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Clinical Trial Paper

Pirfenidone for acute exacerbation of idiopathic pulmonary fibrosis: A retrospective study

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ABSTRACT

Background: Acute exacerbation of idiopathic pulmonary fibrosis (AE-IPF) is a rapid and ultimately fatal condition, and no effective treatment has been established. Pirfenidone has antifibrotic effects in IPF; however, its efficacy for AE-IPF is unclear.
Objectives: To evaluate the efficacy of pirfenidone for AE-IPF.
Methods: We retrospectively reviewed the medical records of 135 IPF patients treated during the period from April 2008 to April 2015 and identified and extracted 47 AE-IPF patients (42 men, 5 women; mean age, 73.5 years). The clinical features and outcomes of the 20 patients treated with pirfenidone were compared with those of the 27 patients treated without pirfenidone. We then excluded the 25 patients who did not receive recombinant human soluble thrombomodulin (rhTM) and analyzed data from the remaining 22 patients (20 men, 2 women; mean age, 73.7 years). Clinical features and outcomes were compared between the 10 patients treated with pirfenidone and the 12 patients who did not receive pirfenidone.
Results: There were no significant differences between the two groups in baseline characteristics, except for pirfenidone use before onset. Three-month survival was significantly better in patients treated with pirfenidone than in the control group (55% vs 34%, $p = 0.042$). In univariate analysis, nonuse of pirfenidone was a potential risk factor for death at 3 months (hazard ratio, 6.993; $p = 0.043$) in patients treated with rhTM.
Conclusion: A regimen of pirfenidone combined with corticosteroids and rhTM may improve survival in patients with AE-IPF.

1. Introduction

Acute exacerbation of idiopathic pulmonary fibrosis (AE-IPF) is associated with a high mortality rate [1–4]. Although many patients with AE-IPF still receive systemic corticosteroids, no effective treatment for AE-IPF has been established [5]. Evidence from a small number of studies showed that recombinant human thrombomodulin (rhTM) was beneficial for AE-IPF [6–9]. Pirfenidone treatment slows progression of chronic IPF (as measured by changes in forced vital capacity and progression-free survival) [10], but its effects have not been demonstrated in patients with AE-IPF. The antifibrotic effect of pirfenidone is believed to be caused by suppression of inflammatory cytokines, as indicated in a mouse model of bleomycin-induced pulmonary fibrosis [11]. Pirfenidone inhibits transforming growth factor-β (TGF-β) and has antifibrotic, anti-inflammatory, and antioxidant effects [12]. Pirfenidone was recently found to be effective for a patient with AE-IPF [13], but this result requires careful evaluation. The present study investigated the efficacy of pirfenidone for AE-IPF.

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2. Material and methods

2.1. Study design

This single-center retrospective cohort study reviewed patient medical records and collected data on the clinical and laboratory characteristics of patients who received a diagnosis of AE-IPF at Toho University Omori Medical Center during the period from April 2008 to April 2015. The records investigated included case histories and computed tomography (CT) images.

2.2. IPF diagnostic criteria

The American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association guidelines [14] indicate that a diagnosis of IPF should be based on 1) exclusion of other known causes of interstitial lung disease (e.g., domestic and occupational environmental exposures, connective tissue disease, and drug toxicity), 2) presence of a usual interstitial pneumonia (UIP) pattern on high-resolution CT (HRCT) in patients who have not undergone surgical lung biopsy, and 3) specific combinations of HRCT and surgical lung biopsy pattern in patients who have undergone surgical lung biopsy.

2.3. AE-IPF definition

In the present study, AE-IPF was defined based on the criteria proposed by The American Thoracic Society [5], as follows: 1) previous or concurrent diagnosis of IPF, 2) acute worsening or development of dyspnea typically < 1 mo duration, 3) computed tomography with new bilateral ground-glass opacity and/or consolidation superimposed on a background pattern consistent with usual interstitial pneumonia pattern, 4) deterioration not fully explained by cardiac failure or fluid overload.

2.4. Treatment protocol for AE-IPF

All AE-IPF patients were treated with corticosteroid (CS) pulse therapy for 3 days, followed by a maintenance dose of CS, as conventional therapy with or without pirfenidone. Pirfenidone administration was continued in patients who had received pirfenidone before AE-IPF onset. For patients who had not received pirfenidone before AE-IPF, pirfenidone was started at 600 mg/day within 4 days (median; 1, range; 1–4 day) and increased to a maintenance dose (1200–1800 mg/day) after confirming that there were no adverse events. In April 2012, pirfenidone administration was added to our institute's AE-IPF treatment protocol for patients who have not received pirfenidone before AE-IPF onset. Because several small studies showed that rhTM was beneficial for AE-IPF [6–9], rhTM use is a confounder in evaluating the efficacy of pirfenidone for AE-IPF. We therefore excluded patients treated without rhTM and performed separate analyses of patients treated with rhTM with and without pirfenidone. rhTM was administered at a dose of 0.06 mg/kg/day for 6 days from onset, after confirming the absence of hemorrhagic disease. In addition, a clinical trial of the efficacy of rhTM for AE-IPF was performed at our institute from April 2006 to March 2013 [6].

2.5. Chest CT

Chest CT was performed before (within 6 months) and after AE-IPF onset, using a SOMATOM Definition AS, Flash and Edge scanner (Siemens Co., Ltd., Munich, Germany). After AE-IPF development, the entire lung was scanned in 5.0-mm-thick sections. Additional thin-section CT scanning was performed in all patients, to obtain images of 1.0-mm thickness. Thin-section CT images were reconstructed with a fixed window setting. The CT images were then independently reviewed by one thoracic radiologist (K.M.) and two pulmonologists (K.F. and S.S.) who were blinded to the identity and clinical, physiological, and pathological characteristics of the patients.

2.6. Pulmonary function testing

Lung volumes and forced expiratory volume in 1 s (FEV 1) were measured by standard methods using a Chestac-8800 or Chestac-8900 spirometer (Chest Co., Ltd., Tokyo, Japan) and expressed as a percentage of the predicted value. These measurements were conducted before AE-IPF onset (within 6 months) but could not be repeated at or after AE-IPF because of the patients' poor general condition. Arterial blood gas analysis was conducted using an ABL510 or ABL800 FLEX analyzer (Radiometer Co., Ltd., Copenhagen, Denmark) before (within 6 months), during, and after AE-IPF onset in all patients.

2.7. Data collection

We collected data on serum values for white blood cells (WBC), C-reactive protein (CRP), lactate dehydrogenase (LDH), sialylated carbohydrate antigen Krebs von den Lungen-6 (KL-6), surfactant protein D (SP-D), and PaO2/FiO2 ratio (P/F ratio) before onset (within 6 months of onset), at onset, and at 14 days after onset. Changes in laboratory findings (Δserum value) were calculated by subtracting the value at onset from the value at 14 days after onset. We calculated presymptomatic Gender, Age, Physiology (GAP) score, Acute Physiology and Chronic Health.

Evaluation (APACHE) II score at onset, and Sequential Organ Failure Assessment (SOFA) score at onset.

2.8. Outcomes

The primary outcome was three-month survival after AE-IPF onset. Adverse events were coded according to the preferred terms in the Medical Dictionary for Regulatory Activities, version 11.0. Safety outcomes are reported as events occurring during the period from baseline to 90 days after the last dose of the study drug.

2.9. Statistical analysis

All values are expressed as the median (range), and differences between groups were analyzed using the χ^2 test and Mann-Whitney nonparametric *U* test for two independent samples. Survival was investigated using the Kaplan-Meier method, and differences were assessed by the log-rank test. Cox proportional hazards regression analysis was used to identify variables that were significant predictors of survival. All p values are two-sided and were considered to be statistically significant when less than 0.05. All statistical analyses were performed using SPSS version 11.0 (SPSS Inc, Chicago, IL, USA).

2.10. Ethical considerations

This study was conducted with the approval of the Institutional Review Board of Toho University Omori Medical Center (project approval number 27–106), which also approved the review of patient medical records.