Association Between Imaging Findings of Airway Obstruction Adjacent to Lung Tumors and the Onset of Interstitial Lung Disease After Nivolumab

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Abstract. *Background:* Compared to conventional cytotoxic chemotherapy, immune checkpoint inhibitors have shown a significant efficacy in the treatment of lung cancer. Although interstitial lung disease (ILD) is an important adverse event in immunotherapy, risk factors for ILD remain unclear. *Patients and Methods:* In this multicenter cohort study (UMIN000025908), 201 patients who were treated with nivolumab were retrospectively reviewed. Associations between the incidence of ILD and patient characteristics were evaluated. ILD grade and progression-free survival were analyzed according to the presence or absence of imaging findings of airway obstruction adjacent to lung tumors (IAOT). *Results:* In the multivariate analysis, the odds ratio (OR) of ILD for patients with a history of radiation pneumonitis or IAOT was 3.96 ($p=0.012$) and 6.59 ($p=0.004$), respectively. ILD occurred in six (37.5%) out of 16 patients with IAOT and 19 (10.3%) out of 185 patients without IAOT. Three out of the six patients with ILD and IAOT had ILD of grade 4 or more. The median progression-free survival of patients with and without IAOT was 0.9 and 3.2 months, respectively ($p<0.001$). *Conclusion:* IAOT was strongly associated with the occurrence of ILD after therapy with nivolumab.

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Key Words: Airway obstruction, interstitial lung disease, lung cancer, nivolumab, risk factor.

Compared to conventional cytotoxic chemotherapy, immune checkpoint inhibitors (ICIs) have shown a significant efficacy in the treatment of lung cancer (1-6). Nivolumab is an ICI that binds to programmed cell death-1 (PD1) on activated immune cells to disrupt its interaction with programmed death ligand-1 (PD-L1) and-2. When administering ICIs, such as nivolumab, unique adverse events known as immune-related adverse events are often problematic. Interstitial lung disease (ILD) is a particularly important immune-related adverse event. Previous studies have reported that the incidence of nivolumab-related deaths due to ILD was higher in patients with non-small cell lung cancer than in patients with other malignancies (*e.g.* melanoma) (7, 8). This suggests that the lung microenvironment may be a crucial factor in inducing ILD. In this study, we analyzed clinical data to clarify the risk of ILD focusing on factors that may affect the lung microenvironment.

Patients and Methods

Study design. A retrospective multicenter cohort study was conducted on 201 patients with advanced or recurrent non-small cell lung cancer who had previously been treated with nivolumab (3.0 mg/kg intravenously every 2 weeks) at the National Hospital Organization Kinki-chuo Chest Medical Center (Osaka, Japan), Osaka International Cancer Institute (Osaka, Japan), and Osaka Habikino Medical Center (Osaka, Japan) between December 2015 (the date nivolumab was approved in Japan) and July 2016. This study was registered with the University Hospital Medical Information Network Clinical Trials Registry in Japan (UMIN000025908).

Data collection and evaluation. Clinical data, including age, sex, Eastern Cooperative Oncology Group performance status, smoking status, histological type, baseline C-reactive protein and

Figure 1. Representative imaging findings of airway obstruction adjacent to lung tumors. The lung tumor is indicated by asterisks.

lactate dehydrogenase concentrations (defined as those within 2 weeks prior to nivolumab treatment), the presence of pleural effusion and pulmonary metastasis, a history of radiation pneumonitis, and imaging findings of airway obstruction adjacent to lung tumors (IAOT) (Figure 1) at the time of commencing treatment with nivolumab, were collected from patient medical records. Data were also collected on the incidence of nivolumab-related ILD and the grade of ILD. Associations between the incidence of ILD and patient characteristics were evaluated. Progression-free survival (PFS) was analyzed according to the presence or absence of IAOT. Clinical responses were defined according to the Response Evaluation Criteria in Solid Tumors (version 1.1) (9). PFS was defined as the duration between commencing treatment with nivolumab and disease progression or death from any cause. The patients were followed-up until March 31, 2017.

Statistical analyses. Multivariate analysis was performed using logistic regression. Survival curves were estimated using the Kaplan–Meier method and differences between the groups were analyzed using the log-rank test. All statistical analyses were conducted using JMP statistical software for Windows (version 13.0; SAS Institute Inc., Cary, NC, USA). A value of $p < 0.05$ was considered statistically significant.

Results

Patient characteristics. A total of 201 patients with advanced non-small cell lung cancer were treated with nivolumab between December 17, 2015 and July 31, 2016. The patient characteristics are summarized in Table I. The median age was 68 (range=27-87) years. Most patients were male (67.2%), and most had a history of smoking (78.1%), and an Eastern Cooperative Oncology Group performance status of 0-1(76.1%). At the time of commencing treatment with nivolumab, 34 patients (16.9%) had a history of radiation pneumonitis and 16 patients (8.0%) had IAOT.

Table I. Patient characteristics (n=201).

Characteristic	Value
Age (years)	
Median (range)	68 (27-87)
Gender, n (%)	
Male	135 (67.2)
Female	66 (32.8)
Smoking status, n (%)	
Current/ex-smoker	157 (78.1)
Non-smoker	44 (21.9)
Histology, n (%)	
Non-squamous	159 (79.1)
Squamous	42 (20.9)
ECOG PS, n (%)	
0-1	153 (76.1)
≥2	48 (23.9)
LDH >240 IU/l, n (%)	
Yes	77 (38.3)
No	124 (61.7)
CRP >0.3 mg/dl, n (%)	
Yes	132 (65.7)
No	69 (34.3)
PE, n (%)	
Yes	89 (44.3)
No	112 (55.7)
Pulmonary metastasis, n (%)	
Yes	115 (57.2)
No	86 (42.8)
History of radiation pneumonitis, n (%)	
Yes	34 (16.9)
No	167 (83.1)
IAOT, n (%)	
Yes	16 (8.0)
No	185 (92.0)

CRP, C-Reactive protein; ECOG, Eastern Cooperative Oncology Group; IAOT, imaging findings of airway obstruction adjacent to lung tumors; LDH, lactate dehydrogenase; PE, pleural effusion; PS, performance status.

Multivariate analysis. In the multivariate analysis, a history of radiation pneumonitis and IAOT were associated with increased ILD risk, with odds ratios of 3.96 ($p=0.012$) and 6.59 ($p<0.004$), respectively (Table II). In contrast, other factors were not associated with the incidence of ILD.

Grade of ILD. ILD occurred in six (37.5%) out of 16 patients with IAOT and 19 (10.3%) out of 185 patients without IAOT. Three out of the six patients with both ILD and IAOT had ILD of grade 4 or more. Conversely, only two (10.5%) out of the 19 patients with ILD without IAOT had ILD of grade 4 or more (Table III).

Progression-free survival. The median PFS of patients with and without IAOT was 0.9 and 3.2 months, respectively ($p<0.001$; Figure 2).

Table II. Multivariate odds ratios (ORs) for interstitial lung disease.

Factor	Comparison	OR (95.0% CI)	p-Value
Gender	Male vs. female	1.98 (0.55-7.07)	0.296
Smoking status	Current/ex-smoker vs. non-smoker	1.24 (0.27-5.69)	0.778
Histology	Squamous vs. non-squamous	1.28 (0.44-3.78)	0.648
ECOG PS	≥2 vs. <2	0.63 (0.18-2.21)	0.471
LDH	>240 vs. ≤240 IU/l	2.10 (0.81-5.38)	0.126
CRP	>0.3 vs. ≤0.3 mg/dl	0.95 (0.30-2.95)	0.925
PE	Yes vs. no	0.77 (0.30-1.98)	0.587
Pulmonary metastasis	Yes vs. no	0.89 (0.33-2.41)	0.821
History of radiation pneumonitis	Yes vs. no	3.96 (1.35-11.60)	0.012
IAOT	Yes vs. no	6.59 (1.82-23.90)	0.004

CI, Confidence interval; CRP, C-reactive protein; ECOG, Eastern Cooperative Oncology Group; IAOT, imaging findings of airway obstruction adjacent to lung tumors; LDH, lactate dehydrogenase; PE, pleural effusion; PS, performance status.

Table III. Grade of experienced Interstitial lung disease (ILD) grade.

IAOT	ILD grade					Total
	1	2	3	4	5	
Yes (n=16; 8.0%)	2	1	0	1	2	6
No (n=185; 92.0%)	9	6	2	1	1	19

IAOT, Imaging findings of airway obstruction adjacent to lung tumors.

Discussion

In our study, a history of radiation pneumonitis and the presence of IAOT were associated with a significantly increased risk of developing ILD. Although in a previous study, a history of radiation pneumonitis was considered a risk factor for ILD (10), in our study, IAOT exhibited a higher odds ratio for ILD than the history of radiation pneumonitis.

PFS was also significantly shorter in patients with IAOT than in those without. There have been reports that showed that patients who develop immune-related adverse events, such as ILD, tended to have better outcomes (11,12). However, in our study, patients with ILD and IAOT tended to exhibit earlier disease progression or death. Furthermore, ILD grade in patients with IAOT was more severe than in those without IAOT. These findings suggest that in terms of the developmental mechanism, ILD with IAOT differs from that without IAOT in patients treated with ICIs.

The PD1-PD-L1 pathway functions not only in antitumor immunity, but also in various immune environments, such as infection, and plays a critical role in negative feedback mechanisms that attenuate immune cell function (13-16).

Figure 2. Kaplan–Meier curves for progression-free survival (PFS) according to imaging findings of airway obstruction adjacent to lung tumors. CI: Confidence interval.

It is common for patients with airway obstruction to develop recurrent obstructive pneumonitis. Therefore, we postulate that airway obstruction may be a source of active inflammation, and in such a lung microenvironment with inflammation, ICIs might induce excessive reactions that lead to severe ILD. Since it is difficult to know whether there is active inflammation or not, we used the term ‘IAOT’ rather than ‘obstructive pneumonia’. Conversely, other factors that can be associated with the lung microenvironment (*e.g.* pulmonary metastasis and pleural effusion) did not correlate with the incidence of ILD in our multivariate analysis.

Our study has several important limitations. Firstly, the retrospective design means there is the potential for bias and confounding factors. We attempted to address this by building multivariate models and adjusting for confounding

factors. Secondly, the number of patients with IAOT was relatively small. However, we were able to demonstrate significant findings from the multivariate analysis despite the small sample size. Finally, the judgment as to whether or not the patients had IAOT was entirely dependent on individual investigators.

In conclusion, a history of radiation pneumonitis and the presence of IAOT were significant risk factors for ILD in multivariate analysis. We suggest that clinicians should be careful in administration of ICIs if patients have IAOT. Further larger prospective studies are needed to determine the association between IAOT and ILD, not only in patients treated with nivolumab, but also patients treated with other ICIs.

Conflicts of Interest

Dr. Y. Taniguchi, Dr. A. Tamiya, Dr. S. Isa, Dr. K. Nakahama, Dr. T. Shiroyama, Dr. H. Suzuki, Dr. T. Inoue, Dr. M. Tamiya, Dr. T. Hirashima, Dr. F. Imamura, and Dr. S. Atagi report grants from Ono Pharmaceutical and Bristol-Myers Squibb. Dr. Y. Taniguchi, Dr. A. Tamiya, Dr. T. Shiroyama, Dr. H. Suzuki, Dr. M. Tamiya, Dr. T. Hirashima, Dr. F. Imamura, and Dr. S. Atagi report personal fees from Ono Pharmaceutical. Dr. Y. Taniguchi, Dr. A. Tamiya, Dr. M. Tamiya, Dr. T. Hirashima, Dr. F. Imamura, and Dr. S. Atagi report personal fees from Bristol-Myers Squibb during the conduct of the study.

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