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Intravenous cyclophosphamide for interstitial lung disease associated to systemic sclerosis: results with an 18-month long protocol including a maintenance phase

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ABSTRACT

Objective. *Cyclophosphamide (CYC) is generally considered the most promising agent available today for systemic sclerosis (SSc)-related interstitial lung disease (ILD). However, the optimal dosage and length of treatment are still undetermined. Our objective was to evaluate the effect of an 18-month long protocol with intravenous (iv) CYC.*

Methods. *In a single-centre, prospective, observational study, 13 patients with SSc and active alveolitis were given 8 iv pulses in a 6-months period (CYC 750 mg + 6-methylprednisolone 125mg every three weeks), as an induction therapy. Patients received maintenance therapy with further cycles at 4 (3 pulses), 6 (3 pulses) and 9 weeks (3 pulses) interval. Total CYC dosage was 12.75g in an 18-month period. Endpoints were modifications of lung function test (LFT).*

Results. *During the first 6 months of treatment with CYC an increase in Forced Vital Capacity (FVC; p = 0.005) and in diffusion lung capacity for carbon monoxide (DLCO; p = 0.10) was observed; during the maintenance therapy, there was a stabilization in FVC and a mild, non significant decline in DLCO. Treatment was well tolerated.*

Conclusion. *iv CYC can induce an initial improvement in LFT (particularly, in FVC) in the first six months, but no further improvement was observed during the maintenance phase.*

Introduction

Interstitial lung disease (ILD) is a leading cause of morbidity and mortality in patients with systemic sclerosis (SSc) (1). Cyclophosphamide (CYC) is generally considered the most promising agent available for these patients (2). As far as the route of drug administration, intravenous (iv) pulses are possibly associated with reduced toxicity as compared with oral route, and 6 months-cycles with iv CYC were shown to induce a significant improvement of lung function test (LFT) (3), and bronchoalveolar lavage (BAL) findings (4). However, the optimal dosage and length of treatment with iv pulses in these patients is still undetermined.

We report here the results of a single centre, prospective, observational study, based on a prolonged 18-month course of iv CYC.

Materials and methods

Patients

Patients were classified as limited or diffuse SSc (lSSc, and dSSc, respectively) according to the criteria of LeRoy. Disease duration was defined as time from the onset of first symptom other than Raynaud's phenomenon and patients were classified as having early disease (less than 3 year disease duration for dSSc, or less than 5 year disease duration for lSSc), or late disease. Fifteen consecutive patients with SSc and active alveolitis were treated with an iv CYC protocol at our Institution between 2002 and 2005. In 2 patients with dSSc treatment was discontinued for disease progression (1 worsening of respiratory insufficiency; 1 renal crisis). Main demographic and clinical features of the 13 patients who received the programmed 18-month long iv CYC protocol are reported in Table I. Data concerning 3 patients were partially described (i.e., the results after the first 6 months of therapy) in a previous paper (3).

Diagnosis of active SSc-related ILD was based on BAL findings (n: 10), and/or ground glass opacities documented by high resolution computed tomography (HRCT). No patient had clinically relevant pulmonary arterial hypertension. In the 6 months preceding the period of CYC treatment, 6 patients received no disease-modifying drugs, 3 were treated with D-penicillamine, 3 with cyclosporine; 1 with methotrexate + cyclosporine + azathioprine. Six patients were receiving also low-dose oral glucocorticoids (median dosage of prednisone: 8 mg/d; range 4-12).

Cyclophosphamide treatment

As an induction therapy, patients were given 8 iv pulses in a 6-months period (CYC 750 mg + 6-methylprednisolone 125 mg every three weeks). Patients received maintenance therapy with further cycles at 4 (3 pulses), 6 (3 pulses) and 9 weeks (3 pulses) interval. Total CYC dosage was 12.75 g in an 18-

month period. In 1 patient the dosage of CYC was reduced to 500 mg for mild episodes of nausea. Fertile women received oral progestinic to block menses and preserve ovarian function. Oral mesna was prescribed for the prevention of haemorrhagic cystitis. Twelve patients received also low-doses oral prednisone at a stable dosage (5-20 mg/die). All patients were treated with vasodilators and low-dose aspirin. Seven patients received cyclic intravenous Iloprost for severe ischemic digital ulcers. No patient received other immunosuppressive drugs during the period of the study.

Lung function tests

Forced Vital Capacity (FVC) and diffusion lung capacity for carbon monoxide (DLCO) were evaluated by standard procedures and results were expressed as percentages of predicted values based on age, sex, and height. Normal values were calculated by reference standard provided by the European Coal & Steel community, as described (3).

Statistical analysis

Data are presented as the median (25th, 75th percentile, IQR). Non-parametric tests were used for statistical analysis. Wilcoxon's matched pair test was used for comparisons of LFT before and after the therapy. Correlations between measures were evaluated by the Spearman rank test.

Results

Among the 13 individuals with SSc and active alveolitis evaluated in this study, ten patients underwent LFT in the period before the therapy with CYC (median follow-up: 31 months), which demonstrated a progressive decline in FVC (-7.9%/year; $p < 0.01$) and DLCO (-6.2%/year; $p < 0.01$).

The variations of LFT during the period of treatment with iv CYC are shown in Figure 1. Median basal FVC was 74% of the predicted value (IQR: 61-84). After 6 months of treatment median FVC was 82% (64-94). The increase from basal values was statistically significant ($p = 0.005$), and 5 patients out of 13 had an improvement > 10% of their entry data, while no patient worsened >10%. During the maintenance period, between month 6 and month 18, 3 patients had a further improvement, but 4/13 worsened. At month 18, median FVC was 76% (64-101) and, comparing with $t = 0$, the increase was still statistically significant ($p = 0.05$). Globally, during the 18-month period of treatment, 5 patients out of 13 improved, but 1 worsened from entry data.

Median basal DLCO was 41% of the predicted value (39-51). After 6 months of treatment DLCO was 47% (40-49), with a trend toward non statistically significant improvement ($p = 0.10$) (Fig. 1). Six patients out of 13 had an improvement > 10% from their entry data, but 1 worsened > 10%. During the maintenance period, 2 patients had a further improvement, but 5/13 worsened. At the end of the 18-month protocol median DLCO was 44% (35-46). Four patients were improved, and 6 were worsened, as compared with $t = 0$.

No difference in the variations of FVC and DLCO was observed comparing patients with lSSc with those with dSSc, as shown in Table II, or patients with early disease with those with late disease (not shown). No significant correlation was found between these variations and BAL parameters (neutrophil percentage). Treatment was well-tolerated: only 1 case of H. Zoster was observed. No other side effects (leucopenia, or haemorrhagic cystitis) were recorded.

Discussion

Currently, CYC is the most widely used

Table I. Main demographic, clinical and laboratory characteristic in 13 patients treated with iv CYC for ILD due to SSc. Data are presented as the median (25^{th}, 75^{th} percentile).

Characteristic	
Sex (M/F)	2/11
Age (years)	48 (41, 53)
Disease subset (dSSc/lSSc)	8/5
Disease duration (years)	7.5 (4.5, 9.5)
Early disease/late disease	4/9
Anti-Scl70	3 (21%)
Oral prednisone dose (mg/d)	9 (7, 12.5)
FVC, % predicted	74 (61, 84)
DLCO, % predicted	41 (39, 51)
BAL (n:10), total cells	311,000 (176,000, 408,000)
BAL (n:10), % neutrophils	13 (10, 15)

Table II. Variations of FVC and DLCO in patients with lSSc or dSSc during the period of treatment with iv CYC. Data are presented as the median (25^{th}, 75^{th} percentile).

	FVC			DLCO		
	From time = 0 to time = 6m	From time = 6m to time = 18m	From time = 0 to time = 18m	From time = 0 to time = 6m	From time = 6 to time = 18m	From time = 0 to time = 18m
lSSc (n.5)	+2% (+1, +16)	+1% (-8, +7)	+3% (+2, +8)	+7% (+4, +8)	-3% (-3, -2)	+4% (-5, +5)
dSSc (n:8)	+3.5% (+3, +6.25)	+1% (0, +4.5)	+5 % (+3, +11.25)	+1.5% (-1, +6)	-4% (-7, +1)	-2.5% (-8, +5.5)
TOTAL	+3% (+1, +10)	+1% (-8, +7)	+5 % (+2, +11)	+4% (-2, +7)	-3% (-7, +1)	+3% (-8, +5)

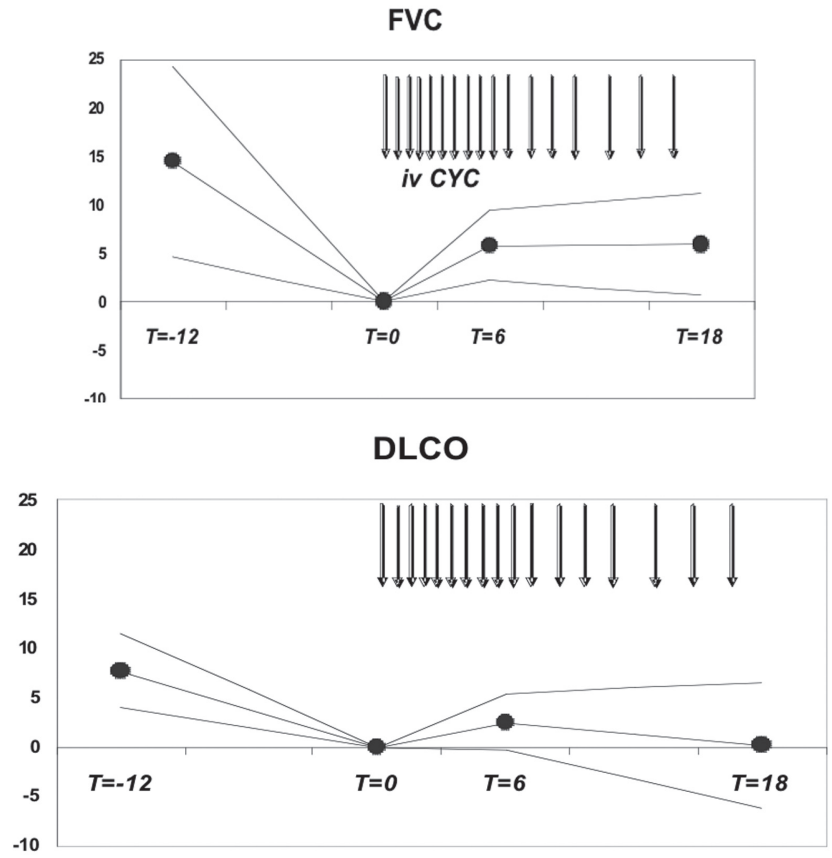

Fig. 1. Changes in Forced Vital Capacity (FVC) and in Diffusion Lung Capacity for CO (DLCO) before and after therapy with iv CYC. In the figure the mean (bold line) and 95% confidence intervals values are indicated, considering data at the initiation of therapy = 0. Data before the treatment were standardized at 12 months.

agent for the treatment of SSc-associated ILD. Oral CYC (1-2 mg/kg/d) was shown to induce a significant improvement of FVC (5-7) and survival (7) in SSc patients with alveolitis. There are concern, however, on the toxicity of oral CYC. In particular, long-term adverse events, including infertility, cumulative bone marrow toxicity, and carcinogenesis, are dose-dependant. In protocols with iv pulses much lesser doses of CYC are used: therefore, side effects are expected to be less frequent and severe than those induced by oral CYC. Several uncontrolled studies have shown that iv CYC for 6 months (at dosages ranging around 0.7-1.5 g/month) can reduce the percentage of neutrophils in the BAL (4), and can improve the LFT of patients with SSc and ILD (3, 4, 8-11). In most studies this improvement was not statistically significant, probably for the small numbers of patients evaluated. However, analysing pooled data from 3 studies which evaluated a total of 53 patients with SSc treated in this way, we found that the improvement of LFT after 6-month treatment with iv CYC in SSc-related ILD, although small, was not casual (3). This finding was confirmed by the preliminary results of a multicentre prospective randomised double-blind placebo-controlled trial, which demonstrated a statistically significant increase in FVC after 6 monthly infusion of iv CYC as compared with placebo-treated patients (12). Since LFT are highly significant prognostic factors for the progression of lung disease and survival of patients with SSc (13, 14), these observations support the use of CYC for the treatment of these patients.

However, there is debate over the optimal regimen: the longer term follow-up data of patients treated with iv CYC for 6 months suggest that deterioration after the stop of treatment occurs in most patients, sometimes at a significant rate (10). As it was reported that in patients prolonging treatment for 12 months, further improvement could be observed (8, 9), we considered that this was a modality worthy to be explored, even if the best schedule was still undetermined. We adopted a regimen adapted from vasculitis protocols, which was already used also in a very small number of patients with ILD-asssociated SSc by Griffiths *et al*. in UK (10). Our experience confirmed that iv CYC can induce an initial improvement in LFT (particularly, in FVC) in the first 6 months, while thereafter a stabilization of FVC was observed, while DLCO tended to a decline. Meanwhile, the British group reported in an abstract its experience: results were very similar to those observed by us: interestingly, they found that the decline in DLCO was significantly reduced in patients receiving prolonged treatment with iv CYC, as compared with a group of patients receiving treatment of a shorter duration (15). Therefore, they concluded that prolonged treatment with iv CYC may be more effective than a shorter course. Nevertheless, even if the lack of further improvement during the maintenance period with reduced iv CYC pulse frequency should be interpreted in the scenario of the natural history of the disease, which carries the probable progressive worsening of lung function, these results cannot be considered very reassuring. However, they suggest that further studies to explore this treatment modality are warranted.

A major question arising from these studies is which are the patients that really improve with this therapy. We did not find any correlation between variations of LFT during the period of treatment and other parameters such as disease duration and subset, or neutrophil percentage in the BAL, but this analysis was limited by the small number of patients treated. Future studies should be designed also to answer to this question.

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