

## Evaluation of the Safety and Efficacy of Combination Chemotherapy with Vinorelbine and Platinum Agents for Patients with Non-small Cell Lung Cancer with Interstitial Lung Disease

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**Abstract.** *Background:* Acute chemotherapy-associated exacerbation of interstitial lung disease (ILD) can occur in patients with non-small cell lung cancer (NSCLC). The safety and efficacy of cytotoxic chemotherapy has not yet been established for NSCLC with ILD. Thus, patients with advanced NSCLC with ILD usually receive only best supportive care. The aim of this study was to assess the safety and efficacy profiles of the combination chemotherapy of vinorelbine and a platinum agent in patients with advanced NSCLC with ILD. *Patients and Methods:* Nineteen patients with advanced NSCLC with ILD treated with vinorelbine and a platinum agent, either cisplatin or carboplatin, were retrospectively reviewed to examine acute exacerbation of ILD, toxicity, response rate, and survival time. Additionally, possible predictive factors for acute chemotherapy-associated exacerbation of ILD were analyzed. *Results:* The response rate was 42.1%, the progression-free survival time was 4.4 months, the median survival time was 7.4 months, and the one-year survival rate was 36.8%. Neutropenia was the most frequent grade 3 to 4 toxicity and it occurred in 63.2% of patients. Acute chemotherapy-associated exacerbation of ILD occurred in three patients (15.8%) and caused the death of one of these patients (5.3%). No variables were identified as being predictive factors for acute chemotherapy-associated

*exacerbation of ILD. Conclusion:* The combination chemotherapy with vinorelbine and a platinum agent can be considered as a treatment option for patients with advanced NSCLC with ILD, with careful management after sufficient evaluation of the risks and the benefits.

Various interstitial lung diseases (ILDs) have been reported to be risk factors for lung cancer (1). In particular, the incidence of lung cancer in patients with idiopathic pulmonary fibrosis (IPF) has been reported to be high and ranges from 4.4 to 38% (1-3). In patients with lung cancer, the prevalence of IPF is 2% to 8% (3). ILDs are typically chronic conditions and gradually cause respiratory insufficiency. However, some patients with ILD have acute exacerbations characterized by acute progressive and severe respiratory failure, with newly-appearing ground-glass opacity or consolidation on computed tomography (CT) of the chest (4-9). Acute exacerbation of ILD can cause death in weeks to months.

Acute exacerbation of ILD can occur with surgery, chemotherapy, or thoracic radiotherapy in patients with lung cancer with ILD (10-14). Retrospective studies have found rates of acute chemotherapy-associated exacerbation of ILD in patients with lung cancer with ILD to be 20.0% to 37.9% (12-15). However, few studies have evaluated the safety, efficacy, and rate of acute exacerbation of ILD associated with specific chemotherapy regimens in patients with lung cancer with ILD. Recently, in a retrospective study, the combination chemotherapy of monthly or weekly carboplatin and weekly paclitaxel was reported to have caused grade 3 or greater pneumonitis in four out of 15 patients (27%) with advanced non-small cell lung cancer (NSCLC) with ILD (15). On the other hand, Minegishi *et al.* reported that combination chemotherapy of carboplatin and weekly paclitaxel caused acute exacerbation of ILD in only one out of 18 patients (5.6%) with advanced NSCLC with ILD (16).

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For patients with advanced NSCLC with ILD, the indication for chemotherapy has not yet been evaluated and a standard regimen has not been established because such patients have been excluded from almost all clinical trials. Thus, patients with advanced NSCLC with ILD usually receive only best supportive care, which is comfort-oriented.

The combination chemotherapy of vinorelbine and a platinum agent, either cisplatin or carboplatin, is a standard chemotherapy regimen for patients with advanced NSCLC. Several studies have shown that this regimen achieves promising survival times and response rates in these patients (17-19). However, to our knowledge, combination chemotherapy of vinorelbine and a platinum agent has not been evaluated in patients with advanced NSCLC with ILD. Therefore, the aims of the present study were to examine the safety, efficacy, and associated rate of acute exacerbation of ILD of the combination chemotherapy of vinorelbine and a platinum agent, either cisplatin or carboplatin, in patients with advanced NSCLC with ILD and to identify factors predicting acute chemotherapy-associated exacerbation of ILD.

## Patients and Methods

**Patients.** From July 2000 through April 2009, 28 patients with advanced NSCLC with ILD were examined at our institution. Out of these 28 patients, 19 (67.9%) met the criteria mentioned below and underwent combination chemotherapy with vinorelbine and cisplatin or carboplatin. Data of these 19 patients were retrospectively analyzed. Out of another 9 patients, 6 received only best supportive care, 2 received single-agent chemotherapy, and 1 received other combination chemotherapy. The criteria for treatment with this regimen were as follows: histologically- or cytologically-proven NSCLC, unresectable stage III or IV disease, a measurable lesion, and adequate bone marrow function (neutrophil count of 1,500/ $\mu$ l or more, platelet count of 100,000/ $\mu$ l or more, and hemoglobin level of 9.0 g/dl or more), renal function (serum creatinine levels less than 1.5 mg/dl and creatinine clearance rate of 50 ml/min or more), and hepatic function (total serum bilirubin level less than the upper limit of the normal range, aspartate aminotransferase and alanine aminotransferase levels less than or equal to twice the upper limits of the normal ranges). Patients who had ILD-related collagen vascular disease were included. Patients who had unstable or acute ILD were excluded. In addition, patients were excluded if they had active infections, severe heart disease, pleural effusion or pericardial effusion that required drainage, or symptomatic brain metastasis. This study protocol for retrospective analysis was approved by the Ethics Committee of Showa University School of Medicine.

**Treatment.** The treatment regimen consisted of vinorelbine at a dose of 20 or 25 mg/m<sup>2</sup> and of cisplatin at a dose of 80 mg/m<sup>2</sup> or carboplatin with a target area under the plasma concentration *versus* time curve of (AUC) of 5 mg min/ml using the Calvert formula. Cisplatin or carboplatin was administered on day 1, and vinorelbine was administered on days 1 and 8. These agents were administered every three weeks. Chemotherapy was discontinued for grade 3 or higher non-hematological toxicity, except for nausea/vomiting,

anorexia, constipation, diarrhea, alopecia, and fatigue; serum creatinine levels greater than 2.0 mg/dl; or a treatment outcome of progressive disease at any time. Vinorelbine was not given on day 8 of treatment if the neutrophil count was less than 1,000/ $\mu$ l or if the platelet count was less than 75,000/ $\mu$ l. Full doses of vinorelbine were then given on day 15 of treatment. If the serum creatinine level was 1.5 to 2.0 mg/dl, cisplatin or carboplatin was withheld. The doses of these agents during the next course were reduced by 20% of the previous doses for grade 4 neutropenia lasting three days or longer, grade 3 or 4 neutropenia associated with a fever greater than 38°C, or grade 4 thrombocytopenia.

**Definition of ILD and acute exacerbation.** ILD was classified as showing an IPF pattern and a non-IPF pattern. Diagnosis of the IPF pattern was made with high-resolution CT of the chest and clinical features according to the American Thoracic Society/European Respiratory Society criteria (20). Typical chest CT findings of the IPF pattern were as follows: basal predominant, sub-pleural reticular abnormality with traction bronchiectasis, honeycomb cysts, and no atypical features of IPF (21, 22). The CT scans were reviewed by two physicians. Acute exacerbation of ILD was diagnosed when the following criteria had been fulfilled within one month; i) exacerbation of dyspnea; ii) decline in arterial oxygen tension (PaO<sub>2</sub>) of 10 mmHg or more under the same conditions; iii) exacerbation of consolidation or ground-glass opacity on CT scan; and iv) heart failure, pulmonary infection, pulmonary embolism, or pneumothorax had been excluded (4-6).

**Clinical evaluation.** Evaluation for staging before treatment included chest radiography, CT of the chest and abdomen, magnetic resonance imaging or CT of the brain, and radionuclide bone scanning. During chemotherapy, complete blood cell counts with differential and routine chemistry profiles were determined at least once a week, and chest radiography was performed once per week. In 15 patients, the percent age vital capacity (%VC) and percent age diffusing capacity for carbon monoxide (%DLCO) were evaluated before chemotherapy.

We investigated serum C-reactive protein (CRP), lactate dehydrogenase (LDH), Klebs von den Lungen (KL)-6, surfactant protein D (SP-D), and PaO<sub>2</sub>, arterial carbon oxygen tension (PaCO<sub>2</sub>), and alveolar-arterial PaO<sub>2</sub> difference (AaDO<sub>2</sub>) in arterial blood while the patient breathed room air before chemotherapy. We compared these variables between patients with and without acute exacerbation of ILD.

Tumor response was classified according to the Response Evaluation Criteria in Solid Tumors criteria version 1.0 (23). The toxicity was evaluated according to the National Cancer Institute Common Terminology Criteria for adverse events 3.0 (24).

**Statistical methods.** Overall survival time was measured from the start of the present treatment until death or last follow-up. Progression-free survival (PFS) time was measured from the start of treatment to the identifiable time of progression. The Kaplan-Meier method was used to construct survival curves. Survival differences between subgroups were compared by means of the log-rank test. The chi-square test was used to determine the significance of differences of laboratory variables between patients with and without acute exacerbation of ILD. Differences with a *p*-value <0.05 were considered statistically significant. Statistical analyses were performed using the Stat View 5.0 software package (SAS Inc., Chicago, IL, USA).

Table I. *Patients' characteristics.*

Total numbers of patients	19
Gender (male/female)	16/3
Median age in years (range)	69 (52-79)
Smoking status	
Current	13
Former	5
Never	1
Performance status (0/1/2/3)	2/12/4/1
Stage (IIIA/IIIB/IV)	4/6/9
Histological type	
Squamous cell carcinoma	7
Adenocarcinoma	10
Other	2
ILD pattern	
IPF pattern	16
Non-IPF pattern	3
Combined with emphysema (yes/no)	6/13
Treatment before chemotherapy	
Surgery	1
Thoracic radiotherapy	5
None	13
Treatment regimen	
Carboplatin+vinorelbine	9
Cisplatin+vinorelbine	10

ILD: Interstitial lung disease; IPF: idiopathic pulmonary fibrosis.

## Results

**Patients' characteristics.** Of the 19 patients, 16 were men and three were women, with a mean age of 69 years (range=52-79 years; Table I). Sixteen patients had a IPF pattern and three patients a non-IPF pattern. Five patients underwent chemotherapy to treat recurrent disease after surgery (one patient) or thoracic radiotherapy (four patients). Additionally, one patient underwent chemotherapy after palliative thoracic radiotherapy because of stenosis of a main bronchus. The median number of cycles of chemotherapy was 2 (range=1-4).

The mean serum levels of CRP, LDH, KL-6, and SP-D were 2.9 mg/dl, 292.7 IU/l, 912.8 U/ml, and 101.5 ng/ml, respectively. Mean PaO<sub>2</sub>, PaCO<sub>2</sub>, and AaDO<sub>2</sub> were 81.1 mmHg, 38.5 mmHg, and 20.7 mmHg, respectively. Mean %VC and %DLCO were 89.6% and 64.5%, respectively.

**Treatment response and survival.** Out of the 19 patients, none achieved a complete response, eight achieved a partial response, six had stable disease, four had progressive disease, and one was not evaluable; the overall response rate was 42.1% (95% confidence interval=20.3%-66.5%) and the disease control rate was 73.7% (95% confidence interval=48.8%-90.9%).

Survival analysis was performed when the median follow-up time of all patients was 7 months. At the time of analysis, two patients (10.5%) were alive, and one patient had been

lost to follow-up. The median PFS time was 4.4 months (range=1-44 months; Figure 1). The median survival time (MST) was 7.4 months (range=1-44 months), and the one-year survival rate was 36.8% (Figure 2).

At the time of evaluation, one patient was alive without recurrence, and three patients had died without cancer recurrence. Out of the 15 other patients who had recurrence, six (40%) received second-line chemotherapy: five (33.3%) received cytotoxic chemotherapy-alone, one (6.7%) received both cytotoxic chemotherapy and an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor. The other nine patients received only best supportive care.

**Acute exacerbation of ILD and other toxicities.** Acute chemotherapy-associated exacerbation of ILD occurred in three patients (15.8%) and caused the death of one of these patients (5.3%). The patient who died of acute exacerbation of ILD was a 56-year-old man with adenocarcinoma and an IPF-pattern ILD. He underwent three cycles of chemotherapy with cisplatin and vinorelbine and achieved a partial response. However, he had high fever 21 days after the completion of the third cycle of chemotherapy and consequently had dyspnea. A CT scan of the chest showed newly-diffuse ground-glass opacity in both lungs. Although corticosteroid pulse therapy (1000 mg of methylprednisolone per day for three days) was administered, the respiratory failure did not resolve, and the patient died of acute exacerbation of ILD. Another patient with IPF-pattern ILD had acute exacerbation of ILD unrelated to chemotherapy 30 months after the completion of chemotherapy. Although she received corticosteroids and immunosuppressive therapy, respiratory function worsened, and she died of her respiratory failure 45 months after the completion of chemotherapy without cancer recurrence.

Of the toxicities other than acute exacerbation of ILD, neutropenia was the most frequent grade 3 to 4 toxicity and occurred in 63.2% of patients (Table II). Infection was the most frequent grade 3 to 4 non-hematological toxicity and occurred in 21.1% of patients. There was one treatment-related death due to enterocolitis accompanied by severe diarrhea.

**Markers for predicting acute exacerbation of ILD.** We evaluated possible markers (CRP, LDH, KL-6, SP-D, PaO<sub>2</sub>, and AaDO<sub>2</sub>) for predicting acute chemotherapy-associated exacerbation of ILD (Table III). However, none were significantly correlated with chemotherapy-associated exacerbation of ILD.

## Discussion

Acute exacerbation of various types of ILD has been reported to occur in patients without lung cancer (4-9). Acute exacerbation of IPF, non-specific interstitial pneumonia, and

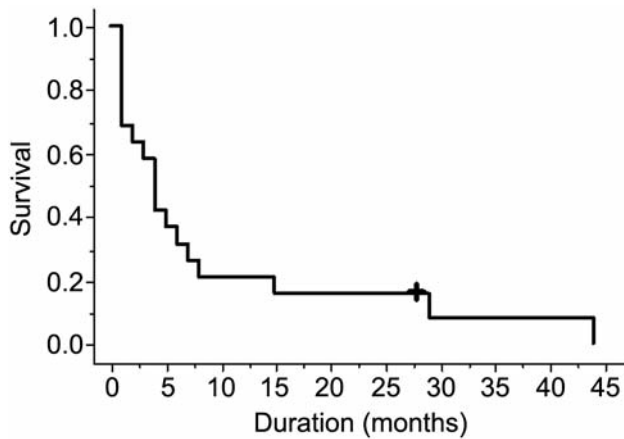


Figure 1. Progression-free survival (PFS) time estimated with the Kaplan-Meier method. The median PFS time was 4.4 months (range=1-44 months).

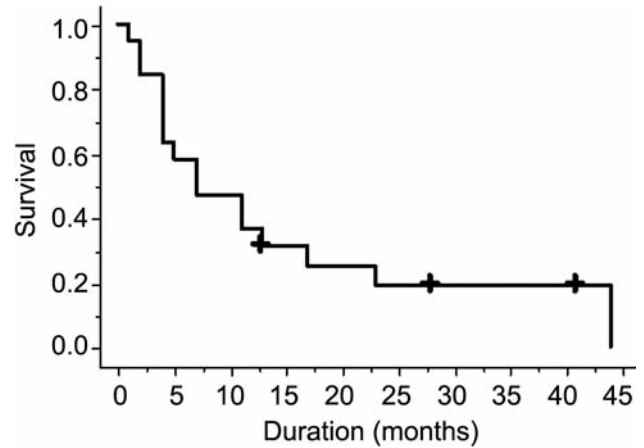


Figure 2. Overall survival estimated with the Kaplan-Meier method. The median survival time was 7.4 months (range=1-44 months).

Table II. Toxicity according to the National Cancer Institute-Common Terminology Criteria (ref. 24)

Toxicity	Grade					
	1	2	3	4	5	3-5 (%)
Neutropenia	1	4	3	9	0	63.2
Thrombocytopenia	4	6	4	3	0	36.8
Anemia	5	0	1	0	0	5.3
Infection	0	2	3	0	1	21.1
Renal dysfunction	1	0	0	0	0	0
Elevation of aminotransferase	1	2	0	0	0	0
Nausea	7	2	0	0	0	0
Diarrhea	0	0	0	0	1	5.5
Peripheral neuropathy	5	0	0	0	0	0
Arthralgia	2	0	0	0	0	0
Shortness of breath	3	1	1	0	0	0
Pneumonitis	0	0	1	1	1	15.8
Hypoxia	0	1	4	1	0	26.3

Table III. Variables before chemotherapy associated with acute exacerbation of interstitial lung disease.

Laboratory data	Cut-off value	Acute exacerbation		p-Value
		Yes	No	
CRP (mg/dl)	>1	3	9	0.15
	<1	0	7	
KL-6 (U/ml)	>500	2	13	0.57
	<500	1	3	
SP-D (ng/ml)	>120	0	8	0.11
	<120	3	8	
LDH (IU/l)	>350	1	2	0.36
	<350	2	14	
PaO <sub>2</sub> (mmHg)	>70	2	16	0.46
	<70	1	3	
AaDO <sub>2</sub> (mmHg)	>20	3	8	0.11
	<20	0	8	

CRP: C-Reactive protein; LDH: lactate dehydroxygenase; KL-6: Klebs von den Lungen; SP-D: surfactant protein D; PaO<sub>2</sub>: arterial oxygen tension; AaDO<sub>2</sub>: alveolar-arterial PaO<sub>2</sub> difference.

ILD related to collagen vascular disease in the year after diagnosis have been reported to occur at rates of 5% to 19%, 4.2%, and 1.3% to 3.3%, respectively (4, 7-9). On the other hand, in patients who have lung cancer without ILD, lung injury associated with anticancer chemotherapy has been reported to occur at rates of 0.5% to 2.5% (25, 26). Such lung injury is more common in patients with ILD than in those without (25). Additionally, the frequency of acute exacerbation of ILD is higher in Japanese patients than in patients from other countries, due, perhaps, to a genetic difference (25).

Retrospective studies in patients with lung cancer with ILD have found acute chemotherapy-associated exacerbation of

ILD at rates of 20.0% to 37.9% (12-15). Recent prospective or retrospective Japanese studies have reported that combination chemotherapy of carboplatin and weekly paclitaxel causes acute exacerbation of ILD in 5.6% to 27% of patients with advanced NSCLC with ILD (15, 16). In the present study, combination chemotherapy of vinorelbine and a platinum agent caused acute exacerbation of ILD in three of 19 patients (15.8%) with advanced NSCLC with ILD. This rate was equivalent to or lower than rates in previous retrospective and prospective studies in Japan (12-16).



Considering that acute exacerbation of ILD can occur without chemotherapy, the combination chemotherapy of vinorelbine and a platinum agent could be administered to patients with advanced NSCLC with ILD, with careful management after sufficient evaluation of the risks and the benefits.

In recent Japanese studies, the response rate with combination chemotherapy of carboplatin and weekly paclitaxel for patients with advanced NSCLC with ILD was 33% to 61%, the median PFS time was 2.5 to 5.3 months, and the MST was 7.0 to 10.6 months (15, 16). In the present study, the response rate was 42.1%, the PFS time was 4.4 months, and the MST was 7.4 months. Response rates and PFS times in patients with advanced NSCLC with ILD in these two earlier studies and the present study were equivalent to those in previous randomized phase III studies of patients with advanced NSCLC without ILD, but the MSTs were inferior (19, 27, 28). The inferior MSTs despite equivalent response rates and PFS times in patients with advanced NSCLC with ILD could be due to some patients having acute exacerbation of ILD both associated and not associated with chemotherapy. In addition, such patients were less likely to receive second-line chemotherapy than patients without ILD, despite the fact that docetaxel, pemetrexed, or EGFR tyrosine kinase inhibitor is recommended as a second-line therapy for relapsed or refractory advanced NSCLC (29). Although patients with advanced NSCLC with ILD have usually received best supportive care because a standard chemotherapy regimen has not been established, our present results and the results of previous studies suggest that chemotherapy would be beneficial for patients with advanced NSCLC with ILD.

Markers have not been established for predicting acute chemotherapy-associated exacerbation of ILD in patients with NSCLC with ILD. Isobe *et al.* reported that smoking index, but not LDH, KL-6, SP-D, PaO<sub>2</sub>, %VC, or %DLCO, is the only predictive marker for acute exacerbation of IPF associated with cancer therapy (13). Minegishi *et al.* reported that CRP, but not KL-6, SP-D, PaO<sub>2</sub>, or %VC, is the only predictive marker for acute exacerbation of ILD associated with chemotherapy (12). In the present study, none of the evaluated markers, including CRP, LDH, KL-6, SP-D, PaO<sub>2</sub>, and AaDO<sub>2</sub>, was identified as a predictive marker for acute chemotherapy-associated exacerbation of ILD.

Our study has several limitations. Firstly, patient characteristics were heterogeneous, because this study was retrospective. This study included five patients who underwent chemotherapy when they had recurrences after surgery or thoracic radiotherapy and one patient who underwent chemotherapy after palliative thoracic radiotherapy. Previous therapies could have affected the development of acute chemotherapy-associated exacerbation of ILD. Secondly, the number of patients was too small to precisely determine the safety and efficacy of chemotherapy and to identify predictive

markers for acute chemotherapy-associated exacerbation of ILD. Performing a large prospective study of specific chemotherapy regimens in patients with advanced NSCLC with ILD is difficult because few patients have both these conditions.

In conclusion, to our knowledge, the present study is the first to evaluate platinum doublet chemotherapy with vinorelbine in patients with advanced NSCLC with ILD. In this study, the efficacy and the rate of acute exacerbation of ILD compared favorably with those of other platinum doublet regimens for patients with advanced NSCLC with ILD. Therefore, combination chemotherapy with a platinum agent and vinorelbine can be considered as a treatment option for patients with advanced NSCLC with ILD, with careful management after sufficient evaluation of the risks and the benefits. Large prospective studies are warranted to evaluate the safety and efficacy of chemotherapy in patients with advanced NSCLC with ILD.

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