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Impact of PD-L1 Expression in Patients with Surgically Resected Non-Small-Cell Lung Cancer

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Programmed cell death ligand-1 · Squamous non-small-cell lung cancer · Prognostic factor

Abstract
Background: Immunotherapy can become a crucial therapeutic option to improve the prognosis of patients with non-small-cell lung cancer (NSCLC). Here, we evaluated the impact of programmed cell death ligand-1 (PD-L1) expression in surgically resected NSCLCs. ***Methods:*** We estimated PD-L1 expression in 229 consecutive NSCLC specimens using rabbit polyclonal antibodies to human PD-L1 in a SP263 immunohistochemical assay and evaluated PD-L1 expression for potential associations with clinicopathological parameters and survival time. ***Results:*** PD-L1 expression was significantly higher in tumors from men or current smokers. Squamous cell carcinoma histology was independently associated with high PD-L1 expression according to multivariate analysis ($p = 0.015$). The 5-year survival rate of patients was 70%, and the difference in the 5-year survival rate according to PD-L1 expression was not statistically significant (high expression group [67%] vs. low expression group [68%]); however, the squamous cell carcinoma group exhibited significantly lower 5-year survival rates as compared to the non-squamous cell carcinoma group (53 and 71%, respectively; $p = 0.026$). ***Conclusion:*** Here, we revealed high PD-L1 expression and poor prognosis observed in patients with surgically resected squamous NSCLC as compared with non-squamous NSCLC. Our results support the identification of patient subsets that most likely respond to anti-PD-1 therapy as the first step in precision medicine.

Introduction

Lung cancer is the leading cause of cancer-related deaths in the USA and worldwide [1], with ~85% of lung cancers diagnosed as the non-small-cell histological sub-

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type, for which conventional platinum-based chemotherapy and molecular-targeted therapy remain the standards in advanced disease stages [2–5]. However, resistance to chemotherapy develops in most patients, and >50% of patients with lung adenocarcinoma lack targetable mutations, thereby necessitating alternative therapeutic approaches [6].

Immunotherapy has been assessed as a means of redirecting host immune responses to cancer tissue. T cells are dominant in host antitumor immune functions, given their ability to recognize tumor cells as abnormal and generate a population of cytotoxic T lymphocytes that can infiltrate the tumor lesion and destroy tumor cells. Checkpoints of T cell activation refer to the inhibitory pathways crucial to maintaining self-tolerance and avoiding physiological immune-response-related bystander tissue damage [7]. Cancer cells can evade host immune responses by expressing specific ligands that downregulate cytotoxic T lymphocytes via inhibitory pathways, which are usually initiated by ligand-receptor interactions. Consequently, blocking the specific ligand or receptor with antibodies may lead to a reactivation of host immune responses and antitumor effects [7]. Programmed cell death ligand-1 (PD-L1) is an immune checkpoint protein expressed on tumor cells and tumor-infiltrating immune cells that downregulates antitumor T cell function through binding to programmed cell death-1 (PD-1) receptors and B7.1 (also known as CD80) receptors [8, 9]. The engineered, humanized IgG1 monoclonal anti-PD-L1 antibody atezolizumab (MPDL3280A) blocks PD-L1–PD-1 and PD-L1–B7.1 interactions, thereby restoring antitumor T cell activity and enhanced T cell priming [10–12]. Clinical studies of anti-PD-1 antibodies (e.g., nivolumab or pembrolizumab) established the therapeutic value of targeting the PD-L1–PD-1 pathway [13–16]; however, the clinical relevance of PD-L1 expression in non-small-cell lung cancer (NSCLC) has not been sufficiently clarified. This study focused on patients with surgically resected NSCLC and examined whether the PD-L1 expression is related to clinicopathological or prognostic factors in patients.

Materials and Methods

Patients

This retrospective cohort study included 229 consecutive patients who had undergone complete surgical resection of a stage I–III NSCLC at the Kitasato University Hospital between January 2002 and December 2005. The patients had not received neoadjuvant chemotherapy or preoperative radiation therapy. We collected clinicopathological data from their medical records for review. The histological diagnosis of squamous or non-squamous cell carcinoma was based on the criteria of the World Health Organization/International Association for the Study of Lung Cancer classification of lung and pleural tumors (2004) [17]. The research ethics committee of our institute approved this study.

Immunohistochemical Analysis of PD-L1 Expression

Paraffin-embedded tumor tissue was sectioned at a thickness of 4 μm, and the sections were mounted on glass slides for immunohistochemical (IHC) analysis of PD-L1 on a VENTANA BenchMark ULTRA automated staining platform with an UltraView detection kit (Ventana Medical Systems, Tucson, AZ, USA). Briefly, each section was heat treated in Ventana CC1 retrieval solution for 30 min and then incubated for 30 min with rabbit polyclonal antibodies to human PD-L1 (SP263, Ventana Medical Systems). Immune complexes were detected with an UltraView Universal DAB detection kit (Ventana Medical Systems). We scored PD-L1 expression on tumor cell membranes using the following scale: 0, no staining; 1, weak staining; 2, moderate staining; and 3, strong staining. The percentage of tumor cells expressing PD-L1 was calculated and multiplied by the staining score to obtain a semiquantitative H score (maximum value: 300, corresponding to 100% of tumor cells positive for PD-L1 and an overall staining score of 3). We also scored tumor cells expressing PD-L1 as a percentage of all tumor cells and tumor-infiltrating immune cells expressing PD-L1 as a percentage of all cells in the tumor area using previously described methods [10] (tumor cells scored as a percentage of PD-L1-expressing tumor cells [TC3 ≥50%; TC2 ≥5%, but <50%; TC1 ≥1%, but <5%; and TC0 <1%] and tumor-infiltrating immune cells scored as a percentage of PD-L1-expressing cells in the tumor area [IC3 ≥10%; IC2 ≥5%, but <10%; IC1 ≥1%, but <5%; and IC0 <1%]). All IHC images were reviewed by 2 experienced observers (Y.S. and S.R.) blinded to the clinicopathological features, and the mean of the 2 determinations was used for analysis.

Statistical Analysis

Relationships between clinical characteristics and PD-L1 expression were statistically analyzed by the χ^2 test. Variables, including age, gender, smoking status, size of the primary lung cancer lesion, pathological stage, and tumor histology, were entered into Cox proportional models to predict the relative ratios for PD-L1 expression. We performed multivariate analysis based on a stepwise selection. Overall survival (OS) was defined as the time from diagnosis to death from any cause. Kaplan-Meier curves, the log-rank test, and Cox proportional hazards models were used to perform survival analysis. The statistical significance level was set at $p < 0.05$, and all statistical analyses were performed using SPSS software (v23.0; SPSS Inc., Chicago, IL, USA) for Windows.

Results

Patient Characteristics

The characteristics of the 229 patients, consisting of 148 men and 81 women and ranging in age from 37 to 85 years (median: 65 years), are summarized in Table 1. Of these patients, 140 (61%) were current smokers, 130

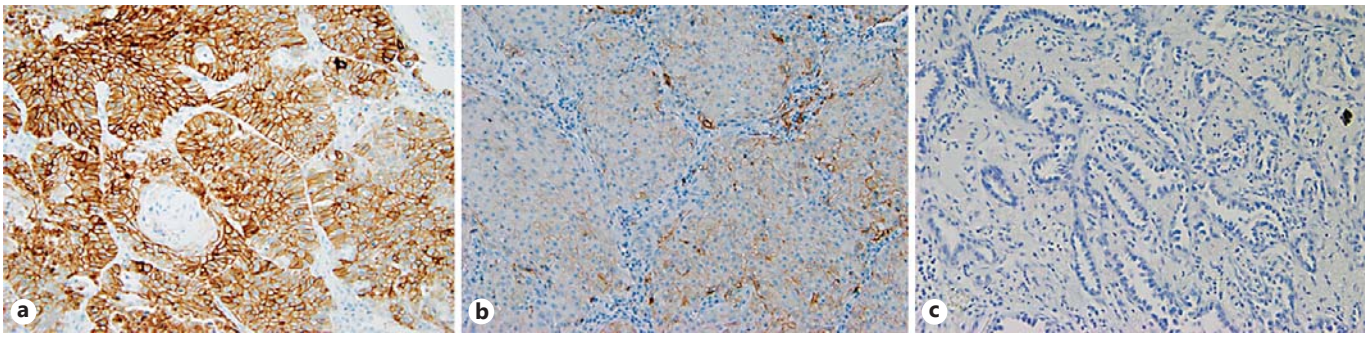

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Fig. 1. Representative images of PD-L1 expression on the cell membranes of tumor cells (×400). **a** H score of PD-L1 expression in tumor cells (300). **b** H score of PD-L1 expression in tumor cells (100). **c** No PD-L1 expression observed.

Table 1. Patient characteristics (n = 229)

Gender	
Male	148
Female	81
Age, years	
Median	65
Range	37–85
Histology	
Squamous	45
Non-squamous	184
Smoking status	
Current smoker	140
Never or former light smoker	89
Size of primary lesion	
<5 cm	196
≥5 cm	33
Pathological stage	
IA/IB	85/45
IIA/IIB	24/25
IIIA/IIIB	45/5
Tumor differentiation	
Well or moderate	176
Poor	53
Adjuvant chemotherapy	
Yes	35
No	194

(57%) had stage I disease, 45 (20%) received a histological diagnosis of squamous cell carcinoma, and 35 received adjuvant chemotherapy.

Correlations between PD-L1 Expression and Clinicopathological Characteristics

IHC staining for PD-L1 was detected on the cell membranes of tumor cells and stromal lymphocytes in surgically resected tumor specimens (Fig. 1). The median H score was 20, and we subsequently used this score as the cutoff point for separating tumors into those exhibiting high or low PD-L1 expression according to a previous method [18]. The relationships between PD-L1 expression and clinicopathological characteristics are summarized in Table 2. We observed that PD-L1 expression was significantly higher in men relative to the levels observed in women (p = 0.039), in squamous cell carcinomas as compared with non-squamous cell carcinomas (p = 0.01), in poorly differentiated tumors as compared with well or moderately differentiated tumors (p = 0.028), and in current smokers as compared with non-smokers or formerly light smokers (p = 0.02). Multivariate analysis revealed that squamous cell carcinoma histology was independently associated with high expression of PD-L1 (hazard ratio [HR]: 2.12, 95% confidence interval [CI]: 1.20–3.76; p = 0.015; Table 3).

Survival Analysis

All patients were included in the survival analysis. The overall follow-up periods ranged from 3 to 129 months (median: 84 months), and the overall 5-year cumulative survival probability was 70%. Because a cumulative survival probability of 50% had not been reached, the overall median survival time (MST) was not determined.

In terms of tumor histology, the 5-year cumulative survival probability was 71% in the non-squamous cell carcinoma group and 53% in the squamous cell carcinoma group, and was significantly lower in the squamous cell carcinoma group (p = 0.026; Fig. 2a).

The 5-year cumulative survival probability was 67% in the high PD-L1 expression group and 68% in the low PD-L1 expression group, with the difference in 5-year cumu-

Table 2. Immunohistochemical staining of NSCLCs for PD-L1 and patient characteristics

Characteristic	Total, *n* (%) (*n* = 229)	PD-L1 expression		*p* value
		high group (*n* = 120)	low group (*n* = 109)	
Gender				
Male	148 (65)	85	63	0.039
Female	81 (35)	35	46	
Median age				
<75 years	199 (87)	102	97	0.37
≥75 years	30 (13)	18	12	
Histology				
Squamous	45 (20)	33	12	0.01
Non-squamous	184 (80)	87	97	
Smoking status				
Current smoker	140 (61)	82	58	0.02
Never or former light smoker	89 (39)	38	51	
Size of primary lesion				
<3 cm	196 (86)	63	49	0.25
≥3 cm	33 (14)	57	60	
<5 cm	196 (86)	105	91	0.39
≥5 cm	33 (14)	15	18	
Pathological stage				
Stage I	130 (57)	63	67	0.17
Stage II/III	99 (43)	57	42	
Tumor differentiation				
Well or moderate	176	85	91	0.025
Poor	53	35	18	
Adjuvant chemotherapy				
Yes	35	15	20	0.22
No	194	77	117	

Table 3. Multivariate analysis of PD-L1 expression in tumor specimens according to patient characteristics

Characteristic		Relative ratio (95% CI)	*p* value
Gender	Male vs. female	Excluded	
Histology	Squamous vs. non-squamous	2.12 (1.20–3.76)	0.01
Smoking status	Current vs. never or former light	Excluded	
Tumor differentiation	Well or moderate vs. poor	Excluded	

lative survival probability according to PD-L1 expression not being significant (Fig. 2b). Similarly, significant differences were not observed in patients with TC3 and IC3 (HR: 1.02; 95% CI: 0.87–1.20; $p = 0.78$), TC2/3 and IC2/3 (HR: 1.02; 95% CI: 0.87–1.19; $p = 0.84$), and TC1/2/3 and IC1/2/3 (HR: 1.03; 95% CI: 0.67–1.59; $p = 0.88$) as compared with patients with TC0 and IC0. The MST of patients with squamous cell carcinoma was 6.8 years, and a cumulative survival probability of 50% had not been reached in patients with non-squamous cell carcinoma.

Univariate analysis revealed that age, smoking status, squamous cell carcinoma histology, tumor differentiation, and pathological stage were significantly associated with OS (Table 4), and multivariate analysis revealed that age, tumor differentiation, and pathological stage were independently associated with OS. In the squamous cell carcinoma group, the MST and 5-year cumulative survival probability according to PD-L1 expression were not significant, but interestingly, the values for both indices appeared lower in the high PD-L1 expression group rela-

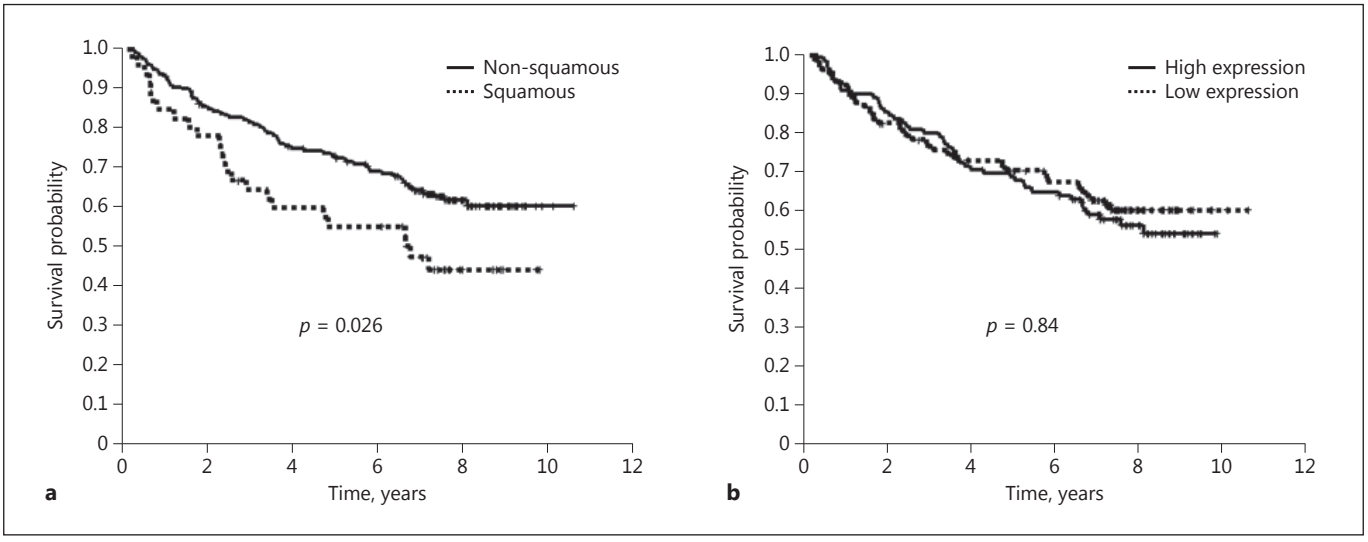

Fig. 2. a Overall survival according to tumor histology. **b** Overall survival according to PD-L1 expression on tumor cells.

tive to those observed in the low PD-L1 expression group (4.9 years/48% in the high PD-L1 expression group vs. 7.2 years/67% in the low PD-L1 expression group, respectively).

Discussion

Our results showed that PD-L1 expression in surgically resected NSCLC was not a prognostic factor, with significantly higher PD-L1 expression and a shorter MST observed in the group of patients with squamous cell carcinoma as compared with levels observed in the group with non-squamous cell carcinoma. To our knowledge, this is the first report of PD-L1 staining of surgically resected tumors using antibodies to human PD-L1 in a SP263 assay. Limited progress has been made in the treatment of advanced squamous NSCLC as compared with non-squamous NSCLC. The MST of patients with squamous cell lung cancer who receive first-line platinum-based chemotherapy is only 10–13 months [19–21], indicating that a new therapeutic strategy is warranted for patients with squamous NSCLC. Recently, a randomized phase III CheckMate 017 trial demonstrated the efficacy and safety of nivolumab as compared with docetaxel in patients with squamous NSCLC that progressed during or after first-line platinum-based chemotherapy, indicating that nivolumab should be considered the standard treatment for squamous NSCLC [14, 22]. Additionally, the Keynote 10 trial showed that pembrolizumab provided a significant survival benefit as compared with docetaxel treatment in patients with non-squamous NSCLC resistant to first-line platinum-based chemotherapy [16]. In that study, the HR of pembrolizumab for the reference arm of docetaxel was 0.74 relative to that observed in patients with squamous cell carcinoma, and although the difference was not statistically significant, the data suggested a survival benefit in patients with squamous disease [16]. Based on the above findings [14, 16, 22], anti-PD-1 antibodies (e.g., nivolumab or pembrolizumab) were recognized as new and indispensable agents, especially for patients with advanced squamous cell lung cancer.

Regarding the correlation between PD-L1 expression and the efficacy of anti-PD1/PD-L1 therapy, previous studies showed higher response rates in tumors exhibiting PD-L1 expression as compared with those lacking PD-L1 expression [15, 23]. Although PD-L1 expression was not revealed as a prognostic factor in our study, 2 of 6 studies of NSCLC showed that it was a negative prognostic factor [24, 25], an additional 2 studies showed that it was a positive prognostic factor [26, 27], and 3 studies showed that it had no prognostic value [28, 29]; therefore, the prognostic relevance of PD-L1 expression in NSCLC is controversial. However, it should be considered that these studies used non-standardized methods to assess PD-L1 expression, including different PD-L1 antibodies and relatively small sample sizes. An adequate pathologi-

Table 4. Predictors of overall survival according to Cox regression model analysis

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
PD-L1 expression				
High H score group	0.90 (0.60–1.35)	0.61		
Low H score group				
Gender				
Male	1.52 (0.97–2.38)	0.069	Excluded	
Female				
Median age				
<75 years	2.41 (1.45–4.00)	0.001	2.68 (1.61–4.46)	0.0002
≥75 years				
Smoking status				
Current smoker	1.60 (1.04–2.48)	0.034	Excluded	
Never or former light smoker				
Histology				
Squamous	1.70 (1.06–2.70)	0.026	Excluded	
Non-squamous				
Tumor differentiation				
Well or moderate	1.45 (1.17–1.81)	0.001	1.29 (1.03–1.62)	0.025
Poor				
Pathological stage				
Stage I	3.08 (2.02–4.72)	0.0002	2.91 (1.88–4.49)	0.0002
Stage II/III				

cal specimen and accurate diagnostic assay for PD-L1 expression are crucial to identifying patients who could benefit from treatment with immune checkpoint inhibitors. Our results suggested that surgically resected specimens are favorable for assessing PD-L1 expression based on sufficient tumor volume and accordingly useful for evaluating whether PD-L1 expression is a potential predictor of the efficacy of anti-PD-1/PD-L1 therapy in the adjuvant setting. Furthermore, fully automated IHC assays have been optimized for the PD-L1 antibodies SP263 and E1L3N (Ventana Medical Systems). Here, we observed that both assays stained PD-L1 on tumor cell membranes and on tumor-associated immune cells, consistent with previous results using other PD-L1 clones [30, 31]. However, a previous study showed that the SP263 assay is superior to the E1L3N assay for detecting PD-L1 expression on tumor cells and/or tumor-associated immune cells, with the SP263 assay resulting in more intense staining of both cell types, as well as generating a broader scoring range, which suggested greater sensitivity [32].

Ultraviolet light and carcinogens in cigarette smoke are generally recognized as causes of high somatic mutations and the development of melanoma and NSCLC, respectively [33, 34]. A large variability in mutation burden within tumor types, ranging from 10 to 1,000 mutations, has been reported [35, 36], with the range particularly broad in NSCLC, because tumors in patients with no history of smoking generally contain fewer somatic mutations as compared with those in smokers [37]. Importantly, a previous study showed that a high mutation burden in tumors was associated with signatures of smoking and higher neoantigen burden, and it was significantly associated with the high efficacy of PD-1 inhibitors [38, 39]. These findings and the results of our study suggest that anti-PD-1/PD-L1 therapy might constitute an effective strategy for the treatment of squamous NSCLC, which is closely based on a history of smoking and high mutation burdens.

There were several limitations to our study. First, because this was a retrospective study performed at a single institution and the sample size of patients with squamous NSCLC was small, the results cannot be regarded as definitive. Second, there were no recurrence-free survival data, and the epidermal growth factor receptor mutation status of each patient was unknown. However, the clinical significance of NSCLC driver mutations, including epidermal growth factor receptor mutations, had not been

standardized in clinical practice during the period from 2002 to 2005. Third, patients were restricted to receiving adjuvant chemotherapy in our study, because adjuvant chemotherapy had not been generally standardized in Japan for patients with surgically resected NSCLC during the period from 2002 to 2005.

In conclusion, our results demonstrated significantly high PD-L1 expression and poor prognosis in patients with surgically resected squamous NSCLC as compared with results for patients with non-squamous NSCLC. Identifying the subset of patients most likely to respond to anti-PD-1/PD-L1 therapy is the first step toward precision medicine.

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Disclosure Statement

The authors have no conflicts of interest to declare.

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Erratum

In the article by Igawa et al., entitled 'Impact of PD-L1 expression in patients with surgically resected non-small-cell lung cancer' [Oncology 2017;92:283–290, DOI: 10.1159/000458412], the VENTANA PD-L1 (SP263) assay is incorrectly described as a polyclonal antibody. As misunderstanding of the type of antibody could lead to inappropriate interpretation of an assay that may be used for a clinical decision, the authors feel it is important that the correct antibody type be described and state that the VENTANA PD-L1 (SP263) assay contains a rabbit monoclonal primary antibody.