), mixed connective tissue disease (MCTD), Sjögren's syndrome (SjS), and systemic lupus erythematosus (SLE).[1] The pathogenesis of ILD is the presence of idiopathic inflammatory and fibrotic alterations in the lung interstitium. Progressive interstitial destruction often leads to hypoxemia due to an impairment of gas exchange, thus resulting in a high mortality rate.[2]

Both the oral administration and pulse infusion of corticosteroid therapy for CVD-associated ILD (CVD-ILD) had been shown to be low in efficacy, while also showing a poor prognosis.[3–5] Recently, the availability of intravenous cyclophosphamide (CYC) pulse therapy for CVD-ILD has been sporadically described.[1,4,6] We also reported a case that needed oral intubation with mechanical ventilation due to ILD associated with DM, and the respiratory distress condition was ameliorated by intravenous CYC pulse therapy.[7] However, the standard protocol concerning the dosage and the interval of CYC pulse therapy has not yet been established. This stemmed partially from the absence of useful serological marker for measuring the ILD activities.

KL-6 has been used in Japan since 1999 as a novel serum marker for the purpose of making a diagnosis of ILD, and for also monitoring its severity and therapeutic efficacy.[8] KL-6 is a sialylated carbohydrate antigen expressed mainly on the surface of alveolar type II cells in the lung. Through the damaged air–blood barrier of the interstitium in the lung of ILD, KL-6 fluxes into the blood circulation.[9]

We herein propose our intermittent CYC pulse therapy protocol for the treatment of CVD-ILD. The characteristics of this protocol are as follows: (i) the dosage of CYC is 400–500 mg per session, which is lower than that of the formerly reported protocols;[1,6] (ii) the interval of CYC pulse therapy is 10 days or 2 weeks, which is more frequent than for those used in previous reports; (iii) the dosage and interval of CYC pulse therapy is adjusted according to the ILD activities, which is estimated weekly by measuring the serum levels of KL-6, and confirmed monthly by chest computed tomography (CT). The main advantage of this "divided administration" protocol is to avoid excessive immuno- and myelosuppression. The objective of this study is to elucidate the efficacy and the safety of our intermittent CYC pulse therapy protocol for CVD-ILD.

Patients and methods

Patient selection

Between June 2003 and March 2006, 18 patients (2 men and 16 women) with active CVD-ILD were enrolled in our intermittent CYC pulse therapy protocol. The institutional Ethics Committee of National Defense Medical College approved the study protocol. Informed consent was obtained from each patient. Diagnosis of each CVD was made based on internationally accepted criteria. The diagnosis of ILD was made by chest CT. The subgroups of ILD were classified by CT findings based on the international multidisciplinary consensus.[10] In case the subgroups of ILD were not classified only by CT findings, a lung biopsy by video-assisted thoracoscopic surgery (VATS) was considered to be performed. The inclusion criteria were as follows: (i) the recent deterioration of respiratory symptoms (dry cough, dyspnea); (ii) the existence of ground-glass appearance or expanding lesion of ILD confirmed by chest CT. Following ILDs were excluded: (i) acute interstitial pneumonia, pathologically diffuse alveolar damage, (ii) infectious ILD, such as cytomegalovirus (CMV) pneumonia and *Pneumocystis jiroveci* pneumonia, by measuring CMVpp65 antigen in white blood cells and β-D-glucan in serum, and (iii) drug-induced ILD. The other excluded conditions were as follows: age under 20 years, pregnancy, previous treatment with cytotoxic drugs within 2 weeks, infectious diseases including HIV infection, malignancies, liver dysfunction (serum alanine aminotransferase (ALT) >70 IU/l), renal failure (serum creatinine >1.3 mg/dl), bone marrow disorders, white blood cell (WBC) count <2000/μl, cardiac failure (NYHA class III or IV), and pulmonary hypertension (mean pulmonary artery pressure >30 mmHg).

Study protocol

Cyclophosphamide (CYC), at a dosage of 400–500 mg, in 200 ml of a multi-electrolyte solution (Solita-T-No.3, Ajinomoto, Tokyo, Japan) was administered intravenously at a speed of 100 ml/h, and followed by 500 ml of Solita-T-No.3, for the prevention of hemorrhagic cystitis. The ILD activities were evaluated mainly by the serum levels of KL-6 weekly, and confirmed by chest CT findings monthly. The respiratory symptoms (dyspnea, dry cough) were monitored, and pulmonary function tests were performed before and after the administration period of CYC. The study protocol consists of 2 steps: step 1, CYC 500 mg as an initial dose, thereafter 400 mg at 10-day intervals (total CYC: 1200–1300 mg/month); step 2, CYC 500 mg at 14-day intervals (1000 mg/month). Intermittent CYC pulse therapy was initiated from the step 1. Thereafter, if neither the increase of KL-6 level nor deterioration of chest CT findings was confirmed for at least one month, the protocol proceeded to the step 2. If neither of them was confirmed at the step 2 for at least 4 weeks, the protocol was terminated, and subjective and objective findings were obtained. If the activity of ILD increased despite this therapeutic regimen, the clinical trail was discontinued. Corticosteroid or immunosuppressive drugs (cyclosporine A: Neoral; tacrolimus: Prograf; mizoribine: Bredinin) were permitted. If a patient complained of nausea and/or vomiting, 10 mg of azasetron hydrochloride[11] was administered. When an infectious disease was complicated, a session of CYC infusion was postponed until its cure.

Chemical analyses

Possible adverse effects associated with intermittent CYC pulse therapy, including bone marrow suppression, immunosuppression, liver dysfunction, and hemorrhagic cystitis, were monitored by measurement of a complete blood cell count, serum immunoglobulin G (IgG), serum chemistry, and a urinalysis. The serum levels of KL-6 were measured by an electrochemiluminescence immunoassay (ELICA) (Picolumi KL-6, Sanko Junyaku, Tokyo, Japan). The upper limit of normal range of KL-6 is 500 U/ml. CMVpp65 antigen was measured by shell vial method (CMV antigen Mitsubishi, Mitsubishi Kagaku Bio-Clinical Laboratories, Tokyo, Japan). β-D-glucan levels in serum were measured by the alkaline-kinetic chromogenic Limulus method (Fungitec G test, Seikagaku Kogyo, Tokyo, Japan)

Pulmonary function tests

FUDAC-70 (Fukuda Denshi, Tokyo, Japan) was used for pulmonary function tests. Vital capacity (VC) was measured by a rolling seal type spirometer. The carbon monoxide diffusion capacity (DLco) was measured by a single-breath method. The results were expressed as a percentage of predicted values.

Chest computed tomography

Chest CT scans were performed using Aquillion (Toshiba, Tokyo, Japan). Thin section radiographs (1-mm thickness) were taken at maximum inspiration at 10-mm intervals from the apex to the base of the lung. A follow-up CT was taken once a month.

Table 1. Characteristics of the study patients

Patient	Age (years)	Sex	Body surface area (m^2)	Diagnosis	Pathology	CT pattern	History of smoking
1	76	M	1.63	MCTD	–	NSIP	+
2	62	F	1.52	SjS	–	NSIP	–
3	64	F	1.31	RA	–	UIP	+
4	62	F	1.34	RA	–	UIP	+
5	63	F	1.41	DM	–	NSIP	–
6	49	F	1.36	DM	–	NSIP	–
7	62	F	1.51	RA	–	UIP	–
8	67	F	1.47	SLE	NSIP	atypical	–
9	69	F	1.62	RA	–	UIP	–
10	61	F	1.30	SLE+SjS	–	LIP	+
11	58	F	1.60	PM	–	NSIP	–
12	65	F	1.43	PM	NSIP	atypical	–
13	47	F	1.66	RA	–	NSIP	+
14	46	F	1.31	SLE	–	NSIP	–
15	72	F	1.20	RA	–	NSIP	–
16	43	F	1.55	SSc	–	NSIP	–
17	56	F	1.53	SjS	–	NSIP	–

CT, computed tomography; MCTD, mixed connective tissue disease; SjS, Sjögren syndrome; RA, rheumatoid arthritis; DM, dermatomyositis; SLE, systemic lupus erythematosus; PM, polymyositis; SSc, systemic sclerosis; NSIP, nonspecific interstitial pneumonia; UIP, usual interstitial pneumonia; LIP, lymphoid interstitial pneumonia

Statistical analysis

A comparison of the means was carried out by either Student's *t*-test or the Welch test. A level of $P < 0.05$ was accepted as statistically significant.

Results

Eighteen patients were enrolled in this study. The mean age of these patients was 59.9 years, ranging from 43 to 76. In 1 patient with polymyositis (PM) and rheumatoid arthritis (RA)-associated ILD, which had been improved by three sessions of CYC infusion, participation in this study was discontinued because of an induction of infliximab therapy for the treatment of RA. The remaining 17 patients (1 man and 16 women) with active CVD-ILD accomplished the study protocol (Table 1), and their data were analyzed. The underlying CVD and the number of the patients were as follows: RA, 6 patients; PM, 2; dermatomyositis (DM), 2; systemic lupus erythematosus (SLE), 2; Sjögren's syndrome (SjS), 2; systemic sclerosis (SSc), 1; mixed connective tissue disease (MCTD), 1; SLE with SjS, 1. In 2 patients (patient nos. 8 and 12), a lung biopsy by VATS was performed because the subgroup of ILD was not determined only by CT findings. The patient number of each subgroup of ILD was as follows: nonspecific interstitial pneumonia (NSIP), 12 patients; usual interstitial pneumonia (UIP), 4; lymphocytic interstitial pneumonia (LIP), 1. Five patients (23.5%) had previously smoked. The sessions of CYC infusion per patient ranged from 5 to 20 (mean, 8.3). Methylprednisolone (4–32 mg/day; mean, 10.9) was concomitantly used in 15 patients; cyclosporine A (100–200 mg/day; mean, 175), 6; mizoribine (150 mg/day; mean, 150), 2; tacrolimus (2 mg/day), 1. Two patients did not receive either corticosteroids or immunosuppressive drugs (Table 2). Improvements in the pulmonary symptoms, such as cough and dyspnea, were noted in all patients (100%).

Regarding the chest CT findings, an improvement in ILD was recognized in 4 patients (patient nos. 5, 8, 14 and 15) (23.5%). The CT images before and after CYC pulse therapy of patient no. 14 are shown in Fig. 1. No deterioration of ILD was recognized in 13 patients (76.5%). Among the 4 patients who showed improvement of ILD, all patients were classified as NSIP (NSIP was noted in 12 patients, Table 1; accordingly, 33.3% of NSIP patients showed improvement of ILD). In contrast to NSIP, 4 UIP patients showed no improvement in CT findings (0%).

The serum levels of KL-6 before and after intermittent CYC pulse therapy are shown in Table 2. The time course of KL-6 in each patient is shown in Fig. 2. The serum levels of KL-6 decreased in all 17 patients (100%). The serum levels of KL-6 in all patients decreased from 1572 ± 904 U/ml (mean ± SD) before the entry to 978 ± 392 after the therapeutic course ($P < 0.01$). The mean level of KL-6 in 4 patients, whose CT findings all improved (patient nos. 5, 8, 14 and 15), decreased from 1445 ± 523 to 664 ± 178 ($P < 0.05$).

The data of pulmonary function tests are shown in Table 2. In 13 patients (patient nos. 1, 3–6, 8–11, 12, 13, 14, and 16), both the %VC and %DLco were determined. In 1 patient (patient no. 2), only the %VC was determined, because of an inability to hold her breath. In the remaining 2 patients, neither was tested. The mean value of %VC in 14 patients was 84.0% ± 17.6% (mean ± SD) before entry, and 88.6% ± 18.0% after the therapeutic course ($P = 0.25$). Improvement of %VC was recognized in 10 patients (71.4%). The mean value of %VC in 4 patients with improvement of CT findings increased from 96.8% ± 7.9% to 103.4% ± 11.6% ($P = 0.19$). The mean value of %DLco in 13 patients was 67.9% ± 18.3% before entry, and 71.9% ± 18.4% after the therapeutic course ($P = 0.29$). An improvement in the

Table 2. Clinical data of the study patients

Patient	Duration of CYC pulse therapy (month)	Concomitant therapy	Improvement of respiratory symptoms	CT change	KL-6 (U/ml)		%VC (%)		%DLco (%)		Outcome	Adverse effect
					Pre	Post	Pre	Post	Pre	Post		
1	3	mPSL 16 mg	(+)	n.c.	3290	1320	96.9	99.3	100.2	99.2	Alive	Upper respiratory tract infection
2	3	mPSL 4 mg	(+)	n.c.	1280	937	51.9	58.2	n.d.	n.d.	Alive	Nausea
3	10	mPSL 16 mg CSA 200 mg	(+)	n.c.	4150	1710	72.6	80.0	39.8	33.6	Alive	
4	3	mPSL 8 mg	(+)	n.c.	1420	840	64.9	74.4	58.2	73.6	Alive	
5	3	mPSL 16 mg CSA 200 mg	(+)	Improved	1090	870	99.1	111.8	68.3	81.4	Alive	
6	3	mPSL 12 mg, CSA 200 mg, MZR 150 mg	(+)	n.c.	1600	1040	70.1	70.4	60.0	50.5	Alive	
7	3	mPSL 4 mg TAC 2 mg	(+)	n.c.	2500	1950	n.d.	n.d.	n.d.	n.d.	Alive	
8	2	mPSL 24 mg	(+)	Improved	1180	450	96.0	94.2	102.5	93.7	Alive	
9	2	mPSL 4 mg	(+)	n.c.	1030	747	95.2	100.4	73.0	75.5	Alive	Nausea
10	2	mPSL 4 mg MZR 150 mg	(+)	n.c.	1090	868	104.3	103.0	72.0	73.2	Alive	Upper respiratory tract infection
11	3	None	(+)	n.c.	1500	1130	100.7	106.3	68.8	70.8	Alive	
12	3	mPSL 4 mg	(+)	n.c.	909	742	94.2	99.5	75.0	93.2	Alive	
13	3	none	(+)	n.c.	805	596	55.2	54.6	42.0	58.8	Alive	
14	2	mPSL 32 mg	(+)	Improved	2220	609	86.5	92.8	60.4	73.0	Alive	
15	3	mPSL 4 mg CSA 150 mg	(+)	Improved	1290	727	n.d.	n.d.	n.d.	n.d.	Alive	
16	3	mPSL 8 mg CSA 100 mg	(+)	n.c.	1100	900	87.7	95.0	62.3	58.0	Alive	
17	3	mPSL 8 mg CSA 200 mg	(+)	n.c.	1380	1190	n.d.	n.d.	n.d.	n.d.	Alive	Nausea

CT, computed tomography; CYC, cyclophosphamide; mPSL, methylprednisolone; CSA, cyclosporin A; TAC, tacrolimus, MZR, mizoribine; n.c., no change; %VC, % vital capacity; %DLco, % diffusing capacity for carbon monoxide; n.d., not detected

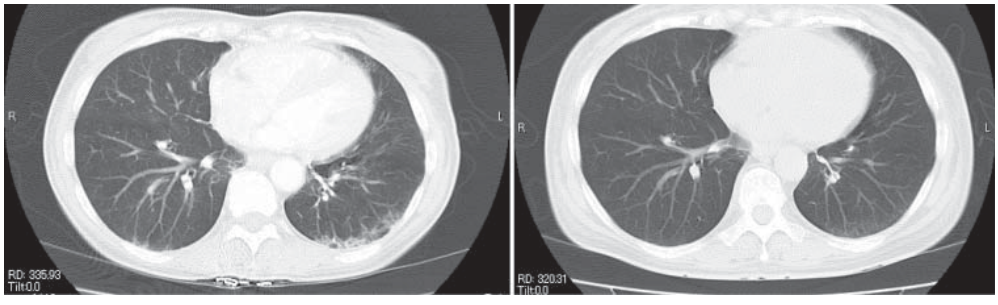

Fig. 1. The non-enhanced computed tomography images (1-mm thickness) of patient no. 14 are shown. The lesions of infiltration consisting of low-attenuation and reticular opacities diminished after 8 weeks after a total infusion of 2300 mg of cyclophosphamide (*right*) in comparison to the images before the entry (*left*)

%DLco was recognized in 8 patients (61.5%). The mean value of the %DLco in the 3 patients with improvement of CT findings increased from 77.1% ± 22.4% to 82.7% ± 10.4% ($P = 0.36$).

No major adverse event(s) occurred, which would have suggested that the study protocol should be discontinued (Table 2). In 2 patients (patient nos. 1 and 10), who were afflicted with an upper respiratory tract infection, the intermittent CYC infusion was postponed until their symptoms disappeared, and thereafter could be restarted. Three patients (patient nos. 2, 9, and 17) complained of nausea after the first infusion of CYC, which subsided by premedication of azasetron hydrochloride from the second infusion. Neither liver dysfunction nor hemorrhagic cystitis was recognized in any patient. Complete blood cell counts and the serum levels of IgG before and after intermittent CYC pulse therapy are shown in Table 3. WBC counts were unchanged: 6824 ± 1944/μl (mean ± SD) before the entry, and 6941 ± 2427/μl after the therapeutic course ($P = 0.44$); lymphocyte counts, 1536 ± 680 and 1522 ± 848 ($P = 0.48$); hemoglobin, 11.9 g/dl ± 1.7 and 11.8 ± 1.8 ($P = 0.39$); platelet counts, $27.0 \pm 10.5 \times 10^4$/μl and $24.5 \pm 9.3 \times 10^4$/μl ($P = 0.24$). The serum IgG levels significantly decreased from 1809 ± 594 to 1360 ± 422 mg/dl ($P < 0.01$).

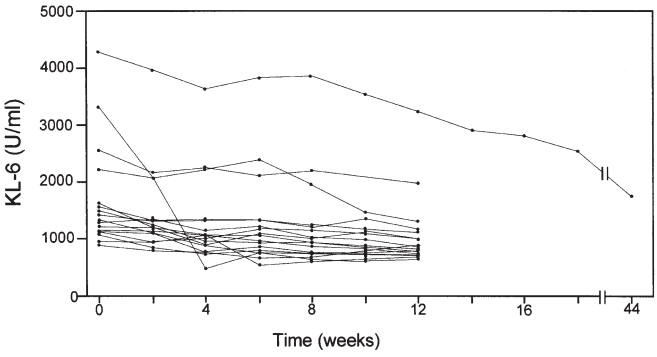

Fig. 2. The time course of KL-6 in each patient during the intermittent intravenous cyclophosphamide pulse therapy is shown. The upper limit of the normal range of KL-6 is 500 U/ml

Table 3. CBC and IgG before and after CYC pulse therapy

	Pre	Post	*P*
WBC (/μl)	6824 ± 1944	6941 ± 2427	0.44
Lymphocytes (/μl)	1536 ± 680	1522 ± 848	0.48
Hb (g/dl)	11.9 ± 1.7	11.8 ± 1.8	0.39
Plt ($\times 10^4$/μl)	27.0 ± 10.5	24.5 ± 9.3	0.24
IgG (mg/dl)	1809 ± 594	1360 ± 422	<0.01

Data are shown as mean ± SD
CBC, complete blood cell counts; WBC, white blood cells; Hb, hemoglobin; Plt, platelet; IgG, immunoglobulin G

Discussion

Since the therapeutic efficacy for lupus nephritis had been demonstrated,[12–14] CYC pulse therapy has been not only used for the treatment of lupus nephritis but has also been applied to treat various CVD, such as Wegener's granulomatosis, and other antineutrophil cytoplasm antibody (ANCA)-associated vasculitides.[15,16] The efficacy of CYC pulse therapy for ILD associated with various CVD has also been shown. Eiser and Shanies described its efficacy in two SLE patients;[6] Steen et al., 14 SSc;[4] Giacomelli et al., 23 SSc;[17] Pakas et al., 28 SSc;[18] Schnabel et al., 6 CVD (PM, 2; SSc, 2; SLE, 1; SjS, 1).[1]

The formerly reported CYC dosage and frequency for the treatment of CVD-ILD were 500 to 1000 mg/m^2 of body surface area once a month: the CYC dosage in the protocol by Eiser and Shanies was 500–600 mg/m^2;[6] Steen et al., 500–750;[4] Giacomelli et al., 1000;[17] Pakas et al., 500 followed by 750;[18] Schnabel et al., 500.[1] Our regimen is characterized by (i) a comparable dosage of CYC per month (the initial dose, 730.3–1083.3 mg/m^2; mean, 900.6) to those described; (ii) a "divided administration," namely, three or two sessions of CYC infusion/month: the dosage of CYC was 400–500 mg/body, and the interval of CYC pulse therapy was every 10 days, and thereafter, to every 2 weeks, according to the decrease of the ILD activities; (iii) the assessment of the ILD activities using serological marker, KL-6, in addition to the monitoring of respiratory symptoms, the conventional chest CT and pulmonary function tests.

In the present study, pulmonary symptoms were improved in 100% of the patients; KL-6, in 100%; %VC, in 78.6%; %DLco, in 61.5%. Nevertheless, mean %VC and mean %DLco did not change significantly. Among the 3 patients with deterioration of %VC, 2 were classified as NSIP; 1, LIP. Among the 5 patients with deterioration of %DLco, 4 were classified as NSIP; 1, UIP. Both %VC and %DLco improved in 7 NSIP patients (58.3%) and 3 UIP patients (75%). In contrast, the improvement of CT findings was more remarkably recognized in NSIP patients (33.3%) than in UIP patients (0%). The reason for the discrepancy between pulmonary functioning tests and CT findings with respect to ILD subgroups is unknown; it might stem form the inability of CT modality to detect the fine improvement of UIP. To prove this hypothesis, a larger number of CVD patients with UIP is necessary to be studied.

In the reported protocols, corticosteroid was also used. The initial dosage of prednisone by Eiser and Shanies was 60 mg/day or 1 mg/kg/day;[6] Schnabel et al., 50 mg/day;[1] Giacomelli, 25 mg/day.[17] In this study, the mean initial dosage of methylprednisolone was only 10.9 mg/day (which was comparable to 13.6 mg/day of prednisolone). Pakas et al. evaluated the efficacy of CYC pulse therapy combined with low- (<10 mg/day) or high-dose (1 mg/kg per day for 4 weeks followed by tapering) prednisone in a prospective open label study for SSc-ILD patients.[18] In their study, improvement of the respiratory symptoms, CT findings, and/or pulmonary functioning tests were not recognized in the low-dose group, but they were noted in the high-dose group. Nevertheless, they described that long-term observation was required because the administration of high-dose corticosteroid might lead to a renal crisis of SSc.[19] In the present study, the mean dosage of methylprednisolone in four patients who showed improvement in CT findings was 19.0 ± 11.4 mg/day, compared to 6.8 ± 5.3 mg/day in 13 who showed no significant change ($P = 0.13$). Such a degree of the difference of methylprednisolone dosages might not have affected the improvement of CT findings.

In this study protocol, immunosuppressive drugs were permitted for the treatment of each patient's CVD and ILD.[20,21] There had been several reports that cyclosporine A has efficacy for the treatment of ILD associated with CVD.[20,21] Nevertheless, in this study three patients (patient nos. 15–17) whose ILD activities were not suppressed by the administration of cyclosporine A alone for 3–4 weeks were successfully treated with CYC pulse therapy.

With respect to the safety of CYC pulse therapy, Austin et al. described that higher frequencies of adverse events, such as hemorrhagic cystitis, premature ovarian failure, herpes zoster, and cancer, were recognized in the oral administration group than in the intermittent infusion of CYC-group in the treatment of lupus nephritis.[12] In the former studies of CYC pulse therapy for CVD-ILD, complications associated with immuno- or myelosuppression had been described in some reports; in the study by Schnabel et al., 1 patient (16.6%) experienced protracted leukocytopenia;[1] in that of Pakas et al., 3 patients (10.7%) developed lower respiratory tract infections.[18] In this study, only two sessions of CYC infusions were postponed because of upper respiratory tract infections, and were able to

be restarted after the infections were cured among a total of 141 sessions of CYC infusion. Comparing the post- with pre-data of the therapeutic course, WBC, lymphocytes, hemoglobin, and platelets remained unchanged (Table 3). The serum IgG levels significantly decreased during the CYC pulse therapy, but those at the post-therapeutic course still remained within the normal range (Table 3).

For measuring the activity of ILD, nonspecific markers, such as lactose dehydrogenase (LDH), has been used, but LDH was elevated in various disorders. Pulmonary function tests or diagnostic imaging, such as CT, cannot be conducted frequently in terms of cost benefit and availability. The carbon monoxide diffusing capacity (DLco), oxygen desaturation on exercise, and the clearance of inhaled Tc-99m diethylenetriamine pentacetate (DTPA) might thus be the most diagnostic predictors of disease progression. Nevertheless, these examinations require specific facilities and/or might cause considerable discomfort to the patient. Recently, KL-6 has been established as an accurate serological marker for the evaluation of ILD activities.[8] We recently found that the serum levels of KL-6 are positively correlated with those of CA15-3 in patients with CVD-ILD.[22] The serum levels of surfactant proteins A and D have almost the same diagnostic values of KL-6. We adjusted the dosage of CYC in accordance with the levels of KL-6 that were measured weekly. Yokoyama et al. described that, among patients with rapidly progressive idiopathic pulmonary fibrosis (IPF) who were treated with corticosteroid pulse therapy, KL-6 levels decreased significantly in patients who survived, whereas those levels tended to increase in patients who died.[23] They also demonstrated the prognostic value of KL-6 levels in IPF at the time of diagnosis: the median survival duration of patients who showed low levels of KL-6 (<1000 U/ml) was more than 36 months; that of patients with high levels of KL-6 (≥1000 U/ml), only 18 months.[24] Bandoh et al. found that the prognoses of six ILD-patients associated with PM/DM corresponded to the levels of KL-6.[25] In this study, KL-6 levels decreased in all of the patients who showed improved or unchanged CT findings (Fig. 2).

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