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□ ORIGINAL ARTICLE □

Survival from an Acute Exacerbation of Idiopathic Pulmonary Fibrosis with or without Direct Hemoperfusion with a Polymyxin B-immobilized Fiber Column: A Retrospective Analysis

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Abstract

Objective Acute exacerbations of idiopathic pulmonary fibrosis (AE-IPF) are fatal episodes of acute respiratory worsening of unknown etiology. Previous studies on acute respiratory distress syndrome have shown that direct hemoperfusion with a polymyxin B-immobilized fiber column (PMX-DHP) can have a beneficial effect on the respiratory status. This retrospective study investigated the prognosis and survival outcome of patients with AE-IPF who underwent PMX-DHP.

Methods We examined the records of 50 patients with AE-IPF treated in our hospital. All patients received corticosteroid pulse therapy. We compared the disease outcome between 27 patients who underwent PMX-DHP (PMX group) and 23 patients who did not (non-PMX group). The independent predictors of survival were determined using Cox proportional hazards analyses.

Results A multivariate analysis of all patients revealed that PMX-DHP therapy was a significant predictor of survival (HR=0.442, 95% CI 0.223-0.873; p=0.019). The 12-month survival rate was significantly higher in the PMX group than in the non-PMX group (41.7% vs. 9.8%; p=0.040). According to a subanalysis of the PMX group, the time from AE-IPF onset to PMX-DHP was a significant predictor of survival (HR=1.080, 95% CI 1.001-1.166; p=0.049).

Conclusion PMX-DHP improved the prognosis of AE-IPF. The time from AE-IPF onset to PMX-DHP may therefore be informative for predicting the patient outcome.

Key words: interstitial pneumonia, acute exacerbation, idiopathic pulmonary fibrosis, polymyxin B-immobilized fiber column, hemoperfusion, prognosis

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Introduction

Idiopathic pulmonary fibrosis (IPF) is characterized by chronic, progressive, fibrosing interstitial pneumonia of unknown cause. The median survival time for IPF from the onset of symptoms and from the initial visit are 105 months and 69 months, respectively (1). Recently, it has been recognized that some patients with IPF experience acute respiratory deterioration, termed acute exacerbation (within 1 month), and often fall into respiratory failure and death. The mean survival time from the onset of acute exacerbation is only 1.5 months (2-5). Current therapies, including high-dose corticosteroids, anti-inflammatory and immunosuppressive agents provide little benefit for patients with acute exacerbations of IPF (AE-IPF) (6-10). Therefore, a new therapy with high efficacy is needed for the treatment of AE-IPF.

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The polymyxin B-immobilized fiber column (PMX) was originally developed for the removal of endotoxin in treating endotoxemia (11). It has been reported that direct hemoperfusion with PMX (PMX-DHP) improves oxygenation in patients with acute lung injury or acute respiratory distress syndrome (ARDS), which usually manifests diffuse alveolar damage (12-14). In addition, PMX-DHP has also been reported to have a beneficial impact in AE-IPF patients on the respiratory status and long-term outcome (15-19). However, it remains unclear whether PMX-DHP treatment is a useful therapeutic option for AE-IPF. Although two recent comparative studies have suggested a better survival of rapidly progressive interstitial pneumonia in patients treated with PMX-DHP, compared to those treated without PMX-DHP, further studies are needed to support their findings (20, 21). The present study includes a larger number of AE-IPF patients to compare the survival between patients treated with and without PMX-DHP and identify the prognostic factors in patients who undergo PMX-DHP and show the effects of PMX-DHP at the early phase of AE-IPF onset.

Materials and Methods

Patients

We retrospectively reviewed the medical records of patients with AE-IPF who were hospitalized at NHO Yamaguchi-Ube Medical Center between July 2006 and July 2014. The patients who had the following disease(s) were excluded from this study: 1) hemodynamic instability, 2) severe cardiovascular disease, 3) severe hemorrhagic disease, 4) terminal cancer. During the study period, PMX-DHP for AE-IPF was initiated at our hospital in April 2008. From July 2006 to April 2008 all patients were treated without PMX-DHP therapy, but with antibiotics and high-dose corticosteroid therapy [methylprednisolone (mPSL) 1,000 mg/day for 3 days] regardless of the severity and course of AE-IPF. After April 2008, patients received PMX-DHP therapy according to the judgement of each physician when the disease was refractory to the initial high-dose corticosteroid therapy. They were informed about the PMX-DHP therapy and those who consented to the treatment and had not immediately responded to mPSL were treated with PMX-DHP. The study subjects consisted of fifty patients, 27 of whom were treated with PMX-DHP (PMX group) and 23 of whom without PMX-DHP (non-PMX group). This retrospective study was approved by the institutional review board of NHO Yamaguchi-Ube Medical Center (Approval number: 27-22, Approval date: January 6, 2016), and written informed consent was obtained from each patient or their family.

Patients with IPF were diagnosed according to the current American Thoracic Society criteria (22). AE-IPF was diagnosed with criteria proposed by Collard et al. (4) and the guideline of the Japanese Respiratory Society (23), with slight modifications. These criteria were: (1) An unexplained worsening or the development of dyspnea within 30 days; (2) high resolution computed tomography that showed a new, bilateral, ground-glass abnormality and/or consolidation superimposed on a background of a reticular or honeycomb pattern, which was consistent with a usual interstitial pneumonia pattern; (3) no evidence of pulmonary infection; and (4) exclusion of alternative causes, including left heart failure, pulmonary embolism, and an identifiable cause of acute lung injury. All patients with AE-IPF in this study were confirmed to be negative for bacteria, fungus, and mycobacterium, based on sputum and blood cultures. Bronchoalveolar lavage (BAL) (n=14), and endotracheal aspiration (n=14) were performed. Serological tests were negative for endotoxin, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Legionella*, and viruses, including cytomegalovirus, influenza virus, parainfluenza virus, hepatitis B virus, hepatitis C virus, and human immunodeficiency virus.

PMX-DHP treatment

After the corticosteroid pulse therapy, PMX-DHP (Toraymyxin 20R; TorayMedical Co., Tokyo, Japan) was performed for 6 h/day, on 2 successive days. Before use, a PMX-fiber cartridge was rinsed with 4 L physiological saline and primed with 2,000 U heparin sodium dissolved in 0.5 L saline. Blood access for PMX-DHP was obtained with a double-lumen catheter inserted into the femoral vein. The PMX-fiber cartridge was then connected to a polymethyl methacrylate membrane (Hemofeel CH-1.0N, Toray Medical Co.) that returned blood to the femoral vein. PMX-DHP was performed at a flow rate of 80-100 mL/min. Heparin sodium was used as an anti-coagulant.

Data analysis

The medical records were analyzed for the clinical background and outcome. The patient characteristics were compared between the PMX and non-PMX groups. Independent predictors of survival were determined by the Cox proportional hazards analysis. The predictors of survival were evaluated in all patients with AE-IPF (n=50) and in patients who received PMX-DHP (n=27).

Statistical analysis

The Mann-Whitney U test and chi-square test were used to determine statistically significant differences in the patient characteristics between the PMX and non-PMX groups. The change in the ratio of partial alveolar O_2 pressure to the fraction of inspired O_2 (ΔP/F ratio) was compared between the groups using the Mann-Whitney U test.

The survival time was calculated from the start of mPSL therapy to the date of data cut-off (July, 2015). Patients lost to follow-up were censored at the date of the procedure or at the last clinical contact. Non-disease-related deaths were censored. The survival rates were estimated using the Kaplan-Meier method and compared between the groups with the log-rank test. Prognostic factors were analyzed with the Cox proportional hazard model. Each variable was in-

Table 1. Comparisons between PMX Group and Non-PMX Group.

Variables	PMX group (n=27)	Non-PMX group (n=23)	p value
Age, years	70 (60-82)	74 (59-85)	0.074
Sex, male / female	24 / 3	22 / 1	0.380
Smoking history, Yes / No	23 / 4	19 / 4	0.804
Diagnosis, surgical lung biopsy / clinical	7 / 20	8 / 15	0.496
Period from IPF diagnosis to AE, months	20 (1-120)	17 (0-89)	0.690
%FVC before AE, %	76.3 (44.4-115.8)	64.5 (39.5-99.5)	0.567
%DLCO before AE, %	46.9 (29.0-92.0)	49.4 (29.6-74.2)	0.711
Intubation, Yes / No	8 / 19	8 / 15	0.697
NPPV, Yes / No	2 / 25	1 / 22	0.650
mPSL pulse therapy, Yes / No	27 / 0	23 / 0	0.999
Time from AE-IPF onset to mPSL pulse therapy, days	4 (1-18)	5 (3-11)	0.183
CyA administration, Yes / No	6 / 21	3 / 20	0.400
IVCY administration, Yes / No	1 / 26	2 / 21	0.459
Sivelestat administration, Yes / No	1 / 26	1 /22	0.908
Anticoagulants administration, Yes / No	7 / 20	6 / 17	0.990
APACHE II score	16 (11-26)	15 (12-26)	0.631
SOFA score	4 (2-10)	3 (2-7)	0.178
P/F ratio	147 (58-234)	143 (57-275)	0.381
WBC, $\times 10^9$/L	13,000 (4,160-30,160)	10,430 (3,320-22,560)	0.120
CRP, mg/dL	6.0 (0.1-25.7)	11.3 (0.4-22.3)	0.083
LDH, IU/L	346 (199-633)	367 (183-1,493)	0.326
KL-6, U/mL	1,383 (360-4,261)	1,272 (484-3,539)	0.985
SP-A, ng/mL	91 (23-202)	112 (32-280)	0.282
SP-D, ng/mL	268 (69-1,041)	270 (114-2,249)	0.627

Values represent the median (min-max), unless otherwise stated. IPF: idiopathic pulmonary fibrosis, AE: acute exacerbation, FVC: forced vital capacity, DLCO: diffusion lung capacity for carbon monoxide, NPPV: non-invasive positive pressure ventilation, mPSL: methylprednisolone, CyA: cyclosporine, IVCY: intravenous cyclophosphamide, APACHE: acute physiology and chronic health evaluation, SOFA: sequential organ failure assessment, P/F: The ratio of the partial pressure of alveolar O_2 (P) to the fraction of inspired O_2 (F), WBC: white blood cell, CRP: C-reactive protein, LDH: lactate dehydrogenase, KL-6: Krebs von den Lungen-6, SP-D: surfactant protein D, SP-A: surfactant protein A, NS: not significant

Table 2. Details of PMX-DHP and Adverse Events.

	PMX-DHP (n=27)
Interval between AE-IPF onset and PMX-DHP, days	
0-7	11
8-14	12
15-21	3
>22	1
Cycles, no	
1	1*
2	26
Duration of 1st cycle, hours	
6	27
Adverse events	
local hematoma	1
pulmonary thromboembolism	1

mPSL: methylprednisolone, PMX-DHP: direct hemoperfusion with polymyxin B-immobilized fiber column

*: This patient died of the underlying disease before the second cycle of PMX-DHP.

vestigated by a univariate analysis; then, a multivariate analysis was performed with a stepwise algorithm.

Differences were considered significant at $p<0.05$. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University), which is a graphical user interface for R (The R Foundation for Statistical Computing, version 2.13.0).

Results

Patient characteristics

The demographic and clinical features of the study cohort are shown in Table 1. There was no significant difference between the two groups with regard to pulmonary function, ICU scoring systems, P/F ratio, additional pharmacological therapy, respiratory care, and laboratory data. There was no evidence of pulmonary infection by BAL (n=14) and endotracheal aspiration (n=14).

Details and safety of PMX-DHP

The details of PMX-DHP are shown in Table 2. After the interval of 1-22 days from the onset of AE-IPF event, PMX-DHP was performed. Eleven patients (40.7%) underwent PMX-DHP within seven days after disease onset. The interval between mPSL pulse therapy and PMX-DHP was 0-13 days: 0 day in seven patients, 1-2 days in nine, 3-6 days in eight and 7-13 days in three. The intervals between mPSL administration and PMX-DHP varied among the patients, due to varying degrees of precipitated subjective symptoms and hypoxia or treatment with mPSL several days before admission to our hospital. All patients, except for one, were treated with two cycles of PMX-DHP. Mild pulmonary thromboembolism occurred in one patient who recovered af-

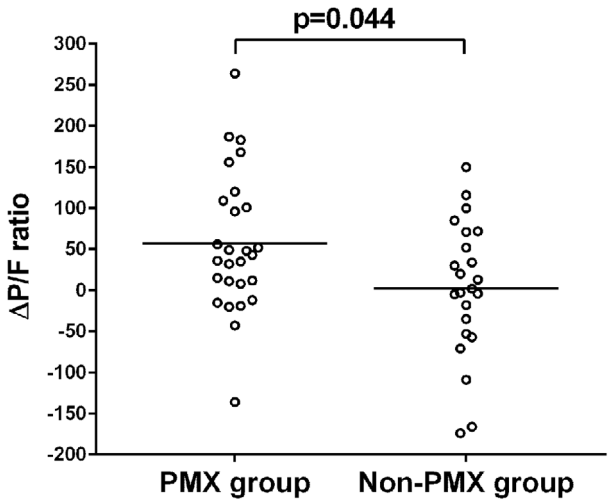

Figure 1. **Effect of treatment on the P/F ratio. The P/F ratios at the start of 1st PMX-DHP and the end of the 2nd PMX-DHP for the PMX group and those at the start of mPSL pulse therapy on day 1 and the end of the therapy on day 2 for the non-PMX group were measured. The positive values of changes in the P/F ratios (ΔP/F) indicate the improvement of oxygenation after treatment. P/F ratio: ratio of partial alveolar O_2 pressure to the fraction of inspired O_2.**

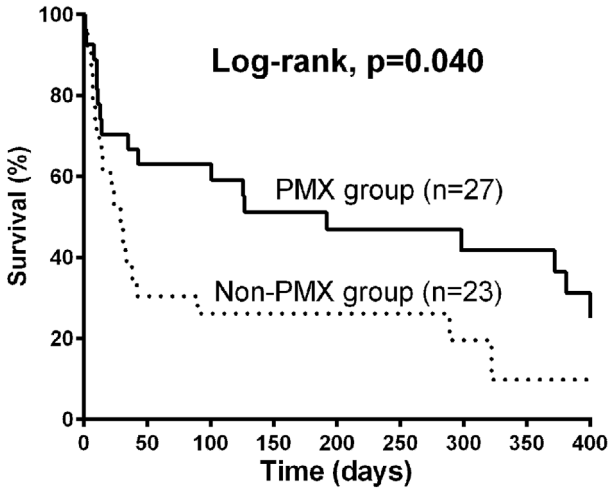

Figure 2. **Comparison of the survival curves in AE-IPF patients. The Kaplan-Meier survival curve (from the start of PMX-DHP or mPSL pulse to death or last follow-up) shows that patients who received PMX-DHP had higher survival rates than those who received mPSL alone (p=0.040). AE-IPF: acute exacerbations of idiopathic pulmonary fibrosis, mPSL pulse: methylprednisolone pulse therapy, PMX-DHP: direct hemoperfusion with polymyxin B-immobilized fiber column**

ter anticoagulant therapy. Mild local hematoma following trans-femoral puncture occurred in one patient, which resolved spontaneously. Several patients had mild thrombocytopenia after PMX-DHP treatment, but all patients recovered without blood transfusion. The effect of treatment on ΔP/F ratio is shown in Fig. 1. P/F ratio was markedly improved in the PMX group whereas it was not in the non-PMX group (59.0±15.9 vs. 2.2±17.2, mean±SEM, p=0.044).

Survival analysis

Throughout the median observational period of 42.0 days (range, 1-1,656 days) 38 patients (76.0%) died. Estimated 30- and 90-day survival rates using the Kaplan-Meier method were 60.0% and 45.9% in the whole study subjects, respectively. The overall survival was significantly longer in the PMX group than the Non-PMX group: median survival time, 192 days in the PMX vs. 29 days in the non-PMX. The estimated 30- and 90-day survival rates were significantly better in the PMX group than in the non-PMX group: 30-day survival rate, 70.4% in the PMX vs. 47.9% in the non-PMX and 90-day survival rate, 63.0% in the PMX vs. 26.1% in the non-PMX (p=0.040, log rank test; Fig. 2). The 12-month survival rate was also significantly better in the PMX group than in the non-PMX group (41.7% vs. 9.8%).

Predictors of survival in patients with AE-IPF

To investigate the effect of PMX-DHP treatment on survival, we constructed a Cox proportional hazard model to analyze the various clinical variables in all patients with AE-IPF (Table 3). A univariate analysis identified a total of 2 statistically significant predictors of survival, i.e., PMX-DHP treatment and P/F ratio. A multivariate analysis also identified these factors, PMX-DHP [HR=0.442, 95% confidence interval (95% CI) 0.223-0.873; p=0.019], and P/F ratio (HR =0.994, 95% CI 0.988-0.999; p=0.021).

Prognostic factors in the PMX group

To investigate the factors that contributed to the prognosis in the PMX group, we constructed a Cox proportional hazard model to analyze the clinical variables of patients in the PMX group (Table 4). According to a univariate analysis, only the time from the onset to PMX-DHP treatment was found to be a significant predictor of survival (HR=1.080, 95% CI 1.001-1.166; p=0.049). Fig. 3 shows the survival curves of two subgroups of the patients stratified by the time from AE-IPF onset to PMX-DHP treatment (<8 days, ≥8 days). The overall survival was significantly longer in the early PMX group than in the late PMX group: median survival time, 381 days in the early PMX vs. 39 days in the late PMX. We carefully analyzed that patients' backgrounds and the disease severity was closely similar between the two subgroups (Table 5). No significant differences were seen in the patients' backgrounds and disease severity, such as age, pulmonary function, P/F ratio, additional pharmacological therapy, and laboratory data except for the CRP level.

Discussion

Currently, there is no established treatment for AE-IPF. Empirically, AE-IPF has been treated with high-dose corticosteroids, antibiotics, and immunosuppressive agents (6-10). However, these agents provide little bene-

Table 3. Predictors of Survival in All Patients with AE-IPF (n=50).

Variables	Hazard ratio	95% CI	p value
Univariate Cox analysis			
Age, years	1.045	0.992-1.101	0.099
Male	0.979	0.299-3.201	0.971
Smoking history	0.920	0.382-2.214	0.852
Diagnosis, surgical lung biopsy	1.039	0.523-2.067	0.912
Period from IPF diagnosis to AE, months	0.996	0.984-1.008	0.479
%FVC before AE, %	0.993	0.970-1.016	0.548
%DLCO before AE, %	1.017	0.986-1.050	0.284
Intubation	1.574	0.811-3.053	0.180
NPPV	1.212	0.288-5.095	0.793
Time from AE-IPF onset to mPSL pulse therapy, days	1.059	0.983-1.140	0.130
PMX-DHP treatment	0.507	0.261-0.984	0.045
CyA administration	1.061	0.465-2.420	0.888
IVCY administration	1.947	0.591-6.416	0.274
Sivelestat administration	1.158	0.157-8.565	0.885
Anticoagulants administration	1.188	0.555-2.546	0.657
APACHE II score	1.065	0.985-1.151	0.112
SOFA score	1.054	0.893-1.243	0.535
P/F ratio	0.994	0.989-1.000	0.049
WBC, $\times 10^9$/L	1.000	0.999-1.000	0.685
CRP, mg/dL	1.028	0.976-1.082	0.294
LDH, IU/L	1.000	0.999-1.002	0.947
KL-6, U/mL	1.000	0.999-1.001	0.347
SP-A, ng/mL	1.000	0.993-1.008	0.945
SP-D, ng/mL	1.001	0.999-1.002	0.343
Multivariate Cox analysis			
PMX-DHP treatment	0.442	0.223-0.873	0.019
P/F ratio	0.994	0.988-0.999	0.021

IPF: idiopathic pulmonary fibrosis, AE: acute exacerbation, FVC: forced vital capacity, DLCO: diffusion lung capacity for carbon monoxide, NPPV: non-invasive positive pressure ventilation, mPSL: methylprednisolone, PMX-DHP: direct hemoperfusion with polymyxin B-immobilized fiber column, CyA: cyclosporine, IVCY: intravenous cyclophosphamide, APACHE: acute physiology and chronic health evaluation, SOFA: sequential organ failure assessment, P/F: The ratio of the partial pressure of alveolar O_2 (P) to the fraction of inspired O_2 (F), WBC: white blood cell, CRP: C-reactive protein, LDH: lactate dehydrogenase, KL-6: Krebs von den Lungen-6, SP-D: surfactant protein D, SP-A: surfactant protein A, NS: not significant

fit (6-10). PMX-DHP has drawn increasing attention for the treatment of AE-IPF (15-19, 24-31). Seo et al. were the first to report the efficacy of PMX-DHP in AE-IPF (15). In the study, four of six patients who were treated with PMX-DHP showed a dramatic improvement in pulmonary oxygenation and survived for longer than 30 days, while later being successfully weaned from mechanical ventilation. After that, several groups reported a therapeutic potential of PMX-DHP for improving oxygenation and safety in a small population of patients with AE-IPF (16, 18, 24-28). Recently, Abe et al. reported the effect of PMX-DHP on pulmonary oxygenation and survival in a multicenter retrospective analysis of patients with AE-IPF, suggesting that PMX-DHP significantly improves the P/F ratio and provides a clear survival benefit (19).

The mechanism underlying the beneficial effects of PMX-DHP in AE-IPF remains uncertain. Recent reports have described the beneficial effects of PMX-DHP on inflammatory cells or mediators. Seo et al. (15) reported that interleukin (IL)-6, IL-8 and plasminogen activator inhibitor 1 all decreased in patients with AE-IPF who responded to PMX-DHP. Noma et al. (24) reported that high mobility group box 1 (HMGB-1), monocyte chemoattractant protein-1 (MCP-1), IL-6 and IL-8 were reduced at 72 hours after PMX-DHP. Hara et al. (18) observed that the serum level of MCP-1 was reduced after PMX-DHP. Abe et al. (17, 28) showed that PMX-DHP reduced HMGB-1, matrix metalloproteinase-9 (MMP-9), and activated neutrophils in patients with AE-IPF. Moreover, using molecular biological and microscopic techniques, they showed that PMX-fibers could bind HMGB-1, MMP-9 and activated neutrophils. We previously analyzed cytokines bound to PMX-fibers after PMX-DHP in patients with AE-IPF (31) and showed that circulating proinflammatory, profibrotic, and proangiogenic cytokines were adsorbed onto PMX-fibers.

Previous studies reported that PMX-DHP treatment resulted in a 3-month survival rate of 26-61% after AE-IPF onset (19-21, 30). In our study, estimated 3-month survival rate of 63.0% in the PMX group was equal to or higher than those reported in the previous studies. Enomoto et al. reported a 12-month survival rate of 48.2% after AE-IPF onset (21). The 12-month survival of 41.7% in the PMX group in our study was comparable with those previously reported.

We also showed that the time from onset to PMX-DHP treatment was informative for predicting the outcome in patients with AE-IPF. As shown in Fig. 3, the prognosis was

Table 4. Predictors of Survival in All Patients with AE-IPF who Received PMX-DHP (n=27).

Variables	Hazard ratio	95% CI	p value
Univariate Cox analysis			
Age, years	0.988	0.916-1.065	0.749
Male	0.946	0.215-4.159	0.942
Smoking history	1.380	0.315-6.048	0.669
Diagnosis, surgical lung biopsy	1.887	0.737-4.833	0.186
Period from IPF diagnosis to AE, months	1.008	0.990-1.027	0.387
%FVC before AE, %	0.981	0.949-1.015	0.272
%DLCO before AE, %	1.000	0.958-1.044	0.989
Intubation	1.312	0.497-3.461	0.584
NPPV	0.901	0.117-6.943	0.920
Time from AE-IPF onset to PMX-DHP, days	1.080	1.001-1.166	0.049
CyA administration	0.961	0.315-2.925	0.944
IVCY administration	3.203	0.394-26.1	0.277
Sivelestat administration	0.000	0-Inf	0.998
Anticoagulants administration	0.774	0.221-2.713	0.689
APACHE II score	1.038	0.933-1.155	0.489
SOFA score	1.041	0.835-1.297	0.721
P/F ratio	0.993	0.984-1.002	0.105
WBC, $\times 10^9$/L	1.000	1.000-1.000	0.255
CRP, mg/dL	0.978	0.909-1.053	0.554
LDH, IU/L	1.003	0.999-1.006	0.120
KL-6, U/mL	1.000	0.999-1.001	0.349
SP-A, ng/mL	0.997	0.986-1.008	0.596
SP-D, ng/mL	1.001	0.999-1.003	0.216

Values represent the median (min-max), unless otherwise stated. IPF: idiopathic pulmonary fibrosis, AE: acute exacerbation, FVC: forced vital capacity, DLCO: diffusion lung capacity for carbon monoxide, NPPV: non-invasive positive pressure ventilation, mPSL: methylprednisolone, PMX-DHP: direct hemoperfusion with polymyxin B-immobilized fiber column, CyA: cyclosporine, IVCY: intravenous cyclophosphamide, APACHE: acute physiology and chronic health evaluation, SOFA: sequential organ failure assessment, P/F: The ratio of the partial pressure of alveolar O_2 (P) to the fraction of inspired O_2 (F), WBC: white blood cell, CRP: C-reactive protein, LDH: lactate dehydrogenase, KL-6: Krebs von den Lungen-6, SP-D: surfactant protein D, SP-A: surfactant protein A, NS: not significant

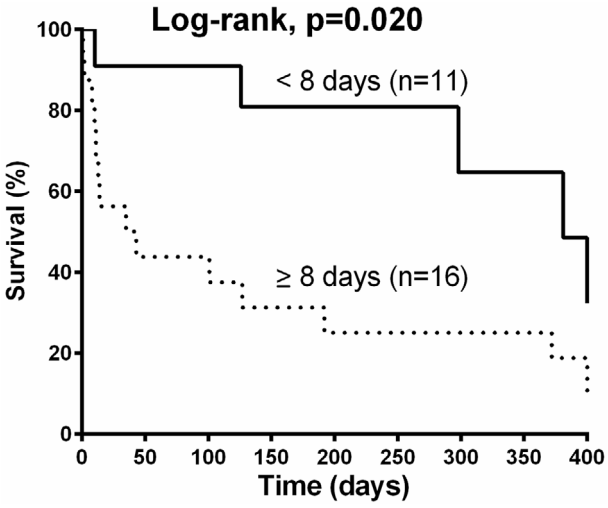

Figure 3. Comparison of the survival curves of patients stratified by time from onset to PMX-DHP. Patients who received early PMX-DHP had higher survival rates than those who received late PMX-DHP (p=0.020).

less favorable when the start of PMX-DHP treatment was delayed. In previous reports, PMX-DHP therapy was performed after corticosteroid pulse therapy. However, according to a multicenter retrospective analysis in Japan, PMX-DHP therapy combined simultaneously with corticosteroid pulse therapy might be more effective than the sequential protocol (32). Enomoto et al. described the possibility that the timing of PMX-DHP may have affected the prognosis (21). In their study, the timing of PMX-DHP was almost the same as high-dose corticosteroid therapy in the majority of patients (85%), and so they did not evaluate the relevance of the timing of PMX-DHP to the prognosis. Because the timing of PMX-DHP therapy in our study tended to vary, we attempted to evaluate the effects of PMX-DHP at the early phase of AE-IPF onset. In the present study, seven patients who underwent PMX-DHP on the same day as the mPSL pulse therapy showed a better 12-month survival rate (83.7%, data not shown). We conducted PMX-DHP therapy as early as possible, because such patients may deteriorate during the evaluation of the effect of corticosteroid pulse therapy. Recently, based on a pathological examination of lung tissue specimens obtained from patients with ARDS, Thille et al. showed that diffuse alveolar damage proceeds to irreversible fibrosis within a few weeks after onset. They proposed that treatments which might potentially suppress inflammation, fibrosis, or both, should focus on the first week after onset of ARDS (33). In this study, because we

Table 5. Comparisons of Predictors of Survival between the Subgroups Stratified by the Interval between AE-IPF Onset and PMX-DHP.

Variables	< 8 days (n=11)	≥ 8 days (n=16)	p value
Age, years	70 (60-82)	71.5 (63-81)	0.443
Sex, male / female	9/2	15/1	0.332
Smoking history, Yes / No	8/3	15/1	0.130
Diagnosis, surgical lung biopsy / clinical	2/9	5/11	0.446
Period from IPF diagnosis to AE, months	15 (1-64)	21 (2-120)	0.374
%FVC before AE, %	76.3 (44.4-86.8)	69.9 (47.4-115.8)	0.702
%DLCO before AE, %	42.55 (29.0-92.0)	55.20 (30.4-68.1)	0.888
Intubation, Yes / No	2/9	6/10	0.280
NPPV, Yes / No	1/10	1/15	0.782
mPSL pulse therapy, Yes / No	11/0	16/0	0.999
CyA administration, Yes / No	2/9	4/12	0.675
IVCY administration, Yes / No	0/11	1/15	0.398
Sivelestat administration, Yes / No	1/10	0/16	0.219
Anticoagulants administration, Yes / No	3/8	4/12	0.895
APACHE II score	17 (11-26)	15 (12-25)	0.940
SOFA score	4 (2-10)	3 (2-8)	0.722
P/F ratio	160 (70-215)	131 (58-234)	0.657
WBC, $\times 10^9$/L	13,650 (4,160-19,910)	12,440 (5,310-30,160)	0.394
CRP, mg/dL	13.05 (1.13-17.73)	3.88 (0.14-25.7)	0.017
LDH, IU/L	348 (222-633)	326 (199-575)	0.981
KL-6, U/mL	1,229 (360-2,101)	1,529 (595-4,261)	0.342
SP-A, ng/mL	75 (23-107)	100 (46-202)	0.142
SP-D, ng/mL	218 (69-474)	281 (108-1,041)	0.445

Values represent the median (min-max), unless otherwise stated. IPF: idiopathic pulmonary fibrosis, AE: acute exacerbation, FVC: forced vital capacity, DLCO: diffusion lung capacity for carbon monoxide, NPPV: non-invasive positive pressure ventilation, mPSL: methylprednisolone, CyA: cyclosporine, IVCY: intravenous cyclophosphamide, APACHE: acute physiology and chronic health evaluation, SOFA: sequential organ failure assessment, P/F: The ratio of the partial pressure of alveolar O_2 (P) to the fraction of inspired O_2 (F), WBC: white blood cell, CRP: C-reactive protein, LDH: lactate dehydrogenase, KL-6: Krebs von den Lungen-6, SP-D: surfactant protein D, SP-A: surfactant protein A, NS: not significant

expected early PMX-DHP treatment to be effective, we decided that the PMX-DHP treatment should focus on the early phase after the onset of AE-IPF. Furthermore, we recognized that it is important to minimize any delays in the diagnosis and treatment of AE-IPF. According to our experience, the causes for the delays lie in both patients and doctors. To minimize such delays, education is important to encourage them to consult medical institutions as early as possible. To minimize doctor delays, smooth cooperation between regional medical institutions is important. On the other hand, whether early PMX-DHP is an adequate treatment remains to be determined. Patients receiving PMX-DHP concurrently with high-dose corticosteroid therapy may have not proved to be refractory to the monotherapy of high-dose corticosteroids. AE-IPF is a heterogeneous complication observed in patients with IPF in terms of both radiological and pathological features (34, 35). Further studies are required to determine the role of PMX-DHP therapy in the management of AE-IPF.

Kono et al. reported that a long duration of PMX-DHP was more efficacious for AE-IPF than a short perfusion duration (29). Therefore, we performed PMX-DHP therapy for 6 h/day. Although our study design did not allow an evaluation in regard to whether the treatment duration affected survival, it seems likely that the treatment duration is a prognostic factor. In our study, the P/F ratio, which is a significant prognostic factor in patients with ARDS (36), has also been found to be a significant prognostic factor in patients with AE-IPF.

The present study is associated with some limitations. First, it was a retrospective study with a small number of patients. Second, various therapies or management strategies combined with PMX-DHP treatment may have influenced the clinical outcomes. Finally, we could not perform pathological examinations of biopsy specimens because of the risk of patient deterioration.

In conclusion, this study showed that PMX-DHP may improve the prognosis of AE-IPF, and that the time from AE-IPF onset to PMX-DHP treatment was an important predictors of outcome. Despite these limitations, our data provide a basis for future, prospective controlled studies on PMX-DHP therapy in AE-IPF patients stratified by time from onset.

The authors state that they have no Conflict of Interest (COI).

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