Concise Report

A novel therapeutic approach to the treatment of scleroderma-associated pulmonary complications: safety and efficacy of combination therapy with imatinib and cyclophosphamide

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Objective. Scleroderma-related interstitial lung disease (SSc-ILD) has limited therapeutic options due to unclear pathogenesis. Recently, PDGF receptor (PDGFR) amplification has been postulated to cause fibrosis. We hypothesized that a combination of imatinib (PDGFR inhibitor), might be useful for treating SSc-related ILD. Our objective was to evaluate the safety and efficacy of this combination therapy in scleroderma-related pulmonary disease.

Methods. Five patients with advanced SSc-ILD underwent comprehensive cardiopulmonary evaluation, followed by administration of oral imatinib (200 mg/day) and intravenous CYC (500 mg every 3 weeks). Safety was assessed by close monitoring of complete blood count, liver and cardiac functions. Efficacy was evaluated by measuring pulmonary functions at 6 and 12 months.

Results. Of the five patients in the study, four had severe and one had mild restrictive lung disease. All patients tolerated the combination treatment without myelosuppression, deterioration of liver functions or cardiac status. Only one patient had mild fluid overload requiring diuretics. Two patients completed 1 yr of treatment. Only the patient with mild restrictive lung disease showed improvement in pulmonary function.

Conclusion. The combination of intravenous CYC and oral imatinib was well-tolerated without major side effects. Clinical improvement was seen in only the patient with mild restrictive disease. To our knowledge, this is the first study examining the safety, tolerability and efficacy of imatinib in combination with CYC in scleroderma-related pulmonary disease. Large prospective trials are needed to further determine optimal timing, dose and duration of this regimen.

Key words: Scleroderma-related interstitial lung disease, Treatment of interstitial lung disease, Imatinib, Intravenous cyclophosphamide in interstitial lung disease, Anti-fibrotic therapy, Pulmonary arterial hypertension, PDGF receptor inhibitor, Systemic sclerosis, Imatinib.

Introduction

Scleroderma (SSc), or systemic sclerosis, is a multisystem fibrotic disorder characterized by excessive deposition of collagen and other extracellular matrix components in the skin and visceral organs. The high morbidity and mortality seen in SSc is generally attributed to the two major pulmonary manifestations of the disease: interstitial pulmonary fibrosis, or interstitial lung disease (ILD), and pulmonary arterial hypertension (PAH).

ILD is seen in ~40–70% of patients with SSc [1, 2]. Although the exact pathogenesis of SSc-related ILD (SSc-ILD) remains obscure, an enhanced response to TGF-β, excessive expression of connective tissue growth factor (CTGF) and PDGF receptor (PDGFR) amplification are postulated to underlie the fibrotic tendency [3–5].

The prognosis of SSc-ILD remains poor. Available therapeutic options are limited, ranging from observation and symptomatic treatment in most patients to stem cell transplantation (SCT) in a highly selected subgroup of individuals. Recently, investigators have utilized oral or intravenous (IV) cyclophosphamide (CYC) in the hope that progression of the disease could be slowed. Unfortunately, even though both routes of administration were well-tolerated, the overall beneficial effect of CYC on pulmonary function and alveolitis was at most modest [6–9].

Imatinib, a tyrosine kinase inhibitor that inhibits the Bcr-Abl, c-Kit and PDGFR tyrosine kinases, is approved for the treatment of chronic myeloid leukaemia (CML), gastrointestinal stromal tumours (GIST), hypereosinophilic syndrome, aggressive systemic mastocytosis and dermatofibrosarcoma protuberance tumour (http://www.fda.gov/cder/offices/OODP/whatsnew/imatinib200610.htm). In patients with CML, the safety profile of imatinib has been well-established, except for the recent report of its cardiotoxicity [10]. Imatinib has also been used in patients with non-oncological conditions, such as RA, idiopathic pulmonary fibrosis, IgA nephropathy and, occasionally, in patients with pulmonary arterial hypertension [11–13]. The use of imatinib in these conditions is based mostly on the known anti-proliferative properties of the drug, its role as an inhibitor of PDGFR function and its demonstrated in vitro ability to inhibit collagen formation by fibroblasts, thereby explaining its effectiveness in diminishing radiation-induced lung fibrosis [14–17].

We postulated that a combination of imatinib (as a PDGFR inhibitor) and CYC (as a B-cell inhibitor) might play a useful role in the treatment of SSc-ILD. Based on this hypothesis, we treated five patients with advanced SSc-ILD with the combination of IV CYC and imatinib. The primary objective was to evaluate the safety and efficacy of this combined therapy in patients with SSc-related pulmonary disease at the end of 1 yr of treatment.

Materials and methods

Patient population

All patients had a clinical diagnosis of diffuse SSc by ACR criteria [18] and a stable modified Rodnan skin score during the month prior to treatment initiation. Disease duration in all patients was...
≤10 yrs. There was no history of exposure to substances known to be associated with development of SSc-like illnesses. The diagnosis of SSc-ILD was based on demonstrated abnormalities on high-resolution computed tomography (HRCT). One patient (patient #3) also had sickle cell disease (SCD), potentially contributing to the development of pulmonary hypertension and fibrotic lung disease [19]. Special informed consent was obtained from all patients explaining the off-label use of imatinib and CYC. The study was conducted with the ethical approval from our institutional review board.

**Laboratory testing**

Complete blood count (CBC), serum chemistries, urinalysis, ANA (detected by indirect immunofluorescence on HEp-2 cells) and anti-topoisomerase antibody (solid-phase enzyme-labelled immunosorbent assay to purified Scl-70 antigen) were performed in all five patients.

**Cardio-pulmonary assessment**

All patients were assessed by HRCT for ILD before initiation and during treatment. Pulmonary function tests (PFTs), including forced vital capacity (FVC), total lung capacity (TLC) and diffusion capacity for carbon monoxide (DLCO), were measured using the standard techniques. Results were expressed as percentage of normal predicted values based on age, sex and height of the patient. All five patients had stable pulmonary functions 4 weeks prior to starting treatment. Six-minute walking test could be performed only in two patients. The remaining three patients were unable to perform the test. A baseline echocardiogram was done to assess cardiac function (ejection fraction). A right heart catheterization was performed in all five patients prior to starting treatment.

**Eligibility criteria**

Main eligibility criteria included:

1. Clinical diagnosis of diffuse SSc by ACR criteria.
2. Evidence of ILD by HRCT of chest (scored on Likert scale).
3. Ejection fraction of greater than 0.40.
5. Adequate end organ function, defined as the following: total bilirubin <1.5 x ULN; AST and ALT <2.5 x ULN; creatinine <1.5 x ULN; ANC >1.5 x 10^9/l; platelets >100 x 10^9/l.

**Treatment regimen**

CYC was administered IV at the fixed dose of 500 mg every 3 weeks. Imatinib was started at the dose of 200 mg by mouth daily for first 6 months, except in patient #3, who received imatinib 100 mg per day. In patients #1 and #2, the dose of imatinib was increased to 400 mg, 6 months after the beginning of treatment.

**Follow-up**

Blood testing, including CBC and serum chemistries, was performed weekly for the first 6 weeks, once every 2 weeks for the next 3 months, and then every month. Rodnan skin score or any other marker for skin fibrosis was not assessed. Clinical monitoring for adverse effects, including congestive heart failure, was done every 4 weeks. Echocardiography, PFTs and HRCT were done at baseline, 6 months and 12 months after initiating the treatment.

**Results**

**Patient characteristics**

Clinical characteristics of the five patients are summarized in the Table 1. The mean age was 50 yrs (range 35–62 yrs). SSc was diagnosed at a median duration of 6.6 yrs (range 2–10 yrs) prior to initiating treatment. No rapid deterioration in clinical status was noted during the 4 weeks prior to drug initiation. All five patients had additional manifestations of SSc including gastrointestinal tract involvement and RP. Four patients had ANA with titres exceeding 1:160. Anti-topoisomerase antibodies were present in all five patients in substantial titre (exceeding 4.27, normal <1.00). Mean duration of diagnosis of ILD was 4.1 yrs (range 1.5–6 yrs). Concurrent background treatment included bosentan in four of the patients, all of whom remained on a stable dose during the course of the study. Three patients had been treated with oral CYC, prior to enrolment in this study. CYC was administered at the dose of 2 mg/kg. These three patients discontinued CYC due to nausea and no improvement. Patient #4 had been treated at another institution with IFN-γ and developed renal failure resulting in discontinuation of treatment.

**Pulmonary and cardiac evaluation**

As evident in the Table 1, four of the five patients had moderate to severe restrictive lung disease, while patient #2 had mild restrictive lung disease. In contrast, severely reduced DLCO was observed in all five patients at the time of initiation of CYC and imatinib. PFTs revealed a median FVC of 49% predicted (range 22–80), median TLC of 49% predicted (range 18–82) and median DLCO of 21% predicted value (range <20–43). Four of the five patients had normal resting ejection fractions by echocardiography. Patient #5 had mild left ventricular dysfunction. Three of the five patients had wedge pressures of <14 mmHg, while one had a wedge pressure of 30 mmHg (pt # 4). No values were recorded for the fifth patient. Baseline mean pulmonary artery pressure and BNP were elevated only in patients #4 and #5 (PAP = 55 and 37, BNP = 250 and 95, respectively).

**Follow-up**

Two patients were able to complete 1 yr of treatment with imatinib and CYC. Patients #1 and #2 were successfully up-titrated to a dose of 400 mg imatinib daily 6 months after initiation of therapy. Patient #1 has continued to receive imatinib for a total duration of 18 months. Only patient #2, who had mild restrictive disease prior to starting therapy, showed some improvement in DLCO (43–50% of predicted) and FVC (80–89% of predicted). Patient #3 was treated with imatinib at the dose of 100 mg daily for 1 yr but eventually died of worsening lung disease. Patient #4 received treatment at 200 mg per day for 8 months. He subsequently

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**Table 1. Summarizing the clinical features, response and outcome in a series of five patients with SSc-related ILD**

<table>
<thead>
<tr>
<th>Pt #</th>
<th>Age yrs/Sex</th>
<th>Duration of SSc/ILD, yrs</th>
<th>Previous therapy</th>
<th>Duration of imatinib therapy, months</th>
<th>Percentage of DLCO at 0/6/12 months</th>
<th>Percentage of TLC at 0/6/12 months</th>
<th>Percentage of FVC at 0/6/12 months</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50/F</td>
<td>9/3</td>
<td>Oral CYC</td>
<td>18</td>
<td>23/24/49</td>
<td>49/99/37</td>
<td>49/38/40</td>
<td>Alive</td>
</tr>
<tr>
<td>2</td>
<td>62/M</td>
<td>7/4</td>
<td>Oral CYC</td>
<td>12</td>
<td>43/57/50</td>
<td>82/101/88</td>
<td>80/81/89</td>
<td>SCT</td>
</tr>
<tr>
<td>3</td>
<td>35/F</td>
<td>2/1.5</td>
<td>Penicillamine</td>
<td>12</td>
<td>20/20</td>
<td>18/18</td>
<td>20/22</td>
<td>Died after 12 months</td>
</tr>
<tr>
<td>4</td>
<td>51/M</td>
<td>4/6</td>
<td>IFN-γ</td>
<td>6</td>
<td>21/20</td>
<td>57/50</td>
<td>57/40</td>
<td>Lung transplant</td>
</tr>
<tr>
<td>5</td>
<td>54/M</td>
<td>10/6</td>
<td>Oral CYC</td>
<td>3</td>
<td>20</td>
<td>40</td>
<td>41</td>
<td>Died after 3 months</td>
</tr>
</tbody>
</table>
underwent successful lung transplantation. Patient #5 received treatment for only 3 months and eventually died of SSc-related pulmonary complications. Although he had known left ventricular dysfunction at the time of enrolment in the trial, no clinical change in left ventricular (LV) size or contractility was noted on serial echocardiography. LV function was essentially unchanged during the course of therapy in the remaining four patients, as well.

**Treatment tolerance and adverse side effects**

All patients tolerated the combination treatment, without gastrointestinal side effects or development of myelosuppression. Three patients required erythropoietic stimulating agents to maintain haemoglobin levels above 11 g. Patient #3 with SCD required transfusion on three occasions over a period of 1 yr. No liver function abnormalities were noted that required any dose adjustment in bosentan or imatinib. Development of fluid retention required intermittent discontinuation of imatinib and an increase in diuretic dosage in patient #5. None of the patients developed signs of overt congestive heart failure while on therapy.

**Discussion**

Pulmonary complications are a major cause of morbidity and mortality in patients with SSC [20]. The exact pathogenesis of SSc-ILD remains unknown. It appears, however, that a complex interaction of various factors leads to alveolitis, fibrosis and vascular damage [21, 22]. In theory, the use of anti-fibrotic agents for SSc-ILD is logical. However, the use of several of these agents, (colchicine, d-penicillamine, relaxin and minocycline) [23, 24] has not demonstrated benefit in this setting. Experimental models have demonstrated that imatinib may have significant anti-fibrotic effects, as well [13]. Specifically, the drug can selectively inhibit both the production of extracellular matrix proteins by SSC dermal fibroblasts and bleomycin-induced experimental dermal fibrosis, thereby supporting its use in SSC-ILD [14, 15]. A recently recognized stimulating autoantibody to PDGF-R-α [5] has attracted significant attention in view of its ability to induce fibrosis by altering PDGF and TGF-β signalling [14]. If this hypothesis proves correct, this stimulating autoantibody may be another potential target of therapy with imatinib by blocking PDGF-R.

Despite much interest in the use of imatinib in the treatment of SSC [25], there has been only one case report of using imatinib in this clinical setting (http://www.clinicaltrials.gov/ct2/results?term=imatinib+and+sclerodermadisease). For that reason, we describe our experience with a combination of IV CYC and imatinib at doses ranging from 100 to 400 mg/day in a series of five cases. This combination was well-tolerated and did not result in any major side effects, which warranted the discontinuation of treatment. Whereas all of our patients had long standing SSC and ILD, modest improvement was seen only in one patient who had mild restrictive lung disease. This serves to emphasize that appropriate patient selection must be an important criterion in future trials.

Although the recent SSC lung study suggested that CYC does have a modest beneficial effect on multiple measured parameters including pulmonary function studies in patients with SSC-ILD, long-term toxicity and tolerability remained important concerns [7, 26]. In an attempt to avoid oral CYC related side effects and reduce the myelosuppression from combination therapy, we chose to use moderate doses of IV CYC and a lower dose of imatinib. Since all five patients received CYC in conjunction with imatinib, it is difficult to determine the relative contribution of each individual medication to ultimate outcome. Our patients had stable pulmonary functions 4 weeks prior to starting treatment, which might have been a mitigating factor for significant improvement.

To our knowledge, this is the first clinical study examining the safety, tolerability and efficacy of imatinib in combination with CYC in SSc-ILD. While this is admittedly a small series, the results nevertheless suggest that imatinib is safe and well-tolerated when use in conjunction with moderate dose CYC. With these preliminary clinical data, along with experimental evidence of its ability to reduce fibrosis, imatinib, a well-tolerated, once daily, oral medication, may emerge as a potential anti-fibrotic agent in the management of SSc-ILD. Large prospective trials are needed to address patient selection criteria, timing and duration of treatment, and the role of associated immunosuppressive treatment with imatinib. Although treatment options currently include empirical use of immunomodulatory/anti-inflammatory agents, (e.g. mycophenolate mofetil) and, occasionally, more aggressive alternatives, including SCT [27–29] there remains no definitive treatment available for these complications of SSC. We suggest that the combination of immunosuppressive and anti-fibrotic therapy might be an appropriate approach to treat SSc-ILD.

**Rheumatology key messages**

- SSc-ILD patients may need a combination of immunosuppressive and anti-fibrotic therapy.
- The combination of IV CYC and imatinib was well-tolerated.
- The treatment should be considered in early stage of disease.

**Disclosure statement:** The authors have declared no conflicts of interest.

**References**