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Original article

A pilot trial of nivolumab treatment for advanced non-small cell lung cancer patients with mild idiopathic interstitial pneumonia

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ABSTRACT

Introduction: Nivolumab has demonstrated efficacy against metastatic non-small cell lung cancer (NSCLC). However, immune-related adverse events can occur, among which pneumonitis is relatively common. Lung cancer patients with idiopathic interstitial pneumonia (IIP) have a higher risk of pneumonitis associated with anticancer therapy. We hypothesized that the benefit of nivolumab may outweigh the risks of pneumonitis in patients with NSCLC who have mild IIP. We performed a pilot trial to evaluate the safety of nivolumab in NSCLC patients with mild IIP.

Methods: Previously treated, inoperable NSCLC patients with mild IIP were enrolled. Mild IIP was defined as having a predicted vital capacity ≥80% and a possible usual interstitial pneumonia (UIP) or inconsistent with UIP pattern on chest high-resolution computed tomography. Patients received nivolumab at a dose of 3 mg/kg biweekly.

Results: Six patients were enrolled in this trial between April 2016 and December 2016. None experienced drug-related nonhematologic grade 3/4 or hematologic grade 4 adverse events in the 12 weeks following the initiation of nivolumab treatment. Furthermore, none of the patients had pneumonitis of any grade. At the time of analysis, all patients were alive, and 3 had experienced a partial response.

Conclusions: Nivolumab therapy may be feasible in NSCLC patients with mild IIP. (Trial registration number: UMIN000022037)

1. Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide [1]. Non-small cell lung cancer (NSCLC) accounts for approximately 80% of lung cancers; the majority are already unresectable and metastatic when first diagnosed [1]. Recently, programmed cell death 1 (PD-1)/PD-1 ligand 1 (PD-L1) checkpoint inhibitors have demonstrated impressive anti-tumor activity for the treatment of metastatic NSCLC [2–4]. However, immune-related adverse events (irAEs) can occur and may be severe. Pneumonitis is a particularly notable irAE that accounted for 3 deaths in an early-phase study with a PD-1 inhibitor [5].

Interstitial lung disease (ILD) is characterized by damage to the lung parenchyma owing to inflammation and fibrosis [6]. ILD, particularly idiopathic interstitial pneumonia (IIP) that is characterized by idiopathic pulmonary fibrosis (IPF), has been shown to be associated with lung carcinogenesis [7]. Several recent studies have shown that IIP is relatively common among smokers in non-specific populations, and its prevalence appears to be increasing [8–10]. In fact, approximately 10% of NSCLC patients have IIP [11,12]. Thus, it is necessary to establish the optimal anticancer therapy for these patients.

Systemic anticancer therapy in lung cancer patients with IIP is often challenging, since acute exacerbation of IIP (AE-IIP) is a fatal adverse event that can occur during therapy. In the absence of AE-IIP data related to PD-1 axis inhibitors, these agents are considered only after careful assessment of the risk of pneumonitis, for which the severity of IIP is a major predictor. A previous clinical trial showed a relationship between poor pulmonary function and acute exacerbation in patients with IPF [13]. Additionally, previous studies of lung cancer patients

Abbreviations: NSCLC, non-small cell lung cancer; irAE, immune-related adverse events; IIP, idiopathic interstitial pneumonia; UIP, usual interstitial pneumonia; PD-1, programmed cell death 1; ILD, interstitial lung disease; AE-IIP, acute exacerbation of idiopathic interstitial pneumonia; ECOG, Eastern Cooperative Oncology Group; PS, performance status; %VC, vital capacity (as percent of predicted)

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with ILD who received chemotherapy demonstrated that low forced vital capacity and a usual interstitial pneumonia (UIP) pattern on computed tomography (CT) were associated with acute exacerbation [14,15]. When considering these predictors of AE-IIP, the benefits of PD-1 axis inhibitors may outweigh the risks of pneumonitis in NSCLC patients with IIP who have relatively good pulmonary function and a less severe interstitial pneumonia pattern on CT (i.e., mild ILD). Indeed, many NSCLC patients are reported to have mild IIP in the clinical setting [16–18]. Hence, it is important to evaluate the safety and efficacy of PD-1 axis inhibitors specifically in such patients.

In this pilot trial, we hypothesized that PD-1 axis inhibitors are feasible for NSCLC patients with mild IIP. To that end, we evaluated the safety of nivolumab, a PD-1 inhibitor, in patients with advanced NSCLC and mild IIP.

2. Patients and methods

2.1. Patients

Patients were considered eligible if they met the following criteria: histologically or cytologically proven stage III or IV NSCLC, including postoperative recurrence; previous treatment with at least 1 chemotherapy regimen; evaluable disease lesions; age ≥20 years; Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–1; adequate organ function; and the presence of mild IIP (as defined below). Patients were ineligible if they received systemic glucocorticoids or other immunosuppressive treatments, had an active autoimmune disease, or had a history of pneumonitis for which they had received glucocorticoids. The trial was approved by the Ethics Committee of Kobe City Medical Center General Hospital.

Preexisting ILD was diagnosed based on clinical features and pretreatment chest high-resolution computed tomography (HRCT) results. All patients received HRCT before commencing nivolumab therapy, and the presence of ILD was evaluated by at least 2 pulmonologists. In order to diagnose IIP, we excluded collagen vascular disease (CVD)-associated ILD, occupational lung diseases, and other alternative diagnoses. In particular, we checked for CVD-associated antibodies such as anti-SS-A, anti-SS-B, anti-scleroderma 70, anti-U1RNP, anti-aminoacyl-tRNA synthetases, and anti-neutrophil cytoplasmic antibodies. When we defined "mild" IIP in this pilot trial, the severity was primarily based on the risks of chemotherapy-related pneumonitis in patients with IIP. Further, we also considered the data on the risk of acute exacerbation and death in IIP patients without lung cancer. Previous studies of lung cancer patients with ILD who received chemotherapy demonstrated that low forced vital capacity and a UIP pattern on CT were associated with chemotherapy-related pneumonitis [14,15]. In previous studies in IIP patients, preserved vital capacity and an HRCT image showing a possible UIP or inconsistent with UIP pattern were also associated with lower incidence of acute exacerbation and death [19,20]. Additionally, a predicted vital capacity (%VC) ≥ 80% was strongly associated with lower incidence of pneumonitis after pulmonary resection in the Japanese large-scale multi-institutional cohort study for patients with lung cancer and ILD, and this cutoff value has served as the widely accepted clinical criteria for restrictive change of pulmonary fibrosis [21].

Therefore, if patients with IIP had a%VC ≥ 80% and an HRCT image showing a possible UIP or inconsistent with UIP pattern, we diagnosed the patient with mild IIP (Fig. 1) [22]. The occurrence of AE-IIP during and up to 4 weeks after the last administration of nivolumab was considered drug-related pneumonitis.

2.2. Study design

This was an open-label pilot trial. The primary objective was to investigate the tolerability and safety of nivolumab therapy in NSCLC patients with mild IIP. The secondary objective was to determine the efficacy of this therapy. We initially enrolled 3 patients with NSCLC and mild IIP to assess the safety of standard nivolumab doses, followed by 3 more after no serious adverse events were observed in the first group. Because the dose of nivolumab is fixed for patients with advanced NSCLC (3 mg/kg, biweekly) and no dose escalation was required, we did not enroll any additional patients. We determined that a larger-scale clinical trial would be warranted if no more than 1 of the 6 patients experienced any of the following: all-grade pneumonitis according to the Common Terminology Criteria for Adverse Events, drug-related grade 3/4 nonhematologic adverse events (except for untreated vomiting, fatigue, or nausea), or drug-related grade 4 hematologic adverse events within 12 weeks after commencing nivolumab therapy. HRCT was performed every 4 weeks to check for drug-related pneumonitis. Clinical tumor assessment was performed using the Response Evaluation Criteria in Solid Tumors v1.1. The duration between the start of treatment and the time of progression or death (progression-free survival [PFS]) was calculated for each patient.

2.3. Statistical analysis

All treated patients were included in the safety and efficacy analyses. We reported the profiles and outcomes for all patients; no statistical tests were conducted.

3. Results

3.1. Patients

Between April 2016 and December 2016, 9 ILD patients were screened for this study. Two patients were ineligible owing to poor pulmonary function, and one owing to HRCT results. Consequently, 6 patients with a median age of 72 years were enrolled (Table 1). All patients had stage IV disease and an ECOG PS of 1. The most common histology was adenocarcinoma (50%). We investigated *EGFR* status in all patients. Only one patient (patient 4) had lung adenocarcinoma with mutated EGFR (exon 21, L858R). The median (range) %VC was 93.4% (88.6–120.7%). One patient had an inconsistent with UIP pattern and 5 had a possible UIP pattern. Two patients (patients 4 and 5) had chronic obstructive pulmonary disease, and 3 (patients 3, 5 and 6) had emphysematous change on HRCT. The median (range) duration of treatment was 9 (6–16) cycles at the time of analysis. Four patients remained on nivolumab therapy at the time of analysis.

3.2. Safety

Safety analysis included all 6 patients; none experienced drug-related grade 3/4 nonhematologic or grade 4 hematologic adverse events within 12 weeks after commencing nivolumab therapy. Furthermore, no patient had pneumonitis (including grades 1/2). There were no treatment-related deaths. One patient (patient 3) developed a grade 2 tremor (possibly associated with treatment) 4 months after starting nivolumab therapy, and chose to discontinue therapy after his neurological symptoms improved. At the time of analysis, 2 patients had discontinued treatment owing to progressive disease and neurological symptoms, respectively. Drug-related adverse events are listed in Table 2.

3.3. Efficacy

At the time of analysis, all patients were alive. Three patients experienced partial response, with a PFS of 9.1+, 7.7+, and 6.5+ months, respectively. Additionally, 3 patients had stable disease, with a PFS of 3.3, 3.8+, and 3.0+ months, respectively. Response (partial/complete) was observed in 3 patients (50%). Treatment details and outcomes are described in Table 1.