Carboplatin plus Weekly Paclitaxel Treatment in Non-small Cell Lung Cancer Patients with Interstitial Lung Disease

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Abstract. *Background: Since advanced non-small cell lung cancer (NSCLC) patients with the interstitial lung disease (ILD) have been excluded from clinical trials, it is uncertain whether chemotherapy really provides a benefit to these patients. Patients and Methods: Fifteen advanced NSCLC patients with ILD that was detected on the chest X-rays were enrolled in this study. Carboplatin plus paclitaxel was administered by two methods (method A or method B). Method A: Carboplatin (AUC 6, day 1) and paclitaxel (70 mg/m^2, days 1, 8, 15) were administered every four weeks. Method B: Carboplatin (AUC 2, day 1, 8, 15) and paclitaxel (60 mg/m^2, days 1, 8, 15) were administered every four weeks. Results: The response rate and the disease control rate were 33% and 53%. The median progression-free survival and the median overall survival time were 2.5 months and 7.0 months, respectively. The hematological toxicities were tolerable, but a grade 3 or higher pneumonitis was observed in 4 patients (27%). Conclusion: Carboplatin plus weekly paclitaxel must be administered carefully to advanced NSCLC patients with ILD that is detected on chest X-rays after a sufficient evaluation of the risks and the benefits.*

In Japan, 63,255 patients died of lung cancer in 2006, and the mortality rate is still increasing (1). Some clinical trials have demonstrated that the combination of platinum and third-generation agents, such as paclitaxel, docetaxel, irinotecan, gemcitabine, and vinorelbine, provided a survival benefit and symptom relief to patients with the inoperable non-small cell lung cancer (NSCLC) (2). However, the patients with a poor PS (performance status), an older age, and severe complications, such as interstitial lung disease (ILD), have been excluded from most clinical trials, and it is therefore uncertain whether chemotherapy can really provide a survival benefit to these patients.

ILD is a disease that affects the parenchyma or the alveolar region of the lung, and it is detected as an interstitial shadow on chest X-rays or computed tomography (CT). It encompasses a variety of diseases; for example, idiopathic interstitial pneumonia-like idiopathic pulmonary fibrosis (IPF), interstitial pneumonia associated with collagen vascular disease, pneumoconiosis, as well as other diseases. Among these diseases, IPF and non-specific interstitial pneumonia (NSIP) are the most common, and the prognosis of the patients with these two diseases is not satisfactory. Due to a lack of effective therapy, the median survival time (MST) of IPF and NSIP patients is 24 months and 52 months, respectively (3).

ILD, especially IPF, is a known complication in patients with NSCLC. The incidence of lung cancer in patients with ILD is 20-30% (4). In patients with advanced or recurrent NSCLC who received at least one chemotherapy regimen, the rate of an acute ILD event, such as acute lung injury or acute exacerbation of interstitial pneumonia, was more common in patients with preexisting ILD than in those without preexisting ILD during chemotherapy, including gefitinib treatment (5). However, the safety and efficacy of a first-line chemotherapy regimen, especially a cytotoxic regimen, in NSCLC patients with ILD are unknown. The combination of carboplatin and paclitaxel is the most common chemotherapeutic regimen currently in the world, including Japan (2). Therefore, we evaluated the safety and efficacy of carboplatin and paclitaxel in NSCLC patients with interstitial lung disease.

Patients and Methods

Patient selection. Fifteen NSCLC patients treated between September 2002 and August 2009 at the Juntendo University Hospital were enrolled in this retrospective cohort study. The study subjects were consecutively registered according to the following inclusion criteria: histological or cytological confirmation of the advanced NSCLC; diagnosis of ILD and the presence of an

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Key Words: Non-small cell lung cancer, carboplatin, paclitaxel, chemotherapy, interstitial lung disease, efficacy, safety.

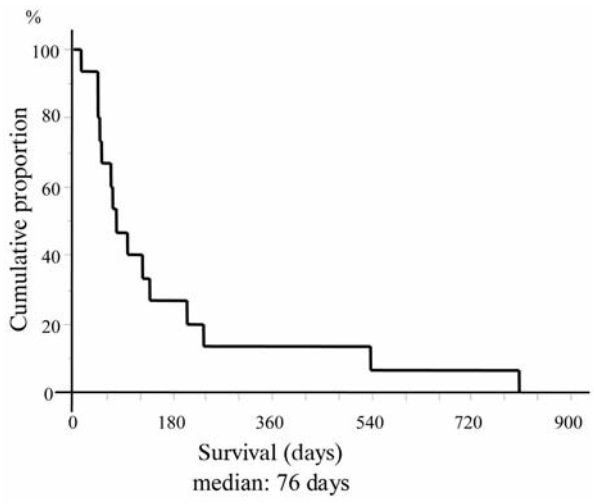

Figure 1. *Kaplan–Meier plot of the progression-free survival of the patients.*

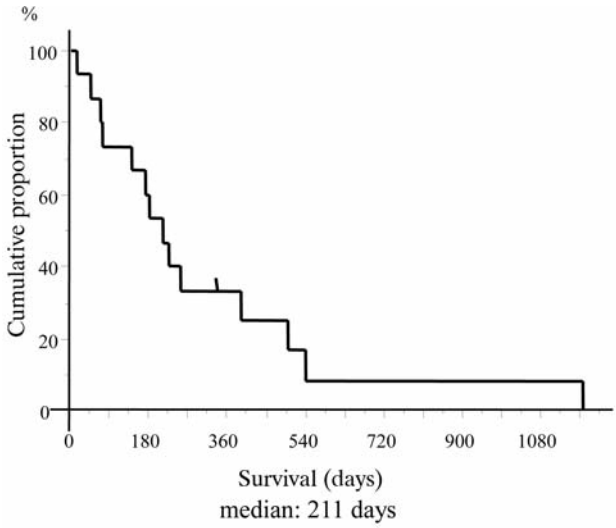

Figure 2. *Kaplan–Meier plot of the overall survival of the patients.*

interstitial shadow on chest X-rays; no prior chemotherapy; presence of measurable disease target lesions on chest X-rays, CT of the chest and abdomen, or additional procedures as specified, including magnetic resonance imaging (MRI) of the head, positron emission tomography (PET), or combined PET/CT; an age less than 75 years; an Eastern Cooperative Oncology Group Performance Status Scale (ECOG PS) of 2 or less; adequate bone marrow, hepatic, and renal functions; no other serious underlying diseases except for ILD; and a willingness to provide written informed consent.

Treatment methods. A carboplatin plus weekly paclitaxel chemotherapy regimen was administered by two methods (method A or method B). Method A: Every four weeks, carboplatin at a dose of AUC 6 was administered on day 1 and paclitaxel at a dose of 70 mg/m^2 was administered on days 1, 8 and 15. Each 4-week treatment schedule was designated as 1 cycle. Method B: Every four weeks, carboplatin at a dose of AUC 2 and paclitaxel at a dose of 60 mg/m^2 were administered on days 1, 8 and 15. Each 4-week treatment schedule was designated as 1 cycle. Before the start of the treatment cycle, the patients were required to have an absolute neutrophil count (ANC) of 1500/mm^3 or more, a platelet count of 100,000/mm^3 or more, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) values of less than 3 times the upper limit of the normal range, and the total serum bilirubin and creatinine levels of less than 1.5 times the upper limit of the normal range. Dose reduction, omission, and discontinuation of the anticancer drugs were based on the judgment of the respective physicians-in-charge. The therapy was continued until there was a progression of the disease, an appearance of intolerable toxicity, or a withdrawal of consent. A complete blood count (CBC) and the biochemistry tests were repeated at least once a week after the initial evaluation.

Evaluation of response and toxicity. The tumor response was classified in accordance with the response evaluation criteria in solid tumors (RECIST). The patients were evaluated to determine the stage of their disease before the start of the treatment as well as at the time of the progression or relapse of the disease. Stage of disease was determined by a complete medical history and a physical examination, including a chest X-ray, a CT of the chest and the abdomen, and additional staging procedures, such as an MRI of the head and a PET. Adverse events were evaluated until 4 weeks after the last administration of chemotherapy or the patient's death, in accordance with the common terminology criteria for adverse events (CTCAE) Ver. 3.0.

Statistical methods. For analyzing the end-points, including the overall survival and the progression free survival (PFS), the survival curves were obtained by the method of Kaplan-Meier. The overall survival was measured from the first day of treatment to the day of death or the last follow-up visit. The PFS was defined as the interval from the initiation of the treatment to the failure (*i.e.* death or disease progression) or the date of the last follow-up visit. All of the analyses were performed using StatView Ver. 5.0 software (SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics. Between September 2002 and August 2009, 15 patients were enrolled in this study. The characteristics of the patients are listed in Table I. Among the 15 patients, 13 were men and the median age was 68 years (range, 58-75 years). One patient had a stage IIIA disease, 5 had a stage IIIB disease, 7 had a stage IV disease and 2 had postoperative recurrences. The histological subtypes were adenocarcinoma in 10 patients and squamous cell carcinoma in 5 patients. The majority of the patients had a performance status (PS) of 0 or 1. Almost half of the patients were treated by method A and method B, respectively. The subtypes of the ILD were IPF in 4 patients

Table I. *Patient characteristics (n=15).*

Characteristic	n	
Gender		
Male	13	
Female	2	
Age (years)		
Median		68
Range		58-75
Stage		
IIIA	1	
IIIB	5	
IV	7	
Postoperative recurrence	2	
Histology		
Adenocaricinoma	10	
Squamous cell carcinoma	5	
IP		
IPF	4	
Non-IPF	11	
PS		
0	6	
1	7	
2	2	
Treatment		
Method A	7	
Method B	8	

IP: Interstitial pneumonia, IPF: idiopathic pulmonary fibrosis, PS: performance status.

Table II. *Compliance (n=15).*

	n	%
Completion of treatment	5	33
Discontinuation of treatment	10	67
Progressive disease	5	
Toxicity	4	
Complication	1	
Dose reduction or omission	5	33
Gr3 ANC	3	
Gr2 ANC	1	
Gr2 Plt	1	
Treatment-related death	2	13

Completion of treatment is defined as the number of administered cycles equal to or more than 4. Gr: Grade, ANC: absolute neutrophil count.

Table III. *Toxicities (n=15).*

Toxicity	Gr1	Gr2	Gr3	Gr4	Gr5
Leukopenia	1	5	2	0	0
Neutropenia	0	3	4	0	0
Anemia	5	6	0	0	0
Thrombocytopenia	4	3	0	0	0
Fatigue	5	1	0	0	0
Anorexia	7	1	0	0	0
Nausea	5	2	0	0	0
Vomiting	3	0	0	0	0
Constipation	5	2	0	0	0
Hiccough	1	1	0	0	0
Myalgia	4	0	0	0	0
Alopecia	7	0	0	0	0
Pneumonitis	0	0	1	1	2
AST	0	1	0	0	0
ALT	1	0	1	0	0
Creatinine	1	0	0	0	0
Febrile neutropenia	0	0	0	0	0

Gr: Grade, AST: aspartate aminotransferase, ALT: alanine aminotransferase.

and non-IPF in 11 patients (NSIP, the collagen vascular disease related ILD and the desquamative interstitial pneumonia in one patient, respectively). The subtypes of the ILD were diagnosed by two or more physicians from the chest CT, except for one patient with desquamative interstitial pneumonia who was diagnosed from the histological findings.

Compliance and toxicity. The compliance of the chemotherapy is shown in Table II. The median number of the administered cycles was 2 (range, 1-6). Five patients completed the carboplatin plus paclitaxel chemotherapy. Completion of the chemotherapy was defined as the patient having received four or more administered cycles. The treatment was discontinued due to progressive disease (PD) in 5 patients and toxicity in 4 patients. Either a dose reduction or an omission of administration was needed in 5 patients.

The toxicities of the treatment are summarized in Table III, which shows the worst toxicity level experimental by patients. Among the hematological toxicities, the principal toxicity was neutropenia. The grade 3 neutropenia and the grade 3 leukopenia were observed in 4 patients and 2 patients, respectively. There were no severe toxicities in terms of anemia or thrombocytopenia. Among the non-hematologic toxicities, those that were grade 3 or higher were pneumonitis in 4 patients and elevated alanine aminotransferase (ALT) in one patient. Two patients died because of pneumonitis and were evaluated as treatment-related deaths.

Response to therapy and survival. There were no patients with complete response (CR), 5 patients with partial response (PR), 3 patients with stable disease (SD), and 3 patients with PD among the 15 patients. The response was not evaluable (NE) in 4 patients. The response rate and the disease control rate were 33% and 53%, respectively (Table IV). The median PFS,

Table IV. *Treatment response (n=15).*

Response	n
CR	0
PR	5
SD	3
PD	3
NE	4
Response rate	33%
Disease control rate	53%

CR: Complete response, PR: partial response, SD: stable disease, PD: progressive disease, NE: Not evaluable.

the MST, and the 1-year survival rate were 2.5 months (76 days), 7.0 months (211 days), and 29%, respectively (Figures 1 and 2). Of the 4 patients who had grade 3 or higher pneumonitis, one patient showed PR and one showed SD. Although the patient who showed PR responded dramatically to chemotherapy, he had grade 3 pneumonitis after 5 cycles of chemotherapy, and was treated by corticosteroids and oxygen supplementation. Corticosteroid therapy stabilized pneumonitis and the lesions did not progress despite the termination of the chemotherapy. He survived 1173 days, the longest of the 15 patients, until he eventually died of ischemic heart disease.

Discussion

At follow-up of IPF patients, NSIP patients and collagen vascular disease-related ILD patients, the 1-year frequency of acute exacerbation has been reported to be about 5 to 15%, 4.5%, and 1.5 to 3.5%, respectively (6-9). In patients with advanced or recurrent NSCLC who receive at least one of the chemotherapy regimens, the rate of an acute ILD event, such as acute lung injury or acute exacerbation of interstitial pneumonia, is more common in patients with a preexisting ILD than in those without preexisting ILD during chemotherapy, including gefitinib treatment (5). Due to these findings, patients with ILD are excluded from most clinical trials, and there are no reports evaluating the safety and the efficacy of a specific chemotherapeutic regimen in NSCLC patients with ILD. To our knowledge, this is the first study which evaluates the safety and the efficacy of a specific chemotherapeutic regimen, carboplatin plus paclitaxel, in NSCLC patients with ILD. The present study is useful due to the fact that ILD is a frequent complication in NSCLC patients, and carboplatin plus paclitaxel, the most common chemotherapeutic regimen, is also sometimes administered to advanced NSCLC patients with ILD.

The response rate in the present study is comparable to that observed in a previous phase III study in which carboplatin plus paclitaxel was administered to NSCLC patients without ILD (2). However, most likely because there were toxicities of severe pneumonitis in 27% of the patients and treatment-related deaths in 13% of the patients, the MST in the present study is shorter than that observed in the previous phase III study in which carboplatin plus paclitaxel was administered to the NSCLC patients without ILD (2). Based on these findings, especially due to the high frequency of pulmonary toxicity, we conclude that carboplatin plus paclitaxel should not be administered to advanced NSCLC patients with ILD that is obviously detected on chest X-rays. Nevertheless, the longest survivor in this study survived more than three years, probably because of the administration of carboplatin plus paclitaxel. Moreover, taking into account the fact that the acute exacerbation of ILD can occur without administration of chemotherapy, carboplatin plus paclitaxel could possibly be administered carefully to NSCLC patients with ILD.

In some reports, the weekly paclitaxel regimen has proven less toxic than the 3-week paclitaxel regimen and is seemingly preferable for unfit (*e.g.* elderly) patients with advanced NSCLC (10, 11). Based on these reports, we administered carboplatin plus paclitaxel treatment to NSCLC patients with ILD weekly. However, since few reports have also suggested that the weekly paclitaxel regimen is related to a frequent pulmonary toxicity (12), there is a possibility that the weekly paclitaxel regimen will result in more cases of pulmonary toxicity in NSCLC patients with ILD, than the 3-week paclitaxel regimen. The incidence of acute exacerbation in IPF patients is more frequent than in non-IPF patients at follow-up (6-9). In this study, the incidence of pulmonary toxicity was more frequent in the IPF patients than in the non-IPF patients (50% in IPF patients, 18% in non-IPF patients). We could not find any correlation between the treatment method, the values of the pulmonary function tests, or the area of the interstitial shadow and the incidence of pulmonary toxicity.

In conclusion, the carboplatin plus weekly paclitaxel treatment regimen must be administered carefully to advanced NSCLC patients with ILD after a sufficient evaluation of the risks and the benefits. However, because it is recognized that the incidence of an acute ILD event, during chemotherapy such as acute lung injury or acute exacerbation of interstitial pneumonia, is more common in Japan than in other countries (5), the results of the present study are not adaptable to patients with ILD in other countries. The interpretation of the results from this study is limited by the small number of patients and the retrospective nature of the study. The development of treatments for NSCLC patients with the ILD is necessary, and further assessment in a large scale prospective study is needed to obtain more information, especially in terms of a safe and optimal chemotherapeutic regimen.

References

1 Cancer Statistics in Japan 2009, http://ganjoho.ncc.go.jp/public/statistics/backnumber/2009_en.html.

2 Ohe Y, Ohashi Y, Kubota K, Tamura T, Nakagawa K, Negoro S, Nishiwaki Y, Saijo N, Ariyoshi Y and Fukuoka M: Randomized phase III study of cisplatin plus irinotecan *versus* carboplatin plus paclitaxel, cisplatin plus gemcitabine, and cisplatin plus vinorelbine for advanced non-small cell lung cancer: Four-Arm Cooperative Study in Japan. Ann Oncol *18*: 317-323, 2007.

3 Nicholson AG, Colby TV, Dubois RM, Hansell DM and Wells AU: The prognostic significance of the histologic pattern of interstitial pneumonia in patients presenting with the clinical entity of cryptogenic fibrosing alveolitis. Am J Respir Crit Care Med *162*: 2213-2217, 2000.

4 Raghu G, Nyberg F and Morgan G: The epidemiology of interstitial lung disease and its association with lung cancer. Br J Cancer *91*: S3-S10, 2004.

5 Kudoh S, Kato H, Nishiwaki Y, Fukuoka M, Nakata K, Ichinose Y, Tsuboi M, Yokota S, Nakagawa K, Suga M, Japan Thoracic Radiology Group, Jiang H, Itoh Y, Armour A, Watkins C, Higenbottam T and Nyberg F: Interstitial lung disease in Japanese patients with lung cancer. A cohort and nested case–control study. Am J Respir Crit Care Med *177*: 1348-1357, 2008.

6 Kim DS, Park JH, Park BK, Lee JS Nicholson AG and Colby T: Acute exacerbation of idiopathic pulmonary fibrosis: frequency and clinical features. Eur Respir J *27*: 143-150, 2006.

7 Hyzy R, Huang S, Myers J, Flaherty K and Martinez F: Acute exacerbation of idiopathic pulmonary fibrosis. Chest *132*: 1652-1658, 2007.

8 Park IN, Kim DS, Shim TS, Lim CM, Lee SD, Koh Y, Kim WS, Kim WD, Jang SJ and Colby TV: Acute exacerbation of interstitial pneumonia other than idiopathic pulmonary fibrosis. Chest *132*: 214-220, 2007.

9 Suda T, Kaida Y, Nakamura Y, Enomoto N, Fujisawa T, Imokawa S, Hashizume H, Naito T, Hashimoto D, Takehara Y, Inui N, Nakamura H, Colby TV and Chida K: Acute exacerbation of interstitial pneumonia associated with collagen vascular diseases. Respir Med *103*: 846-853, 2009.

10 Sakakibara T, Inoue A, Sugawara S, Maemondo M, Ishida T, Usui K, Abe T, Kanbe M, Watanabe H, Saijo Y and Nukiwa T: Randomized phase II trial of weekly paclitaxel combined with carboplatin *versus* standard paclitaxel combined with carboplatin for elderly patients with advanced non-small cell lung cancer. Ann Oncol *21*: 795-799, 2010.

11 Socinski MA, Ivanova A, Bakri K, Wall J, Baggstrom MQ, Hensing TA, Mears A, Tynan M, Beaumont J, Peterman AH and Niell HB: A randomized phase II trial comparing every 3-weeks carboplatin/paclitaxel with every 3-weeks carboplatin and weekly paclitaxel in advanced non-small cell lung cancer. Ann Oncol 17: 104-109, 2006.

12 Yasuda K, Igishi T, Kawasaki Y, Yamamoto M, Kato K, Matsumoto S, Kotani M, Sako T, Shigeoka Y, Sugitani A, Histuda Y and Shimizu E: Phase II trial of weekly paclitaxel in previously untreated advanced non-small cell lung cancer. Oncology *65*: 224-228, 2003.

Received March 17, 2010
Revised June 2, 2010
Accepted June 7, 2010