

Efficacy of Chemotherapy for Advanced Non-Small Cell Lung Cancer with Idiopathic Pulmonary Fibrosis

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Key Words

Chemotherapy · Idiopathic pulmonary fibrosis · Non-small cell lung cancer

Abstract

Background: Idiopathic pulmonary fibrosis (IPF) is the most common type of idiopathic interstitial pneumonia and is associated with an independent increased risk of lung carcinogenesis. The benefit of chemotherapy for lung cancer in cases of IPF remains unknown. **Objectives:** This study was conducted to elucidate the efficacy of chemotherapy for advanced non-small cell lung cancer (NSCLC) in patients with IPF. **Methods:** Advanced (i.e. stage IIIb and IV) NSCLC patients with IPF who received systemic chemotherapy were studied. Response rate, toxicity, overall survival and progression-free survival were investigated. **Results:** Between January 2000 and December 2009, 21 patients were enrolled in this study and treated with chemotherapy. The overall response rate with the 1st regimen was 42.9%. The median overall survival was 11.4 months, the 1-year survival rate was 28.6% and the median PFS was 5.4 months. **Conclusions:** This study showed that advanced NSCLC patients with IPF may benefit from chemotherapy; well-controlled studies are still needed to clarify the efficacy.

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Introduction

Idiopathic pulmonary fibrosis (IPF) is the most common type of idiopathic interstitial pneumonia (IP) and its prevalence in many developed countries appears to be increasing [1]. It is a progressive fibrotic lung disease with a median survival of 3–5 years without a proven effective therapy. Recently, an increase in lung cancer mortality among patients with IPF has been reported [2]. IPF is also associated with an independent increased risk of lung carcinogenesis [1–6]. Furthermore, it has been noted that IPF and cancer have common pathobiological features [7, 8]. To date, no prospective studies have demonstrated the effect of chemotherapy in prolonging the survival of lung cancer patients with IPF, and there are only a few reports that evaluate the clinical efficacy of chemotherapy for lung cancer with IP [9–11]. There are no specific reports on chemotherapy limited to lung cancer with IPF. The purpose of this study is to examine the clinical efficacy of chemotherapy for advanced non-small cell lung cancer (NSCLC) in patients with IPF. In addition, we examined the adverse events that occurred during treatment.

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Table 1. Characteristics of all patients

Male:female	18:3
Age, years	68.4 ± 5.5
Smoking (pack-years)	52.8 ± 26.1
Histology	
Adenocarcinoma	14
Squamous-cell carcinoma	5
Undifferentiated	2
Stage	
IIIB	11
IV	10
PS	
0	8
1	10
2	3

Data are presented as mean ± SD or number.

Materials and Methods

We treated 1,230 lung cancer patients between January 2000 and December 2009 in Tosei General Hospital (Aichi, Japan). We retrospectively identified patients who satisfied the following criteria: (1) histologically or cytologically confirmed advanced (stage IIIB or IV) NSCLC, (2) accompanying interstitial pneumonia of IPF, (3) chemotherapy as the only therapy and (4) Eastern Cooperative Oncology Group performance status (PS) was within the range of 0–2. All clinical and laboratory data were collected retrospectively from medical records. Spirometry (CHESTAC-55V; Chest, Tokyo, Japan) and diffusing capacity of the lung for carbon monoxide (DLCO) (CHESTAC-55V; Chest) were measured according to the American Thoracic Society (ATS)/European Respiratory Society (ERS) recommendation as physiological assessments [12, 13]. The results of pulmonary function tests were expressed as percentages of the normal predicted values. The diagnosis of IPF was made in accordance with the ATS/ERS/Japanese Respiratory Society/Latin American Thoracic Association statement [6] using the following criteria: (1) exclusion of other known causes of interstitial lung disease, (2) the presence of a usual interstitial pneumonia (UIP) pattern on high-resolution computed tomography (HRCT) in patients not subjected to surgical lung biopsy and (3) specific combinations of HRCT and surgical lung biopsy pattern in patients subjected to surgical lung biopsy. The pathological diagnosis of UIP was also based on this statement [6]. Typical chest CT findings of IPF were basal predominant, subpleural reticular abnormality with traction bronchiectasis and honeycomb cysts without findings of atypical features of IPF such as isolated cyst, consolidation and peribronchovascular nodules [14, 15]. We evaluated the overall response rates (ORR), median progression-free survival (PFS), median overall survival (OS), 1-year survival and toxicity. With regard to toxicity, we use the term ‘rapid deterioration’ for acute respiratory worsening [16]. ‘Rapid deterioration’ was defined as an acute (within 30 days) worsening of dyspnea requiring hospitalization and the presence of newly developed radiologic abnormalities [16]; this term there-

fore includes various conditions such as drug-induced lung disease, acute exacerbation of IPF, infection, cardiac failure and others. Histological types of lung cancer were defined according to the World Health Organization Classification of 1999. Tumor response was assessed by response evaluation criteria in solid tumors (RECIST) guidelines and toxicity was evaluated by the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. Evaluation of treatment response by CT scan was repeated every 4–8 weeks.

The median OS and PFS were estimated using the Kaplan-Meier method. The median OS was measured as the period from diagnosis of lung cancer to death. The median PFS was measured as the period from the start of treatment to the identifiable time for progression. Survival was assessed up to June 12, 2010. Deaths were identified by reviewing the hospital-chart records. Because all of the patients had been visiting our hospital once a month and were then admitted when their condition became worse, documentation of their survival could be obtained. All values were given as mean ± standard deviation (SD). The institutional review board of the hospital approved this study and for chemotherapy, written informed consent was obtained from all patients.

Results

Patient Selection

Of 1,230 patients, 90 (7.3%) suffered from lung cancer with IP (idiopathic IP n = 83 and IP associated with connective tissue disease n = 7) (fig. 1). Of these 90 patients, 64 had NSCLC, and in 37 of these, this was in an advanced stage (stage IIIB or IV). Eight patients were treated with best supportive care, these were patients with poor PS. Twenty-nine received chemotherapy: 1 of these was PS 3 and 7 did not have IPF (IP associated with connective tissue disease n = 3 and idiopathic IP other than IPF n = 4). As a consequence, the remaining 21 patients (18 males and 3 females) diagnosed with IPF in this way were included in this study.

Diagnosis of IPF

To exclude other known causes of interstitial lung disease, during the diagnosis of IPF, all 21 patients underwent a careful examination focusing on comorbidities, medication use, environmental exposures, family history as well as a physical examination. Eighteen patients were diagnosed as having IPF with a pattern of UIP on HRCT, and 3 were diagnosed as having IPF with a possible UIP pattern on HRCT and a histological UIP pattern by surgical lung biopsy.

Patient Characteristics and Physiological Data

Patient characteristics are shown in table 1. Eight of 21 patients (38.1%) were already diagnosed with IPF before

the diagnosis of NSCLC. The mean interval between the time of diagnosis of both diseases was 1.8 ± 2.8 years. Before being diagnosed with lung cancer, 2 patients had received treatments for IPF; one with oral prednisolone and the other with oral prednisolone and cyclosporine A. The baseline physiological data are shown in table 2. The mean arterial oxygen tension was 80.1 ± 12.0 mm Hg at rest. In the pulmonary function test, the percent of predicted vital capacity (%VC) was $91.6 \pm 18.6\%$, and the percent of predicted DLCO (%DLCO) was $56.2 \pm 17.5\%$. DLCO was not obtained in 2 patients. VC and/or DLCO were less than 80% of the predicted value in 17 patients. Both DLCO and VC were normal in 3 patients. VC was normal and DLCO was not obtained in 1 patient.

First-Line Chemotherapy and Its Response

In table 3, the ORR of the 1st regimen is shown. The most frequently selected regimen was carboplatin combined with weekly paclitaxel (76.2%). The ORR was 42.9%. Stable disease was observed in 8 patients and progressive disease was observed in 4 patients. Mean cycles of applied 1st-line chemotherapy were 3.9 ± 1.7 (range: 1–6 cycles). No patients had received maintenance therapy, and 11 patients had received 2nd-line or later treatment.

Overall Survival and Progression-Free Survival of First-Line Chemotherapy

We performed a survival analysis on June 12, 2010, the data for which are shown in figures 2 and 3. The median OS was 11.4 months [95% confidence interval (CI) 8.2–14.6] and the 1-year survival rate was 28.6% (fig. 2). Nineteen patients had died, with progression of the lung cancer in 11 and a rapid deterioration in 8. The median PFS of the 1st regimen was 5.4 months (95% CI 4.0–6.8) (fig. 3).

Toxicity

Among 21 patients, 9 experienced rapid deterioration after chemotherapy and 8 of these 9 died. In 1 patient, gefitinib was used as a 2nd-line treatment, and a rapid deterioration occurred 16 days later. The median time from the final treatment to this rapid deterioration was 12.0 days (95% CI 0.0–26.7). The median survival time from the onset of rapid deterioration was 17.0 days (95% CI 0.0–39.4).

Treatment-related adverse events other than a rapid deterioration are listed in table 4. The most common hematological grade 3 or 4 adverse event was neutropenia (38.1%), although febrile neutropenia was observed in only 1 patient (4.8%). The only nonhematological adverse event of grade 3 or 4 observed was peripheral neuropathy. No adverse events other than rapid deterioration were fatal.

Table 2. Baseline physiological data

Pulmonary function test	
VC, l	2.87 ± 0.70
%VC	91.6 ± 18.6
FEV ₁ , l	2.27 ± 0.54
FEV ₁ , %	79.0 ± 7.73
FEV ₁ , % predicted	100.6 ± 22.5
%DLCO (n = 19)	56.2 ± 17.5
Arterial blood gas	
PaO ₂ , mm Hg	80.1 ± 12.0
PaCO ₂ , mm Hg	39.1 ± 3.21
pH	7.43 ± 0.02
Laboratory data	
WBC, /mm ³	$7,900 \pm 2,233$
LDH, IU/l	264 ± 97
KL-6, U/ml	$1,020 \pm 638$
SP-D, ng/ml	131.2 ± 71.9

Data are presented as mean \pm SD. n = 21, except for DLCO, n = 19. FEV₁ = Forced expiratory volume in 1 s; LDH = lactate dehydrogenase; PaCO₂ = partial pressure of carbon dioxide; PaO₂ = partial pressure of oxygen; SP-D = surfactant protein D; WBC = white blood cells.

Table 3. Response to 1st-line chemotherapy

Regimen	n	ORR	DCR
Carboplatin + paclitaxel	16	56.3% (9/16)	87.5% (14/16)
Carboplatin + docetaxel	3	0.0% (0/3)	33.3% (1/3)
Vinorelbine	2	0.0% (0/2)	100.0% (2/2)
Total	21	42.9% (9/21)	81.0% (17/21)

DCR = Disease control rate; n = number of patients.

Table 4. Adverse events other than 'rapid deterioration'

Toxicity	Grade 3	Grade 4	Grade 3 or 4 (%)
Anemia	6	0	6 (28.6)
Leukocytopenia	7	0	7 (33.3)
Neutropenia	2	6	8 (38.1)
Febrile neutropenia	1	0	1 (4.8)
Thrombocytopenia	2	0	2 (9.5)
Peripheral neuropathy	1	0	1 (4.8)

Data are presented as a number or proportion.

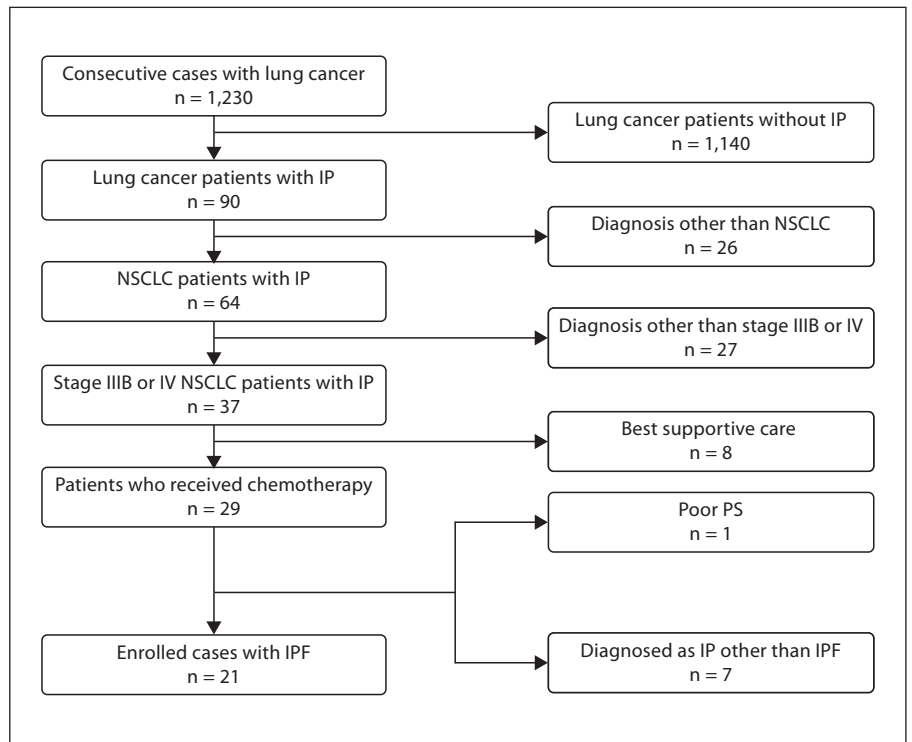


Fig. 1. Analysis profile. All 21 enrolled cases were advanced (stage IIIIB or IV) NSCLC patients with IPF.

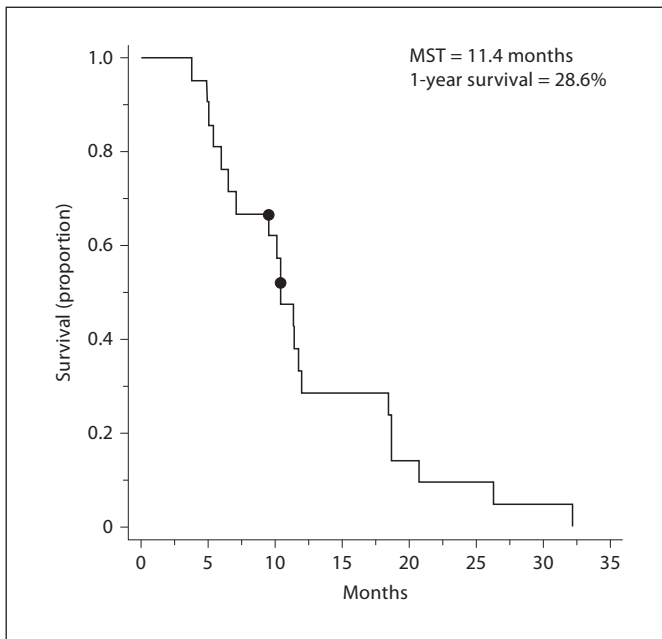


Fig. 2. OS. Circles indicate censored cases at the data cut-off point. The median survival time (MST) was 11.4 months and 1-year survival was 28.6%.

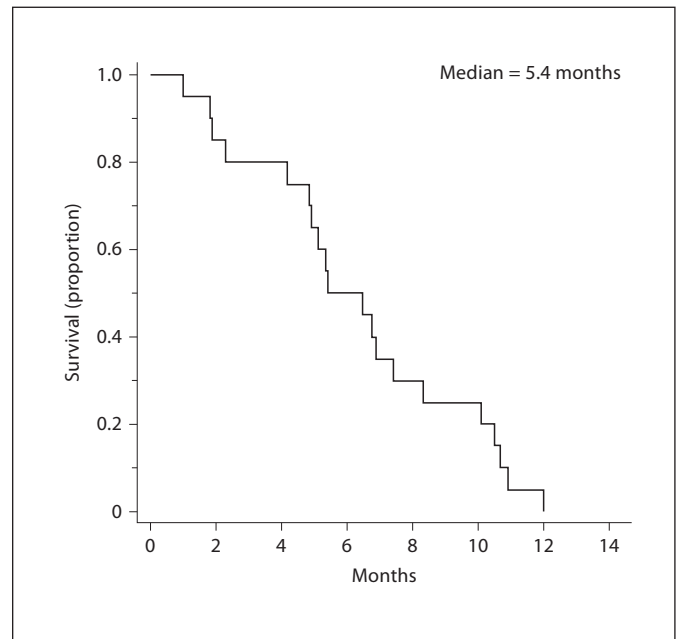


Fig. 3. PFS. The median PFS was 5.4 months.

Discussion

This is the first report, to our knowledge, in which the benefit of chemotherapy was indicated in subjects limited to patients with NSCLC and IPF. We evaluated the clinical efficacy of systemic chemotherapy for advanced NSCLC with IPF. The ORR of the 1st regimen, the median PFS, the median OS and the 1-year survival rate were 42.9%, 5.4 months, 11.4 months and 28.6%, respectively. These comparatively good results suggest that chemotherapy for advanced NSCLC with IPF is indeed efficacious.

In this study, the most frequently selected regimen was carboplatin combined with weekly paclitaxel [17]. In a phase II study of this regimen, the 1-year survival rate was 64% and median survival time was 15.9 months, i.e. comparatively good survival was demonstrated [17]. Chemotherapy with carboplatin combined with paclitaxel is an established treatment for advanced NSCLC, and its clinical efficacy and safety have been reported in several articles [18–20]. In these reports, ORR ranged between 32 and 45%, and the median OS ranged between 12 and 14 months. The results of this study are comparable to those of several previous reports, despite the fact that we evaluated only the efficacy of chemotherapy for advanced NSCLC patients with IPF.

In a report on the efficacy of carboplatin and paclitaxel for NSCLC with IP, Minegishi et al. [9] reported that the ORR of the 1st regimen, the median OS and the 1-year survival rate were 61%, 10.6 months and 22%, respectively. In their report, however, IPF patients included a comparatively small number, only 6 patients. In our study limited to IPF, the prognosis for which is the worst among the idiopathic IPs, the OS and 1-year survival rate were comparable to the results of Minegishi et al. [9]. This is noteworthy. Meanwhile, comparing other baseline characteristics, the %VC of patients in their report (82 ± 20.0) was worse than that of our patients (91.6 ± 18.6), in spite of a similar baseline PaO₂; so the patients in their study might have had more advanced IP. Further studies are needed to evaluate the impact of the severity or category of IP on the efficacy of chemotherapy for NSCLC patients with IP.

With regard to toxicity other than a rapid deterioration, hematological toxicities were mostly mild and manageable, and severe nonhematological toxicity was not observed other than peripheral neuropathy. On the other hand, 9 patients (42.9%) experienced a rapid deterioration and 8 of these 9 died during the study. As for the incidence of interstitial lung disease associated with chemotherapy, Kudoh et al. [21] showed in a cohort and nested case-control study of Japanese NSCLC patients that

preexisting IP was an independent risk factor for developing acute interstitial lung disease, regardless of gefitinib therapy or chemotherapy, and that the risk of developing interstitial lung disease was higher with gefitinib than with chemotherapy. In our study, rapid deterioration included various conditions such as drug-induced acute interstitial lung disease, infection and cardiac failure, which are often difficult to distinguish from other diseases. However, a rapid deterioration can include acute interstitial lung disease as a serious adverse event associated with chemotherapy. Thus, increased physician awareness of the risk of developing acute interstitial lung disease and a careful surveillance of NSCLC patients with IPF during chemotherapy are warranted to manage risks.

Recently, the usefulness of epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) for NSCLC patients has been reported. However, associated lung injury is also increasingly recognized. In our study, 1 patient who received EGFR-TKI therapy subsequently experienced rapid deterioration. Considering the above-mentioned report, it seems that considerable caution must be exercised with regard to the use of any chemotherapy drugs for NSCLC patients with IP [21]. Furthermore, it is reasonable to assume that EGFR-TKI in particular is not recommended.

The limitations of this study are as follows. Firstly, it was a small, retrospective study; to confirm the efficacy of chemotherapy for lung cancer patients with IPF, a large prospective study is required in the future. Secondly, it included only Japanese patients and was a single-center analysis. Some studies of drug-induced lung injury suggest ethnic differences in the susceptibility to acute progressive respiratory failure during the course of IPF [22]. Multicenter, multiregional prospective studies are needed to eliminate an ethnic bias and other possible biases. Thirdly, it is possible that there was a greater tendency for NSCLC patients with IPF to be treated with best supportive care rather than with systemic chemotherapy compared to NSCLC patients without IPF.

In conclusion, this study showed that advanced NSCLC patients with IPF may benefit from chemotherapy. This is the first report indicating the benefit of chemotherapy limited to cases of NSCLC with IPF. Further well-controlled studies will be needed in the future in order to clarify the efficacy of chemotherapy.

Acknowledgements

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