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Corticosteroid and cyclophosphamide in acute exacerbation of idiopathic pulmonary fibrosis: a single center experience and literature review

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Abstract. Acute Exacerbation (AEx) is a frequent and severe complication of Idiopathic Pulmonary Fibrosis (IPF). In the absence of consensus regarding treatment, studies evaluating the efficacy of specific therapies, such as corticosteroids and immunosuppresant agents, are needed. In this case series we evaluated the outcome in terms of survival of intravenous pulse doses of high-dose corticosteroid (methylprednisolone 1000 mg per day for 3 consecutive days) followed by montlhy cyclophosphamide administration (maximum 6 doses) in a cohort of patients with AEx-IPF referred to the Respiratory Unit, San Gerardo University Hospital, Monza, Italy, from 2009 to 2013. A total of 11 patients (7 males, median age 65 years) were enrolled. A median of five monthly pulse doses of cyclophosphamide were administered, with four patients receiving all 6 doses. Four patients died before completion. Three patients developed adverse events. Overall survival at 3 months was 73%, at 6 months 63%, at 12 months 55%, at 18 months 45% and at 2 years 27%. In-hospital mortality was 9%. Causes of death were: six respiratory failures from disease progression, one lung cancer and one breast cancer. Two patients received lung transplantation and were excluded from the Kaplan-Meier analysis. In conclusion, combined intravenous pulse doses of high-dose corticosteroid and cyclophosphamide could be a reasonable add-on therapy for AEx-IPF, considering the few side effects and safe profile. A complete and rapid diagnostic work-up associated to the proper management (e.g. support of respiratory failure with non-invasive ventilation) in the right setting, may also have a positive effect on patients' outcome. *(Sarcoidosis Vasc Diffuse Lung Dis 2016; 33: 385-391)*

Key words: acute exacerbation of idiopathic pulmonary fibrosis, cyclophosphamide, corticosteroids

Introduction

Acute Exacerbation (AEx) is a frequent and severe complication of Idiopathic Pulmonary Fibrosis (IPF). Prognosis is poor, with a median survival between 22 days and 4.2 months and high in-hospital mortality (1-3). Studies on the Asiatic population estimated an AEx-IPF incidence around 14% at 1 year and 20% at 3 years from IPF diagnosis (1).

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The most recent international guidelines for diagnosis and treatment of IPF state that supportive care remains the mainstay in the management of AEx-IPF (4). Furthermore, the evidence regarding a beneficial effect of corticosteroids is weak and based only on anecdotal reports and no other specific therapy is currently recommended (4). Few authors reported the use of immunosuppresant agents, such as cyclophosphamide and ciclosporin A, in AEx-IPF, but given the small sample size, the real benefit of these treatments is far from being clearly understood (Table 1) (1, 5-8).

In this retrospective analysis we aimed to evaluate the outcome in terms of survival of 11 patients with AEx-IPF (7 males, median age 68 years), according to Collard's diagnostic criteria (9), referred to the Respiratory Unit at San Gerardo hospital, Monza, Italy, from 2009 to 2013 treated with combined intravenous pulse doses of high-dose corticosteroid and cyclophosphamide.

Results

Patients' demographic and clinical characteristics at baseline and on hospital admission for AEx-IPF are summarized in Table 2. IPF diagnosis was reached through multidisciplinary expert discussion and in accordance with international guidelines on average 22 months before the onset of AEx (4). In a single case AEx was the onset manifestation of IPF. For all patients this was the first episode of AEx-IPF.

At hospital admission, alternative causes of acute respiratory failure, such as pulmonary thromboembolism, pulmonary infection or left heart failure, were promptly excluded. Fibrobronchoscopy and bronchoalveolar lavage were performed in six patients, as part of the differential diagnostic assessment of AEx-IPF. In 5 patients fibrobronchoscopy could not be performed because of the severity of the respiratory failure.

All patients were treated with daily pulse doses of methylprednisolone (1000 mg) from day 1 to day 3, followed by monthly pulse doses of cyclophosphamide starting on day 5-7 (600mg/m^2 of body surface area, maximum pulse dose 1 g) in association to maintenance-dose of oral prednisone (starting from 0.5 mg/kg with a slow tapering). Furthermore, all patients received *P. jirovecii* chemoprophylaxis with trimethoprim-sulfamethoxazole until 60 days after cyclophosphamide discontinuation.

A median of five monthly pulse doses of cyclophosphamide were administered, with four patients receiving all 6 doses. Four patients died before the completion of the 6 pulses cycle. Three patients interrupted the pulses administration due to the onset of adverse events.

Reported adverse events during the treatment were: haematuria, epistaxis without thrombocytopenia and low respiratory tract infections caused by *P. aeruginosa*.

In a high-dependency unit setting, four patients received continuous positive airways pressure (helmet C-PAP) treatment with satisfactory compliance and improvement of blood gas exchange. One patient was invasively ventilated in the intensive care unit without blood gas exchange improvement and died on day 35.

The median follow up time from treatment starting was 18 months. Overall survival at 3 months was 73%, at 6 months 63%, at 12 months 55%, at 18 months 45% and at 2 years 27% (Figure 1). In-hospital mortality was 9%. The causes of death were, by frequency: six respiratory failures from disease progression, one lung cancer and one breast cancer. Two patients received lung transplantation 14 months and 6 months after the beginning of treatment, respectively. Once transplanted, these patients were excluded from the Kaplan-Meier analysis. Three patients survived to the 2-year follow-up and one of them started pirfenidone treatment.

We evaluated clinical, laboratoristic and functional parameters associated with early mortality (within 3 months from AEx-IPF onset) in our cohort of patients. We considered the 3-month time interval to be a good indicator of mortality directly related to AEx-IPF.

Among previously described prognostic factors of AEx-IPF, we did not find an association between survival at 3 months and smoking status, gender, BMI, GAP index (10), FVC (Forced Vital Capacity), TLco (diffusing capacity of the lung for carbon monoxide) at baseline and C-reactive protein (CRP) levels on admission.

Conversely, we found that patients in the early mortality group had longer disease history (8 *vs.* 20 months), lower PaO2/FiO2 (partial pressure of arterial oxygen to the fraction of inspired oxygen ratio)

Table 1. Retrospective studies investigating the combined treatment of AEx-IPF with corticosteroids and immunosoppressive agents

First Author (year)	Aim	# participants	Comparison groups	Clinical outcomes reported	Results	Conclusion
			Steroid pulses + Cyclophosphamide pulses			
Morawiec (2011) (5)	To evaluate the mortality of AEx-IPF treated with three methylprednisolone pulses followed by pulses of cyclophosphamide.	11	Treatment group: methylprednisolone pulses (1000 mg) at days 1 to 3 followed on day 4 by escalating regimen of cyclophosphamide (initial intravenous dose 500 mg, increased by 200 mg every 2 weeks, maximum dose administered 1500 mg). No control group.	Survival	Survival at 3 months 55%, at 6 months 56%, at 12 months 33%.	The cyclophosphamide treatment regimen may have a beneficial effect on AEx-IPF survival.
			Steroid pulses + Cyclosporin A (CsA)			
Inase (2003) (6)	To examine the effect of CsA on AEx-IPF.	13	Treatment group: 7 patients treated with methylprednisolone pulses (1000mg per day for 3 days) followed by CsA (1.0-2.0 mg/kg per day). Control group: 6 patients treated with methylprednisolone pulses only.	Mortality	4 patients treated with CsA survived for 60, 120, 208 and 276 weeks. 2 died within 8 weeks from the start of CsA treatment. 1 patient experienced re-exacerbation and died 87 weeks after discontinuation of CsA because of viral encephalitis. All 6 patients treated without CsA died within 6 weeks from AEx-IPF onset.	CsA seems to prevent re-exacerbation of IPF and to improve patient's chances for long-term survival.
Homma (2005) (7)	To evaluate the efficacy of CsA in steroid-resistant and acutely exacerbated Interstitial Pneumonia.	33 patients with interstitial pneumonia, of whom 10 classified as IPF. 9 out of 10 patients with IPF developed an AEx.	Treatment group: 9 AEx-IPF patients treated with corticosteroids and CsA (50-200mg/day, blood trough level: 100-150ng/mL). Control group: 35 AEx-IPF patients not treated with CsA	Survival	Median survival of 9.9 months in the CsA-treated group vs. 1.7 months in the non CsA-treated group. 3 out 9 patients in the CsA-treated group survived for more than 11 months.	CsA combined with corticosteroids may be an efficacious treatment for IPF-AEx.

(Continued)

Table 1 (continued). Retrospective studies investigating the combined treatment of AEx-IPF with corticosteroids and immunosoppressive agents

First Author (year)	Aim	# participants	Comparison groups	Clinical outcomes reported	Results	Conclusion
Sakamoto (2010) (8)	To evaluate the efficacy of CsA on AEx-IPF.	22	Treatment group: 11 autopsied AEx-IPF cases treated with methylprednisolone (1000mg pulse for 3 days followed by oral maintenance dosage of 0.5-1.0 mg/kg per day) combined with CsA (100-150 mg/day). Control group: 11 autopsied AEx-IPF cases treated with corticosteroids alone.	Survival	The mean survival period after the first onset of Aex-IPF was 285 days in the CsA-treated group *vs.* 60 days in the non-CsA-treated group.	Administration of CsA combined with corticosteroids may be effective in prolonging survival after AEx-IPF.
			Steroids (pulse or high-dose) + Cytoxic agents			
Song (2011) (1)	To estimate the in-hospital outcome of AEx-IPF.	81	Treatment group: 8 patients treated with steroid pulses (≥500mg/day methyprednisolone for 3 days followed by high-dose steroid) + cytotoxic agent (azathioprine, cyclosporine or cyclophosphamide); 14 patients treated with high-dose steroid (≥0.5 mg/kg/day prednisolone) + cytotoxic agent. Control group: 13 patients treated with steroid pulses; 46 patients treated with high-dose steroid.	In-hospital survival	50.0% survival with steroid pulses + cytotoxic agent vs. 53.8% with steroid pulses alone. 78.6% survival with high-dose steroid + cytotoxic agent vs. 41.3% with high-dose steroid alone.	Treatment did not affect AEx-IPF outcome. Therapy with steroid +/- a cytotoxic agent was an independent poor prognostic factor of overall survival in patients with IPF.

Table 2. Demographic, clinical and functional characteristics at baseline (last functional assessment before AEx-IPF) and on hospital admission for AEx-IPF

Baseline	
Males, n (%)	7 (63)
Caucasian, n (%)	11 (100)
Smokers (current or prior), n (%)	8 (73)
GERD, n (%)	3 (27)
Long-term oxygen therapy, n (%)	5 (45)
FVC % pred, median [IQR]	57.5 [47.75-67.25]
FEV_1/FVC, median [IQR]	0.84 [0.76-0.91]
TLC % pred, median [IQR]	65.5 [42.25-88.75]
TL_{CO} % pred, median [IQR]	32 [21-43]
6MWT SO_2% nadir (%), median [IQR]	87 [84-90]
6MWT distance (m), median [IQR]	300 [220-380]
GAP index, median [IQR]	5 [3-7]
Admission for AEx-IPF	
Age (years), median [IQR]	65 [55-75]
Body mass index (kg/m^2), median [IQR]	26.8 [23.1-30.5]
Time from IPF diagnosis to AEx onset (months), median [IQR]	22 (22)
P_aO2/F_iO2, median [IQR]	208 [178.65-237.35]
Non-invasive ventilation, n (%)	4 (36)
Invasive ventilation, n (%)	1 (9)

Footnotes: GERD=gastresophageal reflux disease; FVC=Forced Vital Capacity; FEV_1/FVC=Forced Expiratory Volume in the 1st second/Forced Vital Capacity; TLC= Total Lung Capacity; TLco= diffusing capacity of the lung for carbon monoxide; 6MWT= 6-minute walking test; SO_2%= oxygen saturation; GAP index= Gender, Age and Physiology index (10); PaO2/FiO2=partial pressure of arterial oxygen to the fraction of inspired oxygen ratio

(195 *vs.* 240) and higher serum levels of NT-proBNP (N-terminal fragment of the prohormone brain natriuretic peptide) (1221 *vs.* 342) on admission for AEx-IPF, compared to patients who survived more than 3 months.

Discussion

Our short report describes AEx-IPF survival in a cohort of patients treated with high-dose corticosteroid pulses followed by montlhy cyclophosphamide administration.

We found a 27% 3-month mortality rate. Overall 3-month mortality rate of AEx-IPF ranges between 60% and 69% (1, 11-12).

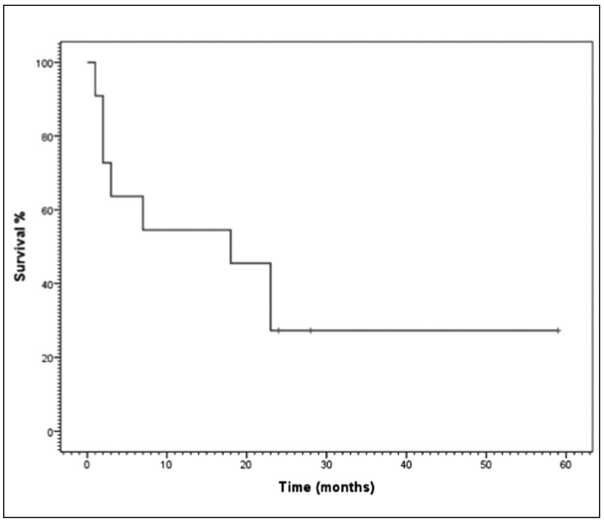

Fig. 1. Kaplan-Meier survival curve of the eleven patients treated with three daily pulses of methylprednisolone, followed by monthly pulses of cyclophosphamide, in association to maintenance-dose of oral prednisone

To date, no randomized controlled trial (RCT) has specifically assessed the treatment of AEx-IPF. Nevertheless, in clinical practice, immunosuppressant agents, such as cyclosporine A and cyclophosphamide, have been used in addition to high-dose corticosteroids for the treatment of AEx-IPF (1, 5-8) (Table 1). Some authors reported a better survival in patients treated with cyclosporin A than in patients treated with corticosteroids alone, suggesting that immunosuppressant agents may be a reasonable add-on therapy in AEx-IPF (6-8). The pharmacological protocol we used was inspired by previuos observation on patients with AEx-IPF (5). The choice of cyclophosphamide as immunosuppressant agent was driven by experience on other connective tissue diseases, such as scleroderma-related interstitial lung disease (13), and vasculitis (14).

Our finding nicely fits with a previous observation by Morawiec *et al.*, who used high-dose pulses of corticosteroid followed by cyclophosphamide regimen in 11 patients with AEx-IPF and found a 45% 3-month mortality rate (5). In this study, median age was similar to our group of patients (67 *vs.* 65 years), whereas the degree of respiratory failure seemed to be less severe (median PaO2/FiO2 on admission 255 *vs.* 208).

Better survival in our small cohort may be due to the rapid diagnostic work-up that allowed us to exclude other identifiable causes of worsening dysp-

noea and to start a proper management within 48 hours from hospital admission. Furthermore, optimization of supportive care (adequate oxygenation and respiratory rate control) in an appropriate setting (high-dependency respiratory unit) allowed us to avoid ICU admission and endotracheal intubation in most cases.

Mechanical ventilation has been associated with worse outcomes in patients with AEx-IPF (15-17), thus, non-invasive ventilation (NIV) (such as helmet C-PAP) might be a suitable option to improve gas exchange in AEx-IPF patients (18).

Interestingly, the early mortality group showed higher NT-proBNP serum levels on admission. The prognostic role of NT-proBNP in AEx-IPF has also been described by Vianello *et al.* (19). The authors reported that Aex-IPF patients who failed a NIV trial had significantly higher NT-proBNP levels on admission compared to those in the success group, hypothesizing for NT-proBNP a role as marker of poor NIV outcome in this group of patients.

The present case series has several limitations. First of all, it is a small retrospective study without a comparison group. Secondly, we do not have any right haemodinamic data supporting the prognostic role of pulmonary hypertension in AEx-IPF.

In conclusion, combined intravenous pulse doses of high-dose corticosteroid and cyclophosphamide could be a reasonable add-on therapy for AEx-IPF, considering the few side effects and safe profile. This regimen need to be further evaluated through a RCT. A complete and rapid diagnostic work-up associated to the proper management (e.g. support of respiratory failure with NIV) in the right setting, may also explain the better outcome we found in our cohort of patients. Longer time from IPF diagnosis to AEx, lower PaO2/FiO2 and higher NT-proBNP serum levels on admission might be considered predictive factors of worse clinical outcome in AEx-IPF. Future studies should aim to develop RCTs to clarify the role and potential benefit of immunomodulatory agents in AEx-IPF treatment.

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