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Predictors of the clinical effects of pirfenidone on idiopathic pulmonary fibrosis

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ABSTRACT

Background: Idiopathic pulmonary fibrosis (IPF) is a progressive interstitial lung disease with a poor prognosis. Recently, pirfenidone was reported to slow the rate of decline in vital capacity and improve progression-free survival in IPF. The purpose of this study was to clarify the factors that predicted a good response to pirfenidone, as well as its adverse effects.

Methods: Forty-one IPF cases, treated with pirfenidone from January 2009 to January 2011, were enrolled in this investigation. Disease severity was classified into grades I–IV, as defined by the Japanese Respiratory Society (JRS). Short-term responsiveness to pirfenidone was evaluated by the modified criteria of the JRS. Predictors of nausea, anorexia, or both that represented important adverse effects were examined by multivariate Cox proportional

Abbreviations: IPF, Idiopathic pulmonary fibrosis; JRS, Japanese Respiratory Society; SLB, surgical lung biopsy; VC, vital capacity; NHO-KCCMC, National Hospital Organization Kinki-Chuo Chest Medical Center; UIP, usual interstitial pneumonia; HRCT, high-resolution computed tomography; ATS, American Thoracic Society; ERS, European Respiratory Society; TLC, total lung capacity; DLco, diffusing capacity of carbon monoxide; KL-6, Krebs von den Lungen-6; (SP)-D, surfactant protein-D; MRC, Medical Research Council; PaO_2, arterial oxygen tension; PPIs, proton pump inhibitors; H2RAs, histamine H2-receptor antagonists

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Anorexia
Acid-secretion inhibitors

hazard analyses. Predictors of short-time responsiveness were examined by multivariate logistic regression analyses.

Results: Diagnosed by a surgical lung biopsy (SLB), the mild cases of grade I/II were predictors of good, short-term responsiveness. Patients taking acid-secretion inhibitors, including proton pump inhibitors and histamine H2-receptor antagonists, showed less anorexia, nausea, or both. Only 1 case was administered drugs to activate gastrointestinal motility.

Conclusions: We concluded that IPF patients with a mild disease, diagnosis by SLB, or both showed indications of a good response to pirfenidone. In addition, acid-secretion inhibitors may reduce the frequency of anorexia, nausea, or both from pirfenidone.

1. Introduction

Idiopathic pulmonary fibrosis (IPF) is a lung disease with a poor prognosis that includes the progressive deterioration of pulmonary function. Its etiology is unknown, and there is no proven effective therapy [1,2]. The pathophysiology of IPF is not fully understood; however, treatments targeting the fibrotic pathway and epithelial injury are supposed to attenuate IPF progression [3].

Pirfenidone (5-methyl-1-phenyl-2-[1H]-pyridone) elicits both antifibrotic and anti-inflammatory effects in experimental pulmonary fibrosis models [4]. Open-label studies have revealed that pirfenidone stabilizes IPF disease progression [5,6]. A phase III clinical trial conducted in Japan showed that vital capacity (VC) declined to a lesser degree in pirfenidone-treated IPF patients than that of placebo-treated patients [7]. A significant difference in the progression-free survival was also observed between the 2 groups. On the basis of these findings, in 2008, pirfenidone was approved for IPF treatment in Japan. However, Noble et al. reported controversial results from 2 concurrent phase III trials in the United States [8].

The adverse effects of pirfenidone have been frequently observed. A phase II trial showed that 98.5% of pirfenidone-treated IPF patients had complications including various adverse effects as compared to that of 88.9% of the placebo group [9]. Photosensitivity, nausea, anorexia, and fatigue were observed in 43.8%, 21.9%, 31.5%, and 21.9%, respectively, of the patients; moreover, a significant increase in the frequency of these side effects was observed in the pirfenidone group than that of the placebo group. Photosensitivity can be controlled by prophylactic sunscreen use, which is recommended in the guideline of Shionogi & Co., Ltd. Gastrointestinal adverse effects are the most important dose-limiting and withdrawal-determining factors of pirfenidone.

Thus, if we can predict the responsiveness and adverse effects of pirfenidone treatment in IPF patients, treatment regimens could be better managed. In this study, we examined the predictors of responsiveness and adverse effects of pirfenidone in IPF patients treated in our institute.

2. Materials and methods

2.1. Subjects

From January 1, 2009 to January 1, 2011, 41 patients with IPF were prospectively enrolled and treated with pirfenidone (Shionogi & Co., Ltd., Osaka, Japan) in National Hospital Organization Kinki-Chuo Chest Medical Center (NHO-KCCMC). Informed consent was obtained from all subjects. The institutional review board at NHO-KCCMC approved this study (approval number: Jutaku-20-22; approval date: January 16, 2009). Twenty-three patients were clinically diagnosed with IPF with an usual interstitial pneumonia (UIP) pattern using high-resolution computed tomography (HRCT), while 18 patients were histologically diagnosed as IPF/UIP by surgical lung biopsy (SLB) specimens under the American Thoracic Society (ATS)/European Respiratory Society (ERS)/Japanese Respiratory Society (JRS)/Latin American Thoracic Society guidelines for IPF [10]. HRCT patterns (*e.g.*, UIP pattern or possible UIP pattern) upon pirfenidone initiation were also evaluated in IPF/UIP cases. The patients' demographics are summarized in Table 1.

Table 1 – Patient demographics at the commencement of pirfenidone.

Parameters	Frequency or median (IQR)
Total (*n*)	41 cases
Gender, male (*n*)/female (*n*)	34/7
Age, (years)	70 (65.5–75.5)
Smoking status (*n*), CS/ES/NS	6/24/11
Diagnosis (*n*), Clinical/SLB	23/18
Modified MRC scale (*n*), grade 0/1/2/3/4	2/6/18/12/3
VC, %predicted (%)	66.7 (54.8–77.8)
Severity grade of IPF (*n*), I/II/III/IV	9/5/9/18
Serum KL-6 (U/mL)	858 (1600 – 687)
Serum SP-D (ng/mL)	187 (138–299)
Serum cholinesterase (U/L)	270 (216–327)
Long term oxygen therapy (*n*), Yes/No	22/19
Treatment before pirfenidone	
Corticosteroid alone (*n*)	3
Corticosteroid and azathioprine (*n*)	4
Corticosteroid and cyclosporine (*n*)	1
Inhalation of N-acetyl-cysteine (*n*)	1

Abbreviations: IQR, interquartile range; CS, current smokers; ES, ex-smokers; NS, non-smokers; SLB, surgical lung biopsy; MRC scale, Medical Research Council score for shortness of breath upon exertion; VC, vital capacity; IPF, idiopathic pulmonary fibrosis; KL-6, Krebs von den Lungen-6; SP-D, surfactant protein-D.