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A multicenter, open-label, phase II trial of S-1 plus carboplatin in advanced non-small cell lung cancer patients with interstitial lung disease

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ABSTRACT

Objectives: The clinical benefit of chemotherapy and the appropriate regimen for non-small-cell lung cancer (NSCLC) patients with interstitial lung disease (ILD) remain unclear. To fulfill this unmet medical need, we conducted a phase II study to elucidate the efficacy of S-1 in combination with carboplatin (CBDCA) in NSCLC patients with ILD.

Materials and methods: A total of 33 advanced or recurrent NSCLC patients with ILD were prospectively enrolled in this multicenter, open-label, phase II study. Every 4 weeks, CBDCA at a dose of AUC 5 on day 1 and S-1 at a dose of 80 mg/m^2 daily for 14 days were administered. The primary endpoint was the investigator-assessed objective response rate.

Results: The median age at initiating chemotherapy was 70. Sixteen patients (48.5%) had squamous cell carcinoma histology. With respect to the types of ILD, the usual interstitial pneumonia pattern was dominant (66.7%). The median number of cycles administered was 3, and the overall response rate and disease control rate were 33.3% and 78.8%, respectively. The median progression-free survival, the median survival time and the 1-year survival rate were 4.8 months, 12.8 months and 51.4%, respectively. Acute exacerbation of ILD caused by chemotherapy was noted in 2 patients (6.1%).

Conclusion: This is the first prospective study designed to evaluate the efficacy of a specific chemotherapeutic regimen as the primary endpoint in patients with advanced NSCLC with ILD. The combination of S-1 with CBDCA may be a treatment option for advanced NSCLC patients with ILD (The clinical trial registration number: UMIN000011046).

Abbreviations: ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; AE, acute exacerbation; AE-ILD, acute exacerbation of interstitial lung disease; NSCLC, non-small cell lung cancer; S-1, tegafur-gimeracil-oteracil potassium; CBDCA, carboplatin; RECIST, Response Evaluation Criteria in Solid Tumors; ECOG, Eastern Cooperative Oncology Group; PS, performance status; IIP, idiopathic interstitial pneumonia; HRCT, high-resolution computed tomography; UIP, usual interstitial pneumonia; NSIP, non-specific interstitial pneumonia; DIP, desquamative interstitial pneumonia; RB-ILD, respiratory bronchiolitis-interstitial lung disease; LIP, lymphoid interstitial pneumonia; BSA, body surface area; CT, computed tomography; CR, complete response; PR, partial response; SD, stable disease; QOL, quality of life; VAS, visual analogue scale; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer QLQ-C30; PFS, progression-free survival; OS, overall survival; ORR, overall response rate; CI, confidence interval; ANOVA, analysis of variance; DCR, disease control rate; PD, progressive disease; mPFS, median progression-free survival; MST, median survival time

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1. Introduction

Lung cancer is the leading cause of cancer death worldwide, and the associated mortality rate is still increasing. Recent evidence has demonstrated that platinum doublet agents provide a survival benefit and symptom relief in patients with advanced lung cancer [1]. However, patients with severe complications, such as interstitial lung disease (ILD), have been excluded from most clinical trials, and it is therefore uncertain whether or not chemotherapy can really provide a survival benefit in these patients.

ILD represents a heterogeneous group of disorders of either known or unknown etiology that have differing pathogeneses and prognoses, and its presence is well known to be a risk factor for lung cancer development [2,3]. The incidence of lung cancer in patients with idiopathic pulmonary fibrosis (IPF) is markedly higher than in the general population, whose relative risk reportedly ranges between 7 and 14 [4,5]. In addition, the complication of ILD has been shown to cause several problems in the diagnosis and treatment of patients with lung cancer. One associated issue is acute exacerbation (AE) of ILD (AE-ILD) which frequently occurs following various anticancer treatment, including surgery, irradiation, molecular-targeted therapy, and chemotherapy [6–8]. AE-ILD is undoubtedly an obstacle to the treatment of lung cancer in clinical practice as well as the performance of clinical trials targeted populations with lung cancer accompanied by ILD.

The incidence of ILD in patients with lung cancer was recently reported to be about 10% [5], which is markedly higher than the rate of lung cancer with driver mutations, such as ALK or ROS1 fusion gene, or gene mutations of BRAF and HER2 except for EGFR [9]. The high rate of incidence of ILD reflects the impact of this population in lung cancer, underscoring the need for a safe and effective therapy for lung cancer patients with ILD.

Several retrospective reports have described the exacerbation of preexisting ILD after surgery [6,10], but there are few reports of chemotherapy that can be used to develop a treatment strategy for lung cancer with ILD given the risk of AE-ILD. While a few studies suggested the feasibility of several treatment strategies [11,12], the benefit of chemotherapy is not yet clear, because no prospective study evaluating the efficacy of chemotherapy as the primary endpoint in these patients has been reported.

We recently performed a retrospective study on the treatment of patients with advanced non-small cell lung cancer (NSCLC) and concomitant ILD and showed the feasibility and efficacy of tegafur-gimeracil-oteracil potassium (S-1) in combination with carboplatin (CBDCA), suggesting that the combination of S-1 with CBDCA might be a potential candidate for the treatment of chemo-naïve advanced NSCLC with ILD [13].

To fulfill aforementioned unmet medical need, we conducted a multicenter, open-label, phase II trial of S-1 plus CBDCA in patients with advanced or recurrent NSCLC concomitant ILD (UMIN000011046). This is the first prospective study designed to elucidate the efficacy of a specific chemotherapeutic regimen as the primary endpoint in advanced NSCLC with ILD.

2. Materials and methods

2.1. Patients and study design

The criteria for patient eligibility included histologically or cytologically confirmed NSCLC; stage IIIB/IV or postoperative recurrent diseases; no prior chemotherapy or a history of postoperative chemotherapy that was completed at least one year before recurrence; ≥1 measurable lesion in accordance with the Response Evaluation Criteria in Solid Tumors (RECIST) criteria (version 1.1) [14]; an age of 20–79 years; an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1; clinically diagnosed ILD; adequate bone marrow, hepatic, and renal functions; and a projected life expectancy of at least 3 months. The main exclusion criteria were pregnancy, pleural effusion necessitating treatment, active concomitant malignancy, symptomatic brain metastasis, serious concomitant diseases, active infection, a history of drug allergy, and patients fitting the definition of AE-ILD as described below.

In this study, we included patients with NSCLC who not only had comorbidities like idiopathic interstitial pneumonias (IIPs) but also connective tissue disease-interstitial lung disease. A diagnosis of ILD was determined in accordance with American Thoracic Society/European Respiratory Society criteria [15,16]. In the absence of histological evidence, the diagnosis of an ILD pattern was based on evidence from chest high-resolution computed tomography (HRCT) reviewed by two pulmonologists (MH and YN) and the clinical features. The patients with usual interstitial pneumonia (UIP), non-specific interstitial pneumonia (NSIP), desquamative interstitial pneumonia (DIP), respiratory bronchiolitis-interstitial lung disease (RB-ILD), or lymphoid interstitial pneumonia (LIP) patterns on histology or HRCT were eligible. Patients with a history of asbestos inhalation were excluded from this study because it is difficult to distinguish between UIP and asbestosis based on HRCT findings.

The study was conducted in accordance with the Declaration of Helsinki and approved by the institutional ethics committee of each of the participating institutions. Written informed consent was obtained from all of the patients.

2.2. Treatment plan

S-1 was administered orally at 40 mg/m^2 twice a day on days 1–14. The actual dose of S-1 was selected as follows: in a patient with a body surface area (BSA) < 1.25 m^2, 40 mg twice a day; BSA of ≥1.25 m^2 but < 1.5 m^2, 50 mg twice a day; and BSA ≥ 1.5 m^2, 60 mg twice a day. CBDCA (AUC 5) was administered intravenously on day 1. The treatment regimen was repeated every 4 weeks for a maximum of six cycles unless there was earlier evidence of disease progression or unacceptable toxicity. Subsequent therapeutic cycles were withheld until the following criteria were met: a leukocyte count of ≥3000/mm^3, a neutrophil count of ≥1500/mm^3, a platelet count of ≥100,000/mm^3, aspartate aminotransferase and alanine aminotransferase levels of ≤100 IU/L, serum creatinine levels of ≤1.2 mg/dL, and other non-hematological toxicities of grade ≤2. A dose reduction of 20 mg per day for S-1 and an AUC of 1 for CBDCA was recommended if grade 4 hematologic toxicities or grade ≥3 non-hematologic toxicities had occurred during any cycle of administration. Dose escalation was not permitted. Patients requiring a 2-step dose reduction or ≥28 days of rest to recover from any toxicity were released from the study.

2.3. Baseline and follow-up assessments

Prior to enrollment in the study, all patients provided their medical history and underwent a complete physical examination, clinical laboratory testing, chest X-ray, and chest computed tomography (CT). The patients' weight, height, and ECOG PS were also determined. CT was performed for tumor assessment within two weeks of commencing treatment and was repeated every four to eight weeks. Physical examinations, symptom evaluations, and routine blood tests and biochemical blood examinations were performed every week during treatment. The responses to treatment were evaluated in accordance with the RECIST criteria. Patients who were documented as having a complete response (CR)/partial response (PR) underwent a confirmatory evaluation after an interval of ≥4 weeks. Patients were regarded as having stable disease (SD) if a response was confirmed and sustained for ≥6 weeks after commencing treatment. Adverse events were graded in accordance with the Common Terminology Criteria for Adverse Events (version 4.0). The definition of AE-ILD is as follows [13,17]: 1) exacerbation of dyspnea within one month; 2) newly-developed diffuse pulmonary opacities on chest HRCT and/or chest