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Nivolumab-induced interstitial lung disease analysis of two phase II studies patients with recurrent or advanced non-small-cell lung cancer

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ABSTRACT

Objectives: Drug-induced interstitial lung disease (ILD) is often associated with high mortality; however it is difficult to predict and manage. we examined the clinical findings and imaging characteristics of nivolumab induced ILD reported in the two phase II studies patients with recurrent or advanced non-small-cell lung cancer.

Materials and methods: We examined the clinical findings and imaging characteristics of all cases of ILD reported in two phase II trials of nivolumab, an anti-programmed death-1 antibody, in Japanese patients with recurrent or advanced non-small-cell lung cancer. These studies are registered with the Japan Pharmaceutical Information Center, numbers JapicCTI-132072, JapicCTI-132073.

Results: Eight (7.2%; two with squamous cell carcinoma, six with non-squamous cell carcinoma) of the 111 patients included in these two studies experienced ILD, and a causal relationship with nivolumab could not be ruled out in any of them. ILD of ≥grade 3 severity was found in four patients (3.6%), and ILD was considered a serious treatment-related adverse event in seven patients (6.3%). All of the patients who experienced ILD were male and had a history of smoking, with a median age of 65 years (range 52–78 years). In seven of the eight patients who experienced ILD, their events were rapidly resolving or resolved spontaneously or with steroid therapy; one patient died of respiratory failure without resolution of ILD, after docetaxel treatment was initiated following nivolumab discontinuation. Chest computed tomography images for the seven patients with resolving or resolution of ILD showed a pattern of organizing pneumonia or nonspecific interstitial pneumonia without traction bronchiectasis, while the patient who died had traction bronchiectasis.

Conclusion: Although the risk factors for nivolumab-induced ILD were not identified, careful monitoring including imaging examinations is important in preventing the worsening of ILD in patients receiving nivolumab.

Abbreviations: ILD, interstitial lung disease; EGFR, epidermal growth factor receptor; TKIs, tyrosine-kinase inhibitors; PD-1, programmed cell death-1; NSCLC, non-small-cell lung cancer; RECIST, Response Evaluation Criteria in Solid Tumors; CT, chest computed tomography; GGO, ground glass opacity.

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1. Introduction

Interstitial lung disease (ILD) is a disease that affects the parenchyma or alveolar regions of the lungs. A number of drugs have the potential to cause ILD, including antineoplastic therapies, which are thought to be the most common drugs that induce ILD. In particular, antineoplastic agents that target molecular pathways, including epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) and mammalian target of rapamycin inhibitors have been associated with a high incidence of ILD [1]. When associated with drug use, ILD can present precipitously with acute diffuse alveolar damage, which is fatal in some patients.

Nivolumab (ONO-4538/BMS-936558/MDX-1106) is a fully human IgG4 monoclonal antibody that targets programmed cell death-1 (PD-1), one of the T-cell surface membrane receptors. Nivolumab received the world's first regulatory approval in Japan in July 2014 for the treatment of unresectable malignant melanoma. nivolumab is also undergoing development for the treatment of other indications [2].

In patients with advanced non-small-cell lung cancer (NSCLC), nivolumab has been generally well tolerated; results from two phase III trials Checkmate 017 [3] and Checkmate 057 [4] have shown that treatment-related adverse events were less common and of lower grade in patients who received nivolumab compared with patients who received docetaxel. However, some patients in these trials developed immune-mediated adverse events with nivolumab treatment, including ILD [3,4]. Nivolumab-induced pneumonitis or ILD were was reported for in 4.6% (6/131) and 3.5% (10/287) of nivolumab treatments groups in the phase III Checkmate 017 [3] and Checkmate 057 [4] trials.

In this analysis, we examined the clinical findings and imaging characteristics of ILD reported in the two Japanese phase II trials, one in patients with squamous NSCLC (ONO-4538-05) and one in patients with non-squamous NSCLC (ONO-4538-06).

2. Materials and methods

2.1. Study design and participants

The aim of this analysis was to examine the clinical findings and imaging characteristics of ILD reported in two phase II trials of nivolumab who developed ILD when receiving nivolumab. These two multicentre, open-label, uncontrolled studies investigated the efficacy and safety of nivolumab in Japanese patients with stage IIIB/IV or recurrent squamous NSCLC (trial ONO-4538-05; JapicCTI-132072 [5]) or non-squamous NSCLC (trial ONO-4538-06; JapicCTI-132073 [6]) unsuited to radical radiotherapy and resistant to platinum-based chemotherapy. In these studies, nivolumab was administered at a dose of 3 mg/kg every 2 weeks. A 6-week cycle of treatment was repeated until progressive disease was documented by the local investigator according to the RECIST guideline version 1.1 or an unacceptable adverse event occurred. The study protocols were reviewed and approved by the institutional review board of each study site before the study and both studies were conducted in compliance with the ethical principles that have their origins in the Declaration of Helsinki. All patients provided written consent.

2.2. Procedures

In these studies, study investigators were required to report all suspected incidences of ILD and record detailed information of these patients, including baseline characteristics and ILD symptoms, chest X-ray and chest computed tomography (CT) imaging before and after nivolumab administration, and laboratory tests. These data were submitted to an independent data monitoring committee, which consisted of one radiologist and four oncologists, and were reviewed retrospectively to unanimously confirm ILD diagnosis. ILD was defined as a general term for events in which interstitial shadows was confirmed on chest CT. In both studies, the CT scan of the chest was taken according to the local site's standard procedures. Image data obtained in these trials were stored on recording media, generally in digital form (DICOM image data), de-identified to ensure the protection of patients' personal information.

3. Results

3.1. Baseline patient characteristics

Eight (7.2%) of the 111 patients enrolled in the phase II trials (n = 35 and n = 76 in ONO-4538-05 and ONO-4538-06, respectively) experienced ILD, as reported by the study investigators and confirmed by the independent data monitoring committee. All eight patients were male, with a median age of 65 years (52–78 years; Table 1). The majority of patients had stage IV disease (n = 5) and a performance status score of 1 (n = 7). All eight patients had a history of smoking. The median number of nivolumab doses administered before the onset of ILD was 3 (1–12).

3.2. Clinical findings at the onset of ILD and treatment

Of all eight cases of ILD, causal relationship with nivolumab could not be ruled out for any of them. ILD of at least grade 3 severity was found in four patients (3.6%), and ILD was considered a serious treatment-related adverse event in seven patients (6.3%). When each study was analysed individually, ILD occurred in two (5.7%) of the 35 patients with squamous NSCLC enrolled in study ONO-4538-05, and both cases were at least grade 3 severity and considered a serious treatment-related adverse event; ILD occurred in six (7.9%) of the 76 patients with non-squamous NSCLC enrolled in study ONO-4538-06, two patients (2.6%) experienced at least grade 3 severity and five patients (6.6%) were considered serious. The median time to onset was 36.5 days (range 16–168 days).

For the treatment of ILD, six of the eight patients received steroid pulse therapy, five patients received oxygen therapy, and one patient received steroid intravenous injection therapy. ILD led to death in one patient, while it was resolving or resolved in the other seven patients. A summary of ILD grades, time to onset, biomarker data, action taken, time from treatment to resolution or resolving, and outcomes for each patient are provided in Table 2.

3.3. Frequency of ILD by baseline characteristics

Of the 111 patients enrolled in the two phase II studies, ILD occurred in 9.0% (8/89) of past smokers versus 0% (0/22) patients without a history of smoking, 9.9% (8/81) of male versus 0% (0/30) of female, 100% (1/1) of patients with concurrent pneumoconiosis versus 6.4% (7/110) of patients without concurrent pneumoconiosis, 5.7% (2/35) of patients with squamous cell carcinoma versus 7.9% (6/76) of patients with non-squamous cell carcinoma, and 8.3% (1/12) of patients with history of prior radiotherapy to lungs versus 7.1% (7/99) of patients without history of prior radiotherapy to lungs.

3.4. Clinical course and chest CT images

The clinical course and chest CT scan for each patient who developed ILD in the two phase II studies are described below.