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Analysis of soluble programmed death-1 ligand-1 of lung cancer patients with different characteristics

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Abstract. – OBJECTIVE: To analyze the association of soluble programmed death-1 ligand-1 (sPD-L1) levels with clinicopathological characteristics, therapy efficacy, and survival outcomes in lung cancer patients.

PATIENTS AND METHODS: The study included two hundred treatment-naive patients with small cell lung cancer (SCLC) (n=12), and non-small cell lung cancer (NSCLC) (n=188). Plasma samples from 96 healthy individuals and 13 patients with benign tumors served as controls. Enzyme-linked immunosorbent assay (ELISA) was used to evaluate sPD-L1 expression. Blood samples of 67 NSCLC patients before and after therapy were collected.

RESULTS: sPD-L1 expression was significantly higher in lung cancer patients compared to the control groups (p=0.002). Moreover, patients with lower performance status had significantly higher sPD-L1 levels (p=0.005). NSCLC patients at later stages of the disease had greater sPD-L1 levels than those at the early stages (p<0.001). The presence of epidermal growth factor receptor (EGFR) mutation was not significantly different with higher sPD-L1 expression (p=0.334). Although sPD-L1 levels and progression-free survival (PFS) were linked with excellent response to therapy and advancing disease (p=0.307), no correlation was seen between sPD-L1 decrease and progression free survival (PFS).

CONCLUSIONS: Elevated sPD-L1 expression in NSCLC patients was associated with more advanced disease and worse overall health of the patients, suggesting a possible association with a negative clinical response and prognosis. sPD-L1 expression may be influenced by the mutation in EGFR.

Key Words:

Epidermal growth factor receptor, Small cell lung cancer, Lung cancer, Non-small cell lung cancer, Soluble programmed death-1 ligand-1.

Introduction

Lung cancer (LC) is responsible for the majority of cancer-related deaths worldwide. Prior to the development of targeted therapy, advanced non-small cell lung cancer (NSCLC) patients had a median survival of 8-10 months and a 5-year survival rate of 3-5%[1,2]. Although targeted therapies have prolonged the survival of certain gene mutation-positive advanced NSCLC patients to 3-4 years, the resistance to targeted therapeutics remains a challenge in clinical treatment. Patients without driver gene mutations could only rely on conventional treatment methods such as chemotherapy, which has limited benefits on survival[3].

In 2013, ipilimumab, the first immune checkpoint inhibitor drug, was launched in the US market. Through this, lung cancer therapy has been advanced and provided new hope for survival for advanced NSCLC, but the 5-year survival rate of patients treated with immune checkpoint inhibitors remained low at 15%[4]. Clinicians also face difficulties in screening potential immunotherapy populations, predicting the therapeutic effects, and understanding the relationships between driver gene mutations and immunotherapy.

Soluble programmed death-1 ligand-1 (sPD-L1) expression in tumor tissue is a widely used predictor of immunotherapy efficacy in clinical studies, and its soluble form in plasma may also have a predictive value for curative effect and prognosis. However, the limited availability of tumor tissue samples restricts its applicability. Therefore, the aim of the current study was to evaluate and analyze the expression of plasma sPD-L1 in advanced LC patients with different clinical features. Furthermore, we explored the value of sPD-L1 as an indicator of the efficiency of LC therapy, as well as prognosis and diagnosis.

Patients and Methods

The Ethics Committee of Shanxi Cancer Hospital approved the current study (No. 201716, Date: 2017-05-24). Between March 2017 and March

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2019, plasma samples were obtained from 200 treatment-naive LC patients, admitted to Shanxi Cancer Hospital's Respiratory and Critical Care Medicine Department. Of them, 12 had small cell lung cancer (SCLC), and 188 had non-small cell lung cancer NSCLC. Sixty-seven of the NSCLC patients were followed up, and plasma samples were obtained from these patients before and after each standard treatment session. Plasma samples from healthy individuals (n=96) and patients with benign tumors (n=13) served as control. Data on the following clinical features were collected: sex, age, smoking history, histologic subtype, epidermal growth factor receptor (EGFR) mutation status, TNM stage, performance status (PS) score, and carcinoembryonic antigen (CEA) expression. Progression-free survival (PFS) and objective response rate (ORR) were recorded. Using an enzyme-linked immunosorbent assay (ELISA), we quantified sPD-L1 expression in the collected plasma samples and analyzed the pre- and post-treatment changes in sPD-L1 expression in patients with diverse clinical features.

Statistical Analysis

SPSS 22.0 (IBM Corp., Armonk, NY, USA) was used for data analysis. Evaluate the normality of the data using the Shapiro Wilk test. Non normal distribution data is represented by median and interquartile intervals. The Kruskal-Wallis H test was used to compare multiple independent samples; ranks of the original variables were determined using the rank transformation method; pairwise comparisons were performed using the Nemenyi test. Correlation analysis between CEA and mean concentration using Spearman analysis. The Log rank text was used to compare the PFS between different concentration expression groups. Statistical significance was set at P=0.05.

Results

sPD-L1 Expression Level

The LC group of patients had significantly higher sPD-L1 expression [2.43(0.94, 4.01)ng/mL] compared to healthy individuals [1.56(1.37, 2.18) ng/mL] and patients with benign tumors [0.98(0.82, 2.38) ng/mL], respectively (p=0.002) (Table I).

Correlation between sPD-L1 Expression and Clinical Features

As shown in Table II, sPD-L1 expression positively correlated with poor functional status [3.28(1.99, 8.23) for PS≥2 *vs.* 2.40(0.90, 3.80) ng/mL for PS<2, p=0.005] of lung cancer patients. No substantial interrelation was observed with age, smoking history, and sex (p>0.05) (Table II). Patients with adenocarcinoma, squamous cell carcinoma, NSCLC-NOS,

Table I. Differences in mean concentration among the treatment-naïve, healthy and benign tumour groups.

Group	No. of subjects	M (IQR)	Mean rank	χ^2	p
Treatment-naïve	200	2.43 (0.94, 4.01)	167.96	12.680	0.002
Healthy	96	1.56 (1.37, 2.18)	133.95*		
Benign tumour	13	0.98 (0.82, 2.38)	111.08*		

*p < 0.05 compared with the treatment-naïve group. The Kruskal-Wallis H test was used to compare multiple independent samples; ranks of the original variables were determined using the rank transformation method; pairwise comparisons were performed using the Nemenyi test.

Table II. Relationships between basic patient characteristics and mean concentration.

Variable	Subgroup	No. of patients	M (IQR)	Mean rank	Z	p
Sex	Male	141	2.26 (0.85,3.78)	96.88	-1.366	0.172
	Female	59	2.70 (1.20,4.22)	109.14		
Age	<60 years	114	2.46 (0.90,4.07)	99.81	-0.055	0.956
	≥60 years	85	2.40 (1.16,3.92)	100.26		
Smoking history	Yes	125	2.43 (0.94,3.80)	100.64	-0.043	0.966
	No	75	2.43 (0.95,4.10)	100.27		
PS score	< 2 points	181	2.40 (0.90,3.80)	96.76	-2.819	0.005
	≥ 2 points	19	3.28 (1.99,8.23)	136.11		

The Wilcoxon rank sum test was used to compare the results of two independent samples.

and SCLC showed no statistically significant correlation between sPD-L1 expression and histologic subtype ($p>0.05$) (Table III).

Mean sPD-L1 expression levels in the various stages of LC were also measured (Table IV). There was a positive statistically significant correlation between sPD-L1 expression and more advanced cancer stages ($p<0.001$).

As shown in Table V, sPD-L1 expression was higher in LC patients carrying EGFR mutation [2.44(0.85, 3.97) ng/mL *vs.* 1.26(0.99,1.99) ng/mL, respectively], however, this difference was not statistically significant ($p=0.334$) (Table V). There was no significant association of sPD-L1 levels with CEA in adenocarcinoma patients (Table VI).

Correlation between sPD-L1 and Clinical Response

Non-progressive disease (non-PD) lung cancer patients had not significantly different decrease in sPD-L1 expression than patients with progressive disease [-0.49(-0.76, -0.08) ng/mL *vs.* -0.11(-0.56, 0.24) ng/mL, $p=0.307$ respectively] (Table VII). Consequently, there was no statistically significant difference in PFS time between different sPD-L1 expression groups (Table VIII & Figure 1).

Discussion

Our study found that the sPD-L1 expression in NSCLC patients was considerably greater than in healthy persons and patients with benign tumors. In NSCLC patients, sPD-L1 expression correlated with the PS score and TNM stage but not with sex, age, or smoking history. Patients with lower functional status and more advanced N and M phases had higher sPD-L1 expression levels. However, no definitive link was found between sPD-L1 downregulation and either treatment efficacy or PFS. Moreover, sPD-L1 levels in adenocarcinoma patients did not correlate with CEA.

Monocytes and dendritic cells are the primary cell types that express the transmembrane protein PD-L1[5]. However, as PD-L1 expression is also triggered by pro-inflammatory cytokines [such

Table III. Relationship between histologic characteristics of patients and mean concentration.

Variable	Subgroup	No. of patients	Mean ± standard deviation	Mean rank	χ^2	p
Histologic subtype	Adenocarcinoma	126	2.89 ± 2.70	101.46	0.459	0.928
	Squamous cell carcinoma	57	3.39 ± 3.66	98.23		
	SCLC	12	3.26 ± 2.65	106.25		
	NSCLC-NOS	5	2.15 ± 1.36	88.40		

The Kruskal-Wallis H test was used to analyse the differences between several different samples.

Table IV. Relationships of cancer stages of patients with mean concentration.

Variable	Subgroup	No. of patients	M (IQR)	Mean rank	χ^2	p
T stage	$T1_{(1)}$	25	1.24 (0.60, 2.50)	70.36	18.260	< 0.001
	$T2_{(2)}$	50	1.41 (0.66, 3.31)	83.87		
	$T3_{(3)}$	36	2.57 (1.14, 3.92)	103.71†		
	$T4_{(4)}$	89	2.88 (1.84, 5.22)	117.01†,‡,§		
N stage	$N0_{(1)}$	36	0.90 (0.44, 2.64)	64.21	19.268	< 0.001
	$N1_{(2)}$	19	2.61 (1.27, 3.78)	104.11†		
	$N2_{(3)}$	67	2.21 (0.92, 4.36)	101.92†		
	$N3_{(4)}$	78	2.95 (1.68, 4.37)	115.15†		
M stage	M0	90	1.37 (0.60, 3.13)	78.72	-4.814	< 0.001
	M1	110	2.90 (1.86, 4.56)	118.32		
TNM stage	$I_{(1)}$	15	0.42 (0.33, 1.55)	43.67	30.537	< 0.001
	$II_{(2)}$	16	1.04 (0.44, 2.65)	64.81		
	$III_{(3)}$	51	2.01 (0.75, 4.02)	91.77†,‡		
	$IV_{(4)}$	118	2.78 (1.70, 4.56)	116.33†,‡,§		

† $p < 0.05$ compared with (1). ‡ $p < 0.05$ compared with (2). § $p < 0.05$ compared with (3). The Kruskal-Wallis H test was used to compare multiple independent samples; pairwise comparisons were performed using the Nemenyi test. The Wilcoxon rank sum test was used to compare the results of two independent samples.

Table V. Differences in concentration between EGFR mutation status and median concentration.

Variable	Subgroup	No. of patients	M (IQR)	Mean rank	Z	p
EGFR mutation status	Mutated Wild-type	18 12	2.44 (0.85, 3.97) 1.26 (0.99, 1.99)	24.21 20.45	-0.966	0.334

Wilcoxon rank sum test compared two independent samples.

as Interferon-gamma (IFN-γ)], it is abundantly expressed on the surface hematopoietic, non-hematopoietic, and tumor cells[5-8]. PD-1, a receptor of PD-L1, is expressed in monocytes, activated T cells, natural killer (NK), and B cells. Studies[5,9] show that PD-L1/PD-1 binding suppresses T cell activation in response to major histocompatibility complex (MHC) antigens. PD-L2 is another ligand[10,11] that binds to PD-1 with stronger affinity compared to PD-L1. Nonetheless, its manifestation is mostly confined to antigen-presenting cells (APCs)[5-8]. Therefore, antigen-sensitized effector T cells are critically regulated by PD-1 and PD-L1. Reduced T cell proliferation, decreased cytokine release, and suppression of cytotoxic effects are the outcomes of the interaction between PD-1 that is produced by activated T cells, PD-L1, and PD-L2, expressed by various cells in peripheral tissues. Although this mechanism prevents an excessive and damaging immune response[5,12,13], it is also exploited by tumors to evade attacks by the immune system[14]. Numerous studies[15,16] suggest a link between high PD-L1 expression and a worse prognosis in a wide variety of tumors. Current studies show that the use of monoclonal antibody therapies that specifically target the PD-1/PD-L1 pathway is associated with a 20% and 40% increase in T cell-mediated antitumor effect and objective response rates (ORRs), respectively[17-19].

Soluble forms of PD-1 and PD-L1 (sPD-1/sPD-L1) have been found20 in various cancers.

Table VI. Relationship between CEA and mean concentration.

Variable	CEA	
	r	p
Mean concentration	0.182	0.287

Spearman correlation analysis was performed.

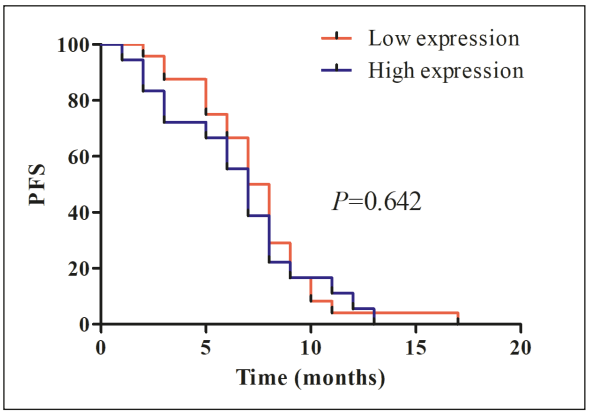

Figure 1. PFS of low and high expression of sPD-L1.

Table VII. Differences in concentration between the therapeutic effect.

Therapeutic effect	No. of patients	M (IQR)	Mean rank	Z	p
Non-PD PD	108 16	-0.49 (-0.76, -0.08) -0.11 (-0.56, 0.24)	61.23 71.06	-1.021	0.307

Wilcoxon rank sum test compared two independent samples.

Table VIII. Comparison of PFS between different sPD-L1 expression groups.

Therapeutic effect	No. of patients	PFS (95% CI)	Logrank χ^2	p
Low expression High expression	62 62	7.2 (5.933-8.067) 7.0 (5.649,8.351)	0.217	0.642

The Log rank text was used to compare the PFS between different concentration expression groups.

Therefore, levels of sPD-1/sPD-L1 in the blood may serve as potential biomarkers for the prediction of the biological characteristics of malignant tumors, therapeutic effects of treatments, and patient survival[20,21]. High sPD-L1 levels are associated with worse prognosis in diffuse large B-cell lymphoma, multiple myeloma, and the development of renal cancer patients[22-24]. Recent meta-analyses[25,26] show that high sPD-L1 expression is linked to poor OS in patients with hematological neoplasms and solid tumors. A study[27] on 22 NSCLC patients receiving PD-L1/PD-1 inhibitor treatment, found no link between the PD-L1 expression in tumor tissue and the levels of sPD-L1. The NSCLC patients with low sPD-L1, particularly those with adenocarcinoma, had better overall survival (OS) compared to patients with higher sPD-L1 expression. Patients with high plasma levels of sPD-L1, as evaluated by ELISA, had a substantially shorter OS than those with lower levels (13.1 months *vs.* 20.4 months, respectively, p=0.037). Twenty patients with NSCLC treated with thoracic radiation showed[28] comparable outcomes; those with a lower baseline sPD-L1 level had a longer OS than those with a higher level (27.8 months *vs.* 15.5 months, respectively, p=0.005).

An *in vitro* study[29] reported that cytokine-activated mature dendritic cells produced sPD-L1. Several studies[25,30] showed that PD-L1-expressing cancer cells or immune cells in humans may produce sPD-L1. However, the exact mechanism by which sPD-L1 is produced, and its clinical significance remain unclear. Furthermore, there are many splice variants of PD-L1, and the PD-L1 variant lacking the IgV domain is likely neither secreted nor functional[31]. It is possible that ELISA, a currently used method of sPD-L1 measurement, is unable to effectively detect and discriminate between sPD-L1 variants. Therefore, additional research is needed to accurately assess the clinical importance of sPD-L1.

Elevated sPD-L1 expression is linked to the presence of EGFR mutations in surgically resected NSCLC tissues and correlates with poor prognosis[28]. In certain studies[32,33], PD-1/L1 inhibitors failed to show clinical benefits in EGFR-mutated NSCLC patients, but the underlying mechanisms have not been elucidated. Yoshida et al[34] reported that nivolumab therapy was highly effective for certain patients with EGFR mutation-positive NSCLC. Our data showed that patients with EGFR mutations had higher sPD-L1 expression levels than those with wild-type EGFR, even though this difference was not statistically significant. However, further studies with larger sample sizes and longer post-therapy follow-ups are needed to determine the clinical importance of sPD-L1 for diagnosing and treating patients with EGFR mutations.

Conclusions

The results of this study show that higher levels of sPD-L1 expression are linked to more advanced tumor stages and worse functional status of LC patients, which may be suggestive of poorer progression and therapeutic response. The presence of EGFR mutations may influence sPD-L1 expression, but its application as a molecular marker in the treatment and prognosis evaluation of lung cancer patients requires further investigation.

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Data Availability
The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Conflict of Interest
The authors declare that they have no competing interests.

Ethics Approval
The study was approved by the Ethics Committee of Shanxi Cancer Hospital (No. 201716, Date: 2017-05-24).

Informed Consent
Patient informed consent was waived because of the retrospective nature of the study.

Authors' Contributions
XS and HZ conceived and designed the study.
HZ collected the data and performed the analysis.
HZ was involved in writing the manuscript of the study.
XS was responsible for the integrity of the study.
All authors have read and approved of the final manuscript.

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