

Retrospective analysis of acute exacerbation of interstitial lung diseases with nanoparticle albumin-bound paclitaxel in patients with advanced lung cancer with preexisting interstitial lung disease

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Abstract. Lung cancer with preexisting interstitial lung disease (ILD) is difficult to treat due to the risk of acute exacerbation of ILD. Nanoparticle albumin-bound (nab-) paclitaxel improves the overall response rate and reduces neuropathy more efficiently compared with conventional solvent-based (sb-) paclitaxel in patients with advanced non-small-cell lung cancer. However, it is not known whether the risk of acute exacerbation of ILD with nab-paclitaxel is higher compared with that with sb-paclitaxel. Advanced lung cancer patients with ILD treated with nab-paclitaxel (n=14) or sb-paclitaxel (n=14) were retrospectively reviewed. Acute exacerbation of ILD developed in 1/14 patients (7.7%) receiving nab-paclitaxel and 3/14 patients (21.4%) receiving sb-paclitaxel; the difference was not statistically significant. To the best of our knowledge, this is the first study to compare the incidence of acute exacerbation of ILD with nab-paclitaxel with that of sb-paclitaxel in patients with advanced lung cancer with preexisting ILD. The results of the present study support conducting a prospective clinical trial to confirm the clinical benefit of this agent.

Introduction

Lung cancer with preexisting interstitial lung disease (ILD) is difficult to treat due to the risk of acute exacerbation of ILD. There are newly developed treatments for advanced lung cancer, such as molecular targeting agents and immune checkpoint blockades, which may be successful in prolonging

the progression-free or overall survival of patients with lung cancer. However, these agents are considered to be associated with a higher risk of acute exacerbation of ILD in lung cancer with preexisting ILD, and their use is not recommended in such patients. Therefore, conventional cytotoxic chemotherapy remains the mainstay of treatment for lung cancer with preexisting ILD.

Chemotherapy for lung cancer with ILD has been previously investigated. One of the most effective treatments for lung cancer with ILD is the combination of platinum agents with paclitaxel or etoposide (1). The incidence rate of acute exacerbation of ILD in patients treated with weekly paclitaxel in combination with carboplatin was reported to be 5.6-27% (2-4).

Nanoparticle albumin-bound (nab-) paclitaxel is a 130-nm albumin-bound form of paclitaxel. Nab-paclitaxel improves the overall response rate and reduces neuropathy more efficiently compared with conventional solvent-based (sb-) paclitaxel in non-small-cell lung cancer (NSCLC) (5). However, the incidence of acute exacerbation induced by nab-paclitaxel in lung cancer with ILD has not been reported.

The aim of the present study was to compare nab-paclitaxel with sb-paclitaxel regarding the incidence of acute exacerbation of ILD in patients with advanced lung cancer.

Patients and methods

Patients. The medical records of lung cancer patients with ILD who were administered nab-paclitaxel or sb-paclitaxel at the Kyoto University Hospital (Kyoto, Japan) between January 2005 and August 2016 were retrospectively reviewed. Patients who received radiation therapy to the chest region prior to and during these treatments were excluded from the study.

Patients with ILD were defined as those who were found to have reticular shadows, ground-glass opacities, honeycombing, or traction bronchiectasis on chest computed tomography (CT). Treatment-related acute exacerbation of ILD was diagnosed according to the following criteria: i) Worsening of dyspnea within the previous month; ii) new ground-glass opacities or

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Table I. Patient characteristics.

Characteristics	Nab-paclitaxel (n=14)	Sb-paclitaxel (n=14)	P-value
Age, years	69.9±9.3	70.1±8.4	0.950
Sex (male/female)	10/4	13/1	0.326
Smoking history (yes/no)	10/4	14/0	0.699
Histological type (adenocarcinoma/squamous/SCLC)	7/6/1	4/3/7	0.0561
KL-6, U/ml	800.4±583.2	1350.8±1,226.5	0.199
SP-D, ng/ml	186.7±235.6	154.0±110.6	0.905
Line of chemotherapy (first-/second- and further-line)	11/3	6/8	0.0530
Preexisting COPD (yes/no)	2/9	1/8	1.000
%FVC, %	90.7±6.0	95.6±7.1	0.603
Platine combination (yes/no)	11/3	7/7	0.115
Classification of ILD (UIP/non-UIP)	12/2	11/3	1.000

Nab-PTX, nanoparticle albumin-bound paclitaxel; sb-PTX, conventional solvent-based paclitaxel; SCLC, small-cell lung carcinoma; KL-6, Krebs von den Lungen 6; SP-D, surfactant protein D; FVC, forced vital capacity; COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; UIP, usual interstitial pneumonia pattern.

Table II. Characteristics of patients with acute exacerbation of ILD.

No.	Chemotherapy	Sex/age, years	Histology	KL-6 (U/ml)	SP-D (ng/ml)	ILD pattern	Best overall response	Time to AE after first administration (days)	AE outcome
1	Nab-PTX	F/75	Adenocarcinoma	859	55.5	UIP	SD	133	Improved
2	Sb-PTX	M/75	Small-cell carcinoma	968	NA	UIP	PR	47	Improved
3	Sb-PTX + CBDCA	M/72	Adenocarcinoma	1,560	104	UIP	SD	79	Improved
4	Sb-PTX + CBDCA	M/61	Adenocarcinoma	3,500	225	UIP	SD	56	Succumbed to the disease

Nab-PTX, nanoparticle albumin-bound paclitaxel; sb-PTX, conventional solvent-based paclitaxel; KL-6, Krebs von den Lungen 6; SP-D, surfactant protein D; CBDCA, carboplatin; M, male; F, female; AE, acute exacerbation; PR, partial response; SD, stable disease; ILD, interstitial lung disease; UIP, usual interstitial pneumonia pattern; NA, not available.

consolidation on chest radiography or CT; iii) no evidence of infection, pneumothorax, pulmonary embolism, or congestive heart failure as a cause of acute dyspnea; iv) <30 days after the last administration of nab-paclitaxel or sb-paclitaxel. All the patients were followed up until November 2016.

High-resolution CT criteria for usual interstitial pneumonia (UIP) pattern. The classification shown in the ATS/ERS/JRS/ALAT statement was adopted (6). Cases inconsistent with the UIP pattern were defined as non-UIP and the remaining cases were defined as UIP pattern in the present study. One radiologist and one respiratory physician with expertise in interstitial pneumonia reviewed the pretreatment CTs; both reviewers were blinded to the patient data. Disagreements in the CT findings between the two reviewers was resolved by a consensus.

Treatment method. Patients were administered nab-paclitaxel at a dose of 100 mg/m² on days 1, 8 and 15, or sb-paclitaxel at

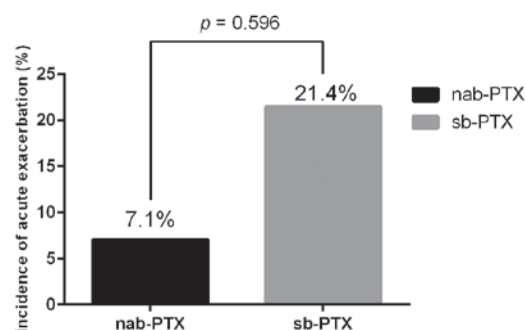


Figure 1. Incidence of acute exacerbation of interstitial pneumonia in all patients. Nab-PTX, nanoparticle albumin-bound paclitaxel; sb-PTX, conventional solvent-based paclitaxel.

a dose of 180-200 mg/m² on day 1 or a dose of 70-80 mg/m² on days 1, 8 and 15. Certain patients were co-administered carboplatin with an area under the curve of 4-6 on day 1.

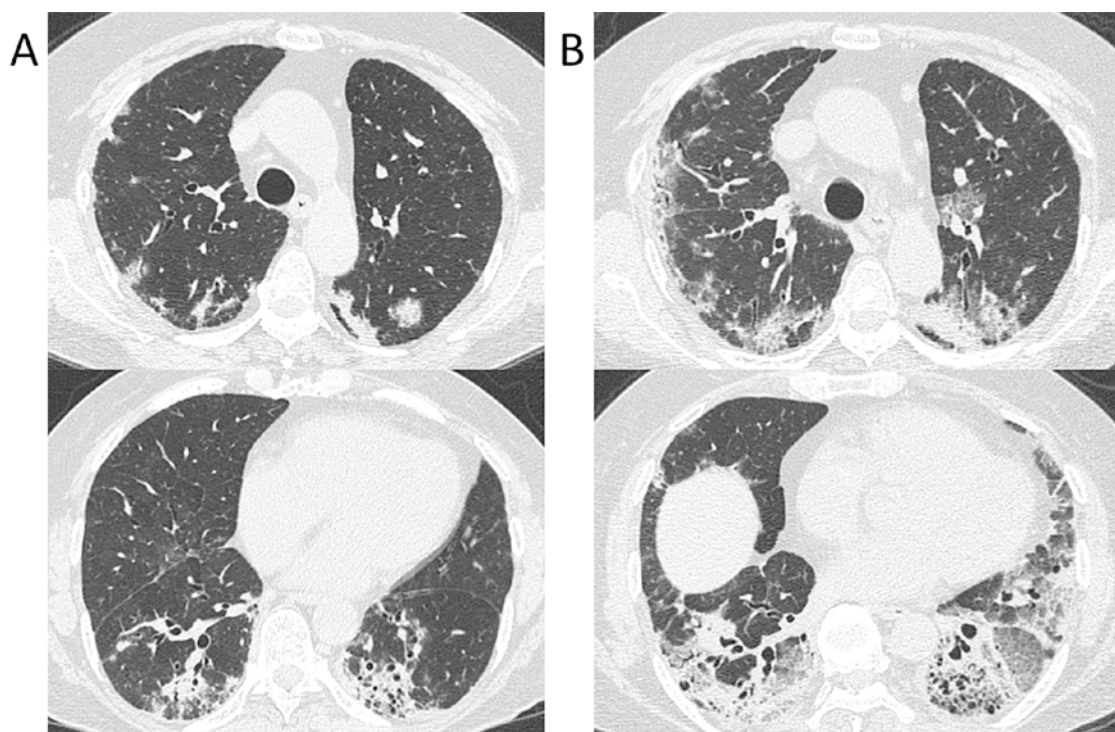


Figure 2. Chest high-resolution computed tomography (HRCT) images. (A) HRCT scan showing subpleural basal dominant reticular abnormalities prior to treatment with nab-paclitaxel. (B) HRCT scan showing additional patchy ground-glass opacities during the fourth course of nab-paclitaxel treatment.

These agents were administered every 3-4 weeks. Dose reduction and discontinuation of chemotherapy were based on the physician's discretion. Treatment was continued until disease progression, intolerable toxicity, or refusal by the patient.

Statistical analysis. The Fisher's exact test, Chi-squared test, Student's t-test or Wilcoxon's two-sample test were used to compare patient characteristics and the incidence of acute exacerbation of ILD. All P-values <0.05 were considered to indicate statistically significant differences. All statistical analyses were performed using JMP 12.2 software for Windows (SAS Institute Inc., Cary, NC, USA). The protocol of the present study was approved by the Institutional Review Board of the Kyoto University Hospital.

Results

Patient characteristics. A total of 27 patients were included in the study. The numbers of patients administered nab-paclitaxel and sb-paclitaxel were 14 and 14, respectively (1 patient received both agents). There were significantly more patients with small-cell carcinoma in the sb-paclitaxel group compared with the nab-paclitaxel group (P=0.0329). The performance status was 0-1 in 25 patients and 2 in 2 patients. None of the patients had been previously treated for ILD. The mean serum level of Krebs von den Lungen-6 (KL-6) prior to treatment in the sb-paclitaxel group was higher compared with that in the nab-paclitaxel group, but the difference was not statistically significant. Some of the patients with a higher KL-6 level exhibited tumor progression.

The number of patients with the UIP pattern was similar to that of patients with the non-UIP pattern. Inter-observer

agreement on the classification of ILD was high ($\kappa=0.85$). There were no significant differences between the groups regarding other patient characteristics (Table I).

Acute exacerbation of ILD. Acute exacerbation of ILD occurred in 1 patient (7.1%) in the nab-paclitaxel group and 3 patients (21.4%) in the sb-paclitaxel group; the difference was not statistically significant (Fig. 1). All the patients had a performance status of 0 prior to treatment. CT images of a patient receiving nab-paclitaxel prior to treatment and following acute exacerbation of ILD are shown in Fig. 2. Acute exacerbation of ILD was managed with corticosteroid therapy and only 1 patient in the sb-paclitaxel group succumbed to acute exacerbation of ILD. The patients' characteristics are summarized in Table II.

Discussion

To the best of our knowledge, this is the first study to evaluate the incidence of acute exacerbation in lung cancer patients with ILD treated with nab-paclitaxel. ILD is one of the risk factors for the development of lung cancer (7). Acute exacerbation of ILD has been reported to occur in patients with advanced lung cancer in association with various chemotherapies. The incidence of acute exacerbation of ILD has been found to be significantly higher with gefitinib compared with cytotoxic chemotherapy (8). Although there are currently no available studies on the safety of anaplastic lymphoma kinase inhibitors in NSCLC patients with ILD, a case report demonstrated the risk of acute exacerbation of ILD treated with crizotinib (9). Therefore, molecularly targeted agents are not recommended in patients with preexisting ILD. Immune checkpoint inhibitors are a novel treatment for NSCLC and they may be successful

in improving progression-free and overall survival, both as first-line treatment and after failure of platinum-based doublet chemotherapy. However, there are also no studies on immune checkpoint inhibitors in association with preexisting ILD, since they are considered as risk factors for acute exacerbation. Hence, cytotoxic chemotherapy may still be of value in lung cancer patients with ILD.

There are several reports evaluating the safety of cytotoxic chemotherapy in lung cancer patients with ILD (1,10,11). However, the safety of nab-paclitaxel has not been previously investigated, apart from one case report (12). The incidence of acute exacerbation of ILD with nab-paclitaxel in the present study was 7.7%. Although there was no significant difference in the incidence of ILD between nab-paclitaxel and sb-paclitaxel, it was relatively lower with nab-paclitaxel compared with sb-paclitaxel, and almost equal to the previously reported incidence of acute exacerbation in association with sb-paclitaxel (2,3). In addition, Cremophor EL® (BASF, Ludwigshafen am Rhein, Germany), which is contained in sb-paclitaxel for dissolution, is known to increase hypersensitivity, which may lead to acute exacerbation of ILD (13).

It is important to evaluate the risk of acute exacerbation prior to chemotherapy. A UIP pattern on CT was reported to be a risk factor for chemotherapy-induced acute exacerbation of ILD (1,11,14). Another report demonstrated that lower forced vital capacity is a risk factor, but a UIP pattern is not (4). The rate of the UIP pattern may differ among institutions, since inter-observer agreement for a UIP pattern was only moderate among thoracic radiologists (15). In the present study, there were no significant differences in patient characteristics including these known risk factors; thus, the safety of nab-paclitaxel may be comparable to that of sb-paclitaxel in lung cancer patients with ILD.

The present study had several limitations. First, this was a retrospective chart review study and certain data, such as surfactant protein D levels and diffusing capacity of the lung for carbon monoxide, could not be obtained. It is important to evaluate ILD prior to treatment. Although a precise evaluation of ILD was not performed, the study population was likely uniform based on the good performance status and lack of previous treatment for ILD. Second, the number of cases was too small to perform multivariate analysis of risk factors for acute exacerbation of ILD. To elucidate the risk of acute exacerbation, studies including a larger patient sample from several institutions are required. In addition, it may be preferable to limit studies to NSCLC or small-cell lung cancer to compare the incidence of acute exacerbation of ILD. A multicenter study may enable the collection of more cases. Finally, acute exacerbation of ILD was diagnosed only based on clinical and radiological findings. Bronchoscopy for differential diagnosis was not performed in the patients included in the present study, and other causes, such as lymphangitic carcinomatosis, cannot be definitively excluded.

In conclusion, the findings of the present study indicate that nab-paclitaxel is a safe option for patients with advanced lung carcinoma with ILD and support conducting a prospective clinical trial to confirm the clinical benefits of this agent.

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