Effect of Perioperative Pirfenidone Treatment in Lung Cancer Patients With Idiopathic Pulmonary Fibrosis

Takekazu Iwata, MD, PhD, Shigetoshi Yoshida, MD, PhD, Taiki Fujiwara, MD, PhD, Hironobu Wada, MD, PhD, Takahiro Nakajima, MD, PhD, Hidemi Suzuki, MD, PhD, and Ichiro Yoshino, MD, PhD

Department of General Thoracic Surgery, Chiba University Graduate School of Medicine, Chiba, Japan

Background. **Acute exacerbation of idiopathic pulmonary fibrosis (AE-IPF) is a life-threatening complication of lung cancer operation for patients with IPF, and no effective prophylaxis has ever been reported. In this study, we investigate the effect of perioperative treatment with an anti-IPF agent on reduction of the risk of developing AE-IPF.**

Methods. **A consecutive series of 50 lung cancer patients with IPF who underwent operations at our institution from October 2006 to October 2014 was retrospectively investigated. Since September 2009, pirfenidone was orally administered to patients from 4 weeks before operation to 4 weeks after operation. Thirty-one patients received the perioperative pirfenidone treatment (PPT), and their clinical outcome was retrospectively compared with that of 19 patients who did not receive PPT.**

Results. **No differences were found in age, smoking history, sex, vital capacity, KL-6, procedure, or risk score (10.5 ± 2.2 versus 11.2 ± 1.5) between the PPT and non-PPT groups. The incidence of AE-IPF for the PPT/non-PPT groups was 0.0%/10.5% within 30 postoperative days ($p = 0.07$) and 3.2%/21.1% within 90 postoperative days ($p = 0.04$), respectively. Logistic regression analysis showed a significant association between PPT and the incidence of AE-IPF within 30 ($p = 0.045$) and 90 ($p = 0.04$) postoperative days.**

Conclusions. **A prophylactic effect of PPT for postoperative AE-IPF in patients with lung cancer was suggested. Further confirmatory prospective studies should be considered for PPT.**

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Interstitial lung diseases are often accompanied by lung cancer. Acute exacerbation (AE) of interstitial lung disease is a life-threatening complication of lung cancer operations in patients with preexisting interstitial lung disease. Among the interstitial lung diseases, idiopathic pulmonary fibrosis (IPF) accompanied with lung cancer is especially known for a high incidence of AE occurring after operation and a poorer prognosis [1–4]. The reported factors for predicting the risk of postoperative AE such as preoperative computed tomography (CT) findings [5, 6], serum KL-6 concentrations [7], VC [7], or intraoperative fluid balance [8] vary among different studies, so it can be difficult to predict the incidence of postoperative AE. Recently, a large Japanese cohort study conducted by the Japanese Association for Chest Surgeons (JACS) revealed seven risk factors for AE after lung cancer operation: history of AE, surgical procedure, usual interstitial pneumonia (UIP), male sex, steroid use, elevated serum KL-6 concentration, and low vital capacity (VC) [9]. A risk scoring system has been advocated [10].

Until now, no effective prophylaxis for postoperative AE has been reported [9, 11]. We previously published a small retrospective chart review of a practical trial of perioperative oral administration of pirfenidone, which is known to be an effective drug for prevention of the natural worsening of IPF [12–15] and for reducing the incidence of AE-IPF [16]. In that prior study, which reported the initial experience of perioperative pirfenidone treatment (PPT), we demonstrated the feasibility and histopathologic effect of this treatment as a proof of the concept of this trial. Although no AE-IPF was observed in the PPT group and several instances of AE-IPF were observed in the control group, it was not statistically significant in this small pilot study [16]. A subsequent multi-institutional phase 2 study (WJOG6711L) was performed; however, it was a single-arm study [17].

In the present study, we focused on the postoperative outcomes between the PPT group and the historical non-PPT group. We evaluated the published risk scores and incidence of AE-IPF in our consecutive series of patients

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Address correspondence to Dr Yoshino, Department of General Thoracic Surgery, Chiba University Graduate School of Medicine, 1-8-1 Inohana, Chiba 260-8670, Japan; email: iyoshino@faculty.chiba-u.jp.

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Abbreviations and Acronyms

AE = acute exacerbation
HRCT = high-resolution computed tomography
IPF = idiopathic pulmonary fibrosis
JACS = Japanese Association for Chest Surgeons
POD(s) = postoperative day(s)
PPT = perioperative pirfenidone treatment
UIP = usual interstitial pneumonia
VC = vital capacity

with lung cancer with IPF who underwent operation with or without PPT.

Patients and Methods

Study Patients

Among 1,024 patients who underwent pulmonary resection for lung cancer at our institution from October 2006 to October 2014, 50 consecutive patients with IPF were retrospectively reviewed. We did not change the selection criteria of the surgical candidates among patients with lung cancer with IPF at this stage. PPT was begun in September 2009 and was subsequently performed for all patients with lung cancer with IPF. The clinical characteristics, including JACS risk scores and incidence of AE-IPF after operation, of 31 PPT patients were evaluated in comparison with 19 non-PPT patients. This population includes the 28 patients (12 PPT and 16 non-PPT patients) that we have already reported in our previous study [16]. In all patients, lung cancer was pathologically confirmed by preoperative biopsy or was suspected based on high-resolution CT (HRCT). For PPT patients, IPF was identified by radiologists and pulmonologists reading the HRCT before pirfenidone treatment. Other known causes, such as connective tissue disease, drug-induced pneumonia, or inhalation of pollutants, were excluded. In all patients, coexistence of UIP in resected specimens was confirmed by pathologists (the final decision of each pathologic diagnosis was made by a single pathologist in this study stage), after which time IPF was finally diagnosed according to the diagnostic criteria published by the American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association in 2011 [18]. Some of the non-PPT patients were diagnosed with IPF after operation. During the study, perioperative and intraoperative treatment for patients with lung cancer with IPF was unchanged, except for the pirfenidone treatment. Oxygen administration, perioperative rehabilitation, and endotracheal pressure/oxygen inhalation level at ventilation during anesthesia were uniformly managed. In routine postoperative management, continuous monitoring with electrocardiogram/pulse oximetry was performed until day 7, and a chest roentgenogram was taken daily during the first 4 days and on day 7. When AE was suspected, a chest CT was promptly taken, and diagnosis of AE was made through discussion with radiologists and pulmonologists. After operation, no anticancer therapy in the adjuvant setting was performed for these patients with IPF. All patients were followed at the outpatient office of the general thoracic surgery for lung cancer every 1 to 6 months for more than 5 years, and they were also followed by the respirologists for IPF at the outpatient office of the same hospital. AE of IPF in the postoperative follow-up phase was primarily diagnosed and treated by the respirologists. The clinical data were retrospectively obtained from medical charts. This retrospective study was approved by the institutional review board of Chiba University Graduate School of Medicine.

JACS Risk Score

Patient backgrounds were compared not only by using the raw data extracted from medical charts but also by JACS risk score, which consists of history of AE (5 points), anatomic resection more extensive than segmentectomy (4 points), UIP pattern (4 points), preoperative steroid usage (3 points), male sex (3 points), KL-6 >1,000 U/mL (2 points), and percentage of VC <80 (1 point) [10].

AE-IPF

AE-IPF was defined according to the published definition of a subjective worsening of dyspnea; new bilateral radiologic opacities; no evidence of infection; and the exclusion of alternative causes of dyspnea and radiologic changes, including left heart failure, pulmonary embolism, or an identifiable cause of acute lung injury [19, 20]. Postoperative AE-IPF within 30 PODs and 90 PODs were evaluated in this study.

PPT

Pirfenidone (Shionogi & Co, Ltd, Osaka, Japan) was administered 2 to 5 weeks before the operation. The starting dose of 600 mg/day was continued for 1-2 weeks, was increased to 1,200 mg/day for 1 to 2 weeks, and was then increased to 1,800 mg/day, if possible. After the administration of pirfenidone 1,200 to 1,800 mg/day for 1 to 4 weeks, the operation was performed. Patients restarted pirfenidone, beginning on the first POD, and continued receiving 1,200 to 1,800 mg/day for as long as possible.

Statistical Analysis

Quantitative clinical variables were reported as the mean ± SD of the mean, and each variable of PPT patients and control patients was compared by Pearson's χ^2 test (for categorical data), by unpaired Student's t test (for continuous variables with appropriate SD), or by the Wilcoxon test (for continuous variables with a SD too large for parametric tests; used in comparison of smoking history, serum KL-6, and estimated blood loss in this study). For examining the relation between AE-IPF and PPT or JACS risk score, logistic regression analysis was performed by using a likelihood ratio test. Progression-free survival of IPF and cumulative incidence curves of first AE-IPF were calculated from the date of operation. Progression-free survival was estimated by the Kaplan-