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Use of intravenous cyclophosphamide in known or suspected, advanced non-specific interstitial pneumonia

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Abstract. *Background:* In severe, progressive interstitial lung disease (ILD), specific diagnosis is often difficult, and treatment therefore empirical. An effective, rapidly acting, well-tolerated therapy is desirable. This study reviews the tolerability and efficacy of IV cyclophosphamide in known or suspected non-specific interstitial pneumonia (NSIP) following the introduction of an IV cyclophosphamide protocol. *Methods:* Records of 54 patients with biopsy-proven (n=7) or suspected NSIP, based on clinico-radiological consensus (n=47), receiving IV cyclophosphamide over 2004-6 were reviewed (excluding systemic sclerosis). Lung-function trends over six months were evaluated, and comparative analysis of paired pulmonary-function before and after the start of therapy was performed. *Results:* IV cyclophosphamide was well tolerated, with two withdrawals from therapy, and four deaths, not directly related to treatment. IV cyclophosphamide was associated with disease stability at six-months. Despite having severe, progressive disease, patients receiving IV cyclophosphamide had stable lung function at six months. A greater therapeutic response was associated with coexistent HRCT abnormalities indicative of organizing pneumonia. In 22 patients with paired pulmonary-function tests, pulmonary function trends were significantly improved (p=0.03) and change in DLco differed significantly (p<0.0001), following cyclophosphamide treatment. *Conclusion:* In the empirical treatment of advanced, rapidly progressive known or suspected NSIP, IV cyclophosphamide is a well tolerated, rapidly acting immunosuppressant, associated with improvement or stability in most cases. *(Sarcoidosis Vasc Diffuse Lung Dis 2009; 26: 132-138)*

Key words: intravenous cyclophosphamide, interstitial lung disease, idiopathic interstitial pneumonia, connective tissue disease, non-specific interstitial pneumonia, organizing pneumonia

Abbreviations

ILD: Interstitial lung disease
IV: Intravenous
NSIP: Non-specific interstitial pneumonia
OP: Organizing pneumonia
DLco: Diffusing capacity for carbon monoxide
FVC: Forced vital capacity
PaO_2: Arterial partial pressure of oxygen
IPF: Idiopathic pulmonary fibrosis
HRCT: High-resolution computed tomography
SLE: Systemic lupus erythematosus

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Introduction

In severe progressive interstitial lung disease (ILD), immunosuppression is widely used when it is believed that inflammation has a prominent patho-

genetic role. In rapidly progressive, severe disease, surgical biopsies are high risk, and often impracticable. Diagnosis is, therefore, based on clinico-radiological consensus, and precise differentiation between specific ILD diagnoses may be impossible. In a significant patient sub-group, a working diagnosis of non-specific interstitial pneumonia (NSIP) is made, based on clinical and high-resolution computed tomography (HRCT) features. In such cases, treatment is necessarily empirical, and often includes a trial of immunosuppressant therapy.

Traditional oral immunosuppressive agents have a slow-onset of action, and are limited by side-effect profiles. Thus, there is a need for a rapidly acting, effective, non-toxic immunosuppressant for use in such cases. Intravenous (IV) cyclophosphamide has a rapid onset of action, and is well tolerated. IV cyclophosphamide is effective in the short-term in systemic sclerosis (1-3), and some reports suggest a benefit in patients with steroid-resistant NSIP (4), autoimmune-related ILD (5) and organizing pneumonia (6).

An IV cyclophosphamide treatment protocol was introduced at our institution for patients in whom a rapid, non-toxic immunosuppressive treatment was required. The present study reviews the indications, duration, tolerability and success of IV cyclophosphamide in patients with known or suspected NSIP, over a two-year period.

Patients and methods

Study Design

We reviewed the use of IV cyclophosphamide in patients with known or suspected NSIP, following the institution of a treatment protocol (all patients who completed treatment, or withdrew from treatment from 1st October 2004 to 31st October 2006). Patients with systemic sclerosis were excluded from this study.

Local ethical approval was in place for retrospective ILD studies. The clinical records of all subjects were reviewed (n=54), taking as baseline the assessment prior to the start of cyclophosphamide treatment. The collected data covered the period from six months before and after the start of treatment. In addition to basic demographic, clinical and physiological parameters, details of the treatment regimen and adverse events were collected. Pulmonary function data were collected over this time period (using tests closest to and within three months of each date) and six-month lung function trends were evaluated. Decline in pulmonary function tests was defined as a fall in diffusing capacity (DLco) ≥15% or forced vital capacity (FVC) ≥10%.

Seven patients had known (biopsy-proven) NSIP. Despite our usual practice of referral for surgical biopsy in indeterminate cases, biopsy was not possible in 47 patients. In these patients, the diagnosis was suspected NSIP, based on multi-disciplinary consensus. Patients were considered to have NSIP/organizing pneumonia (NSIP/OP) overlap, if radiological evidence of NSIP was associated with consolidation.

Treatment Regimen

All patients were given information about potential side effects prior to commencing cyclophosphamide therapy, including infertility and teratogenicity if appropriate. IV cyclophosphamide was given at 600 mg/m^2. The frequency and duration of the therapy was patient specific, determined by the treating physician. Cyclophosphamide was prepared in pre-filled syringes and bags diluted in 100 ml normal saline solution, and given as a 30 minute infusion. Full blood count, renal function tests, hepatic function tests and urinanalysis were performed before each cyclophosphamide dose. IV and oral mesna were given to prevent urothelial toxicity when individual doses exceeded 1g (n=44). IV mesna was given at 20% of the cyclophosphamide dose diluted in 100 ml normal saline, as a 30 minute infusion. Oral mesna (40% of cyclophosphamide dose) was given at two and six-hours post-cyclophosphamide. Patients were routinely dispensed anti-emetics on discharge.

Statistical Analysis

Data are shown as mean with standard deviation or median with ranges. Pulmonary function trends are expressed as percentage change from start of therapy. Group comparisons were performed by univariate analysis (Wilcoxon's ranksum test). Multiple linear regression models were evaluated with change in DLco at six-months as the dependent variable, and ILD diagnosis, baseline DLco and age

as covariates. Standard regression diagnostics were performed, including testing for heteroscedasticity and omitted variables. Cateogorical trends (stability, decline or improvement) over the six months before and after treatment were defined according to ATS/ERS guidelines, using either ≥10% change in FVC or ≥15% change in DLco as threshold values. Wilcoxon's paired test was used to compare pulmonary function trends for the six months before and after treatment. A value of $p<0.05$ was considered to be statistically significant.

Results

Patient Details

Fifty-four patients (mean age 57 ± 13 yrs, 25 male) with known or suspected NSIP were started on IV cyclophosphamide in this two-year period. Seven patients had undergone surgical biopsy. Nine patients met American College of Rheumatology criteria for connective tissue disease [rheumatoid arthritis (n=3); dermatopolymyositis (n=4), mixed connective tissue disease (n=2)], and two patients had features of overlap connective tissue disease. All but nine patients had received prior anti-inflammatory or immunosuppressive treatment [prednisolone (n=45), azathioprine (n=24), mycophenolate mofetil (n=3), oral cyclophosphamide (n=3)]. Baseline DLco was 31 ± 12% and FVC was 59 ± 18%. Twelve patients had pulmonary hypertension (defined as right ventricular systolic pressure ≥40 mmHg on echocardiogram).

Details of Treatment

Mean cyclophosphamide dose was 1143 ± 182 mg. Fifty (93%) of patients received cyclophosphamide at monthly intervals, with four patients receiving an escalated regimen of three-weekly cyclophosphamide. The median number of cyclophosphamide doses was six (range 1-12), with five patients receiving cyclophosphamide for more than six doses.

The primary reason for commencing cyclophosphamide therapy was most commonly progressive disease (n=44), followed by severe disease at presentation (n=10). During treatment, all but two patients received low to moderate dose prednisolone (11 ± 5mg). Following treatment, all patients were continued on low dose prednisolone, and most on a second agent [azathioprine (n=31), mycophenolate (n=11), oral cyclophosphamide (n=4) and continued IV cyclophosphamide (n=2)].

Adverse Events

Treatment was well tolerated, with 38 patients (70%) having no adverse events during treatment (Table 1). The most common adverse event was infection (n=6). Only one patient experienced each of alopecia and elevated liver enzymes both which resolved following cessation of therapy. One patient developed transient hematuria, that resolved spontaneously. Two patients ceased therapy, due to intercurrent infection (n=1), and patient request (n=1). Four patients died within 12months of treatment from progressive disease (n=3) and acute coronary syndrome (n=1).

Response to Treatment

a) IV cyclophosphamide

In the six months prior to treatment, 51 of 54 (94%) patients declined [decline in symptoms (World Health Organization functional class) n=46; imaging data n=12; pulmonary function n=17]. During treatment, there was stability in 25 (46%), improvement in 22 (41%), progression in six patients (11%), and one death. Overall, there was stability of pulmonary function during treatment, with a median change in DLco of +6.8% (-74.6 to 92.0%) and FVC of −0.5% (-22.0 to 102.2%).

b) Patients with HRCT features of NSIP/OP overlap

IV cyclophosphamide patients with HRCT features of NSIP/OP overlap had a greater improve-

Table 1. Adverse events and deaths within 12 months of treatment

Adverse event	N
None	38
Infection	6
Nausea, vomiting	5
Fever, sweats	2
Alopecia	1
Elevated liver enzymes	1
Death	4
Early cessation of therapy	2

ment in DLco at six months compared to patients without consolidation on HRCT scan (p=0.005) (Table 2). On multiple linear regression this finding remained robust (Regression Coefficient = 17.0, 95% Confidence Intervals 1.2, 32.8; p=0.04) after adjustment for baseline DLco, age and gender.

c) Paired Pulmonary Function Trends

Pulmonary function tests were available six months before and after treatment in 22 patients. Prior to treatment, the majority of these patients (n=13) had declining pulmonary function, whilst following therapy most patients (n=14) showed improvement in pulmonary function. On paired testing of categorical trends in lung function, there was a significant improvement following cyclophosphamide treatment (p=0.03).

The median fall in DLco of 15.7% over the six months before treatment differed significantly from the stability seen over the next six months (p=0.0006) (Figure 1). This result remained highly statistically significant with the exclusion of patients with NSIP/OP overlap (p=0.0003) (Table 3). By contrast, the FVC trends did not differ significantly before and after treatment (p=0.60).

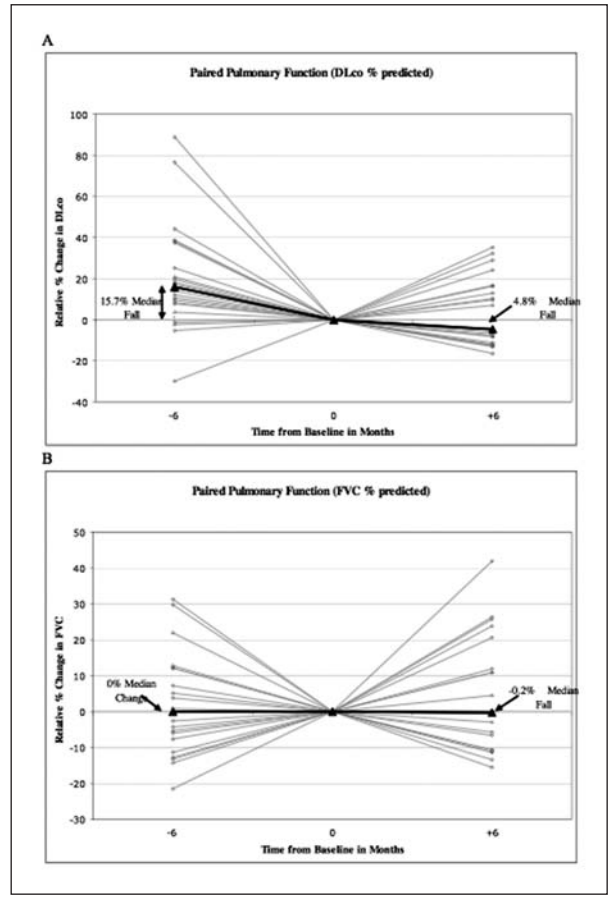

Fig. 1. Paired Pulmonary Function 6months before and after commencement of Intravenous cyclophosphamide therapy: (a) DLco % predicted; (b) Forced vital capacity % predicted. A significant difference is seen for change in DLco %, which fell prior to treatment, and stabilised during treatment (p=0.0006)

Discussion

This study reports the use of IV cyclophosphamide in patients with known or suspected NSIP, according to a pre-specified protocol. We observed that IV cyclophosphamide was well tolerated in this patient group and associated with stable pulmonary function variables over the next six months. Secondly, patients with a HRCT diagnosis of NSIP had better outcomes at six months if there was associated consolidation indicative of a component of organizing pneumonia.

Rationale For IV Cyclophosphamide Protocol

In severe, progressive fibrotic lung disease, prognosis is uniformly poor. Lung biopsy is often not practicable due to high associated risks. In such

Table 2. Change in pulmonary function during treatment: patient subset comparisons

	Median (range)
DLco	
IV Cyclophosphamide patients with NSIP HRCT pattern	-7.1% (-65.8 to +35.1%)*
IV Cyclophosphamide patients with NSIP/OP overlap	+14.9% (-74.61 to +92%)*
FVC	
IV Cyclophosphamide patients with NSIP HRCT pattern	-2.3% (-22.2 to +26.4%)
IV Cyclophosphamide patients with NSIP/OP overlap	-0.5% (-11.3 to 102.2%)

* p= 0.005; (Wilcoxon's ranksum test)

Table 3. Paired pulmonary function data six months before and after start of therapy.

	6 months prior	6 months after	p value*
Patients receiving IV cyclophosphamide			
DLco % predicted (n=22)	-15.7% (-88.8 to 29.9%)	-4.8% (-16.4 to 35.0%)	p=0.0006
FVC % predicted (n=22)	0.0% (-31.3 to 21.5%)	-0.2% (-17.9 to 41.9%)	p=0.6
Exclusion of patients with HRCT features of NSIP/OP			
DLco % predicted (n=14)	-20.2% (-88.8 to 1.1%)	-0.8% (-16.4 to 35.1%)	p=0.0003
FVC % predicted (n=14)	-4.5% (-31.3 to 14.2%)	-1.6% (-15.5 to 26.4%)	p=0.36

All data expressed as relative change from baseline as Median (range)
* Paired Wilcoxon's signed rank test

cases, diagnosis is based on clinico-radiological consensus, and differentiation between specific ILD diagnoses is often difficult. In this situation, treatment is empirical, often including a trial of immunosuppression and must be rapid in onset and well tolerated. IV cyclophosphamide is not a traditional therapy in respiratory medicine. However, rheumatologists have long-viewed IV cyclophosphamide as routine treatment (with some patients being treated for years with doses similar to those used in the current study) (7-10). Our interest in connective tissue related lung disease has resulted in exposure to this 'rheumatological' approach, and instigated reappraisal of our approach to treatment of aggressive disease.

In principle, cyclophosphamide should be most efficacious in predominantly inflammatory disorders, such as Wegener's granulomatosis (11-13), other vasculitides and refractory organizing pneumonia (6). However, a benefit is also apparent when disease is predominantly fibrotic but ongoing inflammation is central to pathogenesis (such as scleroderma). In the USA oral cyclophosphamide study in scleroderma lung, the treatment effect, consisting of the prevention of progression, was largely confined to patients with extensive fibrotic disease on HRCT (14). It appears likely that benefits in NSIP and autoimmune-related ILD (4-6, 15, 16) relate in part to prevention of progression of fibrosis as a direct result of suppression of inflammation.

IV cyclophosphamide has potential advantages over other immunosuppressants, including its rapid speed of onset, and side-effect profile. Its onset of action is estimated at 10-14 days based upon its effect upon haematopoiesis. In contrast, oral immunosuppressants such as azathioprine and mycophenolate require progressive up-titration, resulting in a period of insufficient therapy of up to two months. This may be a critical period for patients with rapidly advancing disease.

Furthermore, IV cyclophosphamide is well tolerated. In the current study, less than five percent of patients were unable to continue treatment due to toxicity. This finding mirrors our experience with IV cyclophosphamide in the general ILD population (data not shown). By contrast, side effects necessitate early withdrawal from therapy in up to 25% of patients receiving oral azathioprine (17, 18) and oral cyclophosphamide has an even higher prevalence of unacceptable toxicity (12, 19-22). In the context of aggressive disease, selection of a treatment that is likely to be well tolerated is important, as delays in therapy may be life threatening.

Treatment Effects

Despite severe, progressive disease in the six-months before treatment, we found no net decline during IV cyclophosphamide therapy. In a severe and progressive fibrosing disease, major regression of disease with treatment is seldom attainable, and stabilisation of pulmonary function trends should be viewed as a success. In the USA oral cyclophosphamide study in systemic sclerosis, the treatment effect against placebo consisted of disease stability in patients with extensive fibrosis on HRCT (14). In the current study, comparisons in trends before and after treatment further reinforce the concept that absence of improvement with treatment is not synonymous with absence of benefit.

Patients with known or suspected NSIP receiving IV cyclophosphamide had stable pulmonary function over six months. However, a worse outcome might have been anticipated, as a histological diagnosis was seldom practicable, due to disease severity. Patients in whom the diagnosis of NSIP was based

on HRCT appearances were likely to have IPF in some cases, as documented in biopsy-proven disease (23). However, despite this malignant prognostic determinant, lung function trends were stable over the treatment period.

We demonstrate a strong association between therapeutic response at six months, and HRCT features of NSIP with coexistent consolidation indicative of organizing pneumonia. In the absence of elements of organizing pneumonia on HRCT, pulmonary function tests stabilised in many cases but seldom improved. These findings provide support for the concept of a clinical dichotomy in NSIP, with features of organizing pneumonia predicting a better treated outcome (24). A similar dichotomy is apparent when previous series are compared. In one large series, NSIP patients had a high prevalence of consolidation on HRCT and lymphocytosis on bronchoscopic lavage and the outcome was usually excellent (25). By contrast, in a cohort in which consolidation on chest radiography or HRCT was an exclusion criterion, bronchoscopic lavage findings in NSIP were identical to those in IPF, and the five-year survival in NSIP patients was only 50% (26). Our results mirror this dichotomy and provide further support for a reappraisal of the entity of NSIP, based upon differences in morphologic features and treated outcomes.

Study Limitations

In severe rapidly progressive disease with a major inflammatory component, a placebo-controlled study would be unacceptable to patients and ethically questionable. However, without placebo-controlled evaluation, the efficacy of IV cyclophosphamide cannot be quantified with precision. Thus, our findings do not establish that IV cyclophosphamide is intrinsically more active than oral agents. The advantages of IV cyclophosphamide lie in its rapidity of onset and observed tolerability, both crucial considerations in advanced rapidly progressive disease.

Additionally, the paired pulmonary function analysis was limited to patients in which paired data were available. However, immediate treatment at referral was required in the majority of cases. This requirement may have biased results, with patients with preceding serial lung function coming to attention due to more prolonged, aggressive disease. However, no difference in change in DLco or FVC at six months was seen for those with and without preceding lung function estimation.

Lastly, this study did not address which treatment regimen for IV cyclophosphamide is best used in ILD patients. IV cyclophosphamide may be given at low-dose, at frequent intervals in Goodpasture's syndrome. However, our treatment protocol was based on experience in systemic sclerosis (1, 27) in which IV cyclophosphamide is given at moderate doses (600-750 mg/m^2) at monthly intervals. In our study, most patients received six doses of cyclophosphamide at monthly intervals, followed by oral immunosuppressant therapy. Four patients with rapidly progressive disease received cyclophosphamide at three-weekly intervals, and five had a prolonged course of cyclophosphamide. The problem of ongoing therapy following the six months cyclophosphamide remains unresolved. In systemic lupus erythematosus (SLE) there is a precedence to continue IV cyclophosphamide therapy indefinitely (9, 28), however, experience with SLE and Wegener's granulomatosis suggests changing to oral immunosuppression may be beneficial (7, 8).

Conclusion

In patients with severe, progressive known or suspected NSIP, IV cyclophosphamide is well tolerated, and associated with an observed reduction in disease progression. Further studies are required to prospectively evaluate its therapeutic role, however, IV cyclophosphamide should be considered a well-tolerated alternative when selecting an immunosuppressive agent in patients with advanced progressive ILD with a HRCT pattern compatible with NSIP.

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