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# Feasibility of the administration of chemotherapy using cisplatin plus etoposide for non-small cell lung cancer patients with interstitial lung disease on chest computed tomography

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ABSTRACT

*Background:* Chemotherapy for non-small cell lung cancer (NSCLC) patients with interstitial lung disease (ILD) has been challenging due to the possibility of the acute exacerbation of ILD as a life-threatening adverse effect. No acceptable regimen for such patients has been established. Therefore, we herein assessed our series of NSCLC patients with ILD who were treated with cisplatin plus etoposide (PE).

*Patients and methods:* The unresectable NSCLC patients with ILD detected on chest computed tomography (CT) who received PE at our department between December 2006 and December 2013 were retrospectively reviewed. Cisplatin (80 mg/m$^2$, day 1) and etoposide (100 mg/m$^2$, days 1 to 3) were administered every three weeks.

*Results:* Thirty-two consecutive NSCLC patients with ILD were evaluated. Twenty-four received PE as first-line treatment, while the other eight received it as second-line or later treatment. Twenty-three patients exhibited the usual pneumonitis (UIP) pattern, eight possible UIP pattern and one was inconsistent to UIP on CT. Grade 3/4 hematological toxicities were frequently seen, including neutropenia in 23 (74.2%). Febrile neutropenia was seen in six (19.4%) patients. Two patients experienced grade 2 pneumonitis after PE, but successfully recovered. The overall response rate was 31.2%. The median progression-free survival was 3.4 months and the median overall survival for all patients was 8.5 months.

*Conclusion:* PE treatment for unresectable NSCLC patients with ILD in our series was considered to be relatively safe, with an acceptable tumor response and survival. Obviously, careful patient selection and management are warranted. A prospective evaluation should also be performed.

## 1. Introduction

Lung cancer is a well-known comorbidity of interstitial lung disease (ILD), and the proportion of lung cancer among such patients has been reported to range from 4.4% to 12.9% in analyses including more than 100 patients [1–4]. In addition, in the recent data from the British Thoracic Society (BTS) cryptogenic fibrosing alveolitis (CFA) study, the results of 11-year observation of their cohort of ILD patients demonstrated that 9% of them had died of lung cancer [5].

Although ILD itself is considered to be associated with poor survival despite several treatment strategies [6,7], especially when it involves acute exacerbation, unresectable non-small cell lung cancer (NSCLC) patients are strongly recommended to receive both first-line [8] and second-line chemotherapy [9] rather than best supportive care to prolong their lifespan. However, despite the recent remarkable progress in anti-cancer drugs, chemotherapy for patients with ILD is still challenging since there is a higher probability of acute exacerbation of the underlying ILD, leading those patients to severe, often fatal, respiratory insufficiency. No acceptable chemotherapy regimen for patients with ILD has been established. Therefore, we assessed our series of unresectable NSCLC patients with ILD who were treated with cisplatin plus etoposide (PE).

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## 2. Patients and methods

### 2.1. Treatment

The medical charts of 32 consecutive unresectable NSCLC patients with ILD detected on chest computed tomography (CT) treated with PE between December 2006 and December 2013 at the Department of Thoracic Oncology, National Kyushu Cancer Center, Japan, were retrospectively reviewed. The patients included in this analysis were those with cytologically or histologically confirmed NSCLC before treatment. Although the eligibility for PE in this series of patients was decided based on clinical practice, basically it included those patients with an age between 20 and 80 years, an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2, a stable respiratory condition without oxygen administration, and adequate bone marrow, renal or hepatic function. Patients who had another concomitant uncontrolled malignancy or serious comorbidities, such as a clinically significant cardiac disease, an active infection, or a neurological or psychiatric disorder, were excluded. Patients being orally administered a low dose of steroids as maintenance were not excluded. Chest radiography, computed tomography of the chest and the upper abdomen, computed tomography or magnetic resonance imaging of the brain, flexible optical bronchoscopy and a bone scan or fluorodeoxyglucose positron emission tomography (FDG-PET) were routinely performed for all patients.

The diagnosis of ILD on chest CT was performed according to the criteria of An Official ATS/ERS/JRS/ALAT Statement [10] by an independent radiologist [A.F.] without any knowledge of the patients' clinical background. ILD was classified into the usual interstitial pneumonia (UIP) pattern (Fig. 1A), possible UIP pattern (Fig. 1B) or inconsistent to UIP pattern. The staging of the tumors was in accordance with the TNM Classification of Malignant Tumours, 7th edition [11]. The histological analysis of the tumor was based on the WHO classification for cell types [12]. The response of the tumor was evaluated using the Response and Evaluation Criteria of Solid Tumors, version 1.1 [13], and adverse events were classified depending on the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 [14].

Patients received cisplatin at a dose of 80 mg/m$^2$ as a 120-min infusion on day 1 while the patients were hydrated with 2500 ml of saline by infusion, and etoposide was administered at a dose of 100 mg/m$^2$ on days 1 to 3, every three weeks. An anti-emetic agent was administered at the discretion of each patient's physician.

Written informed consent was obtained from all patients in this analysis. The institutional review board and an ethics committee reviewed and approved this retrospective analysis.

### 2.2. Statistical analysis

Statistical analyses were performed using the chi-square and Student's *t*-tests for the comparison of variables. The Kaplan-Meier method was used to assess the overall survival and disease-free survival curves. Progression-free survival (PFS) was defined as the time from the starting date of PE until disease progression or death. Overall survival (OS) was defined as the time from the starting date of PE until death from any cause. The median follow-up time was 8.4 (1.6–35.8) months at the time of the analysis. All statistical analyses were performed with the IBM SPSS Statistics 18 software package (SPSS Japan, an IBM company, Tokyo, Japan).

## 3. Results

### 3.1. Patients' characteristics

Of the 32 patients analyzed in this study, 24 received PE as first-line chemotherapy (first-line group) and the remaining eight received it as second-line or later chemotherapy (second-line or later group), including three patients at the second line, one patient at the third line, and two patients each at the fourth and fifth lines of chemotherapy. As shown in Table 1, there were 31 males and one female with a median age of 66 (range 53–79) years old. The ECOG PS was 0 in 17 patients, 1 in 13 patients and 2 in two patients. All patients had Stage III or IV disease: five (15.6%) cStage IIIA, eight (25.0%) cStage IIIB and 19 (59.4%) cStage IV disease, including three patients with postoperative recurrence. Histologically, 17 had adenocarcinoma, six squamous cell carcinoma, seven NSCLC not otherwise specified (NOS) and one each pleomorphic carcinoma and large cell neuroendocrine cancer. Oncogene driver mutation was examined based on clinical practice: epidermal growth factor receptor (EGFR) for 16 patients or additional anaplastic lymphoma kinase (ALK) for eight patients, mostly for those with adenocarcinoma or NSCLC (NOS). None showed an EGFR mutation or ALK rearrangement. No statistically significant differences between the two groups were found for the variables listed above Table 2.

The radiological features of ILD on CT were classified as described previously [10]. Twenty-three patients exhibited the usual pneumonitis (UIP) pattern, eight possible UIP pattern and one was inconsistent to UIP. Five of the eight patients in the second-line or later group had a previous history of drug-induced interstitial pneumonia. In the first-line group, there was a significantly higher frequency of the UIP pattern

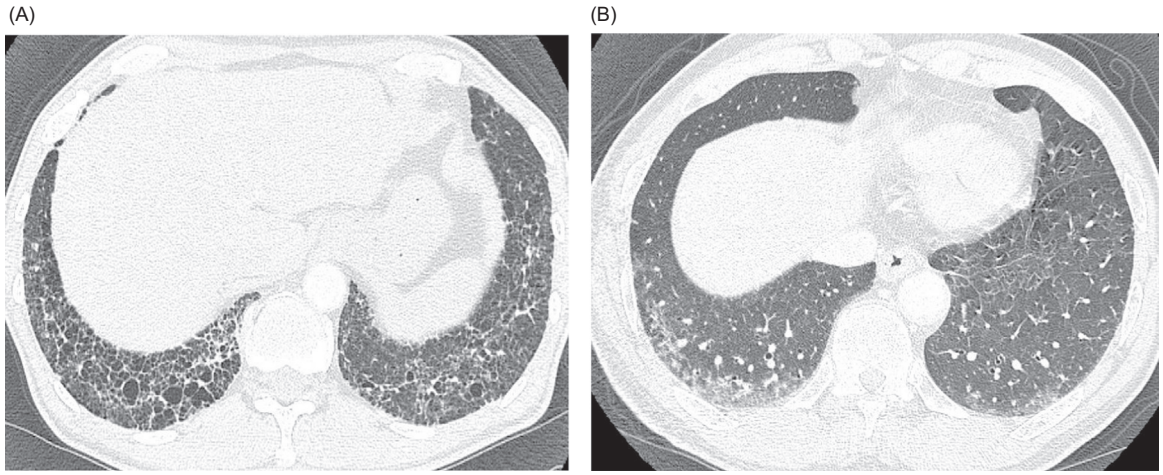


**Fig. 1.** The diagnosis of ILD on chest CT was performed according to the criteria of an official ATS/ERS/JRS/ALAT statement. ILD was classified into, The figure 1A represents the usual interstitial pneumonia (UIP) pattern, while figure 1B represents the non-specific interstitial pneumonia (NSIP) pattern.