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High plasma levels of soluble programmed cell death ligand 1 are prognostic for reduced survival in advanced lung cancer☆

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ABSTRACT

Objectives: Programmed cell death-ligand 1 (PD-L1) expressed in tumor tissues is a key molecule for immune suppression, given its role in immune checkpoints. The significance and implication of soluble PD-L1 (sPD-L1) in the blood of lung cancer patients remain unknown.
Patients and methods: Blood samples were prospectively collected from patients with advanced lung cancer, and the plasma sPD-L1 concentrations were measured by enzyme-linked immunosorbent assay. The correlations of the plasma sPD-L1 levels with clinico-pathological status, laboratory data, and survival of the patients were analyzed.
Results: Ninety-six patients with advanced lung cancer were analyzed, including 73 with adenocarcinoma, 12 with squamous cell carcinoma, and seven with small-cell lung cancer. Sixty-five were naïve to chemotherapy, and 20 had received two or more lines of chemotherapy. The mean plasma sPD-L1 concentration of all the patients was 6.95 ± 2.90 ng/ml (range 2.30–20.0 ng/ml), and this value is significantly increased compared with that previously reported for normal subjects. No correlation of the plasma sPD-L1 level with histological subtypes, adenocarcinoma genetic status, smoking history, clinical stage or laboratory data was found. However, overall survival was significantly reduced in patients with high (≥7.32 ng/ml) compared with low (<7.32 ng/ml) plasma sPD-L1 levels (13.0 vs. 20.4 months, p = 0.037). Multivariate analysis revealed that high sPD-L1 levels were significantly related to poor prognosis (hazard ratio 1.99, p = 0.041).
Conclusion: High plasma sPD-L1 levels were associated with poor prognosis in patients with advanced lung cancer, possibly associated with suppression of anti-tumor immunity.
Clinical trial register and their clinical registration number: UMIN%000014760

1. Introduction

Lung cancer is a leading cause of cancer-related deaths worldwide and has a poor prognosis, with five-year survival rates that are below 50% in patients with early-stage cancer and are less than 5% in patients with advanced-stage cancer [1]. Recent progress in molecular targeted therapies for the oncogenic driver mutations of advanced non-small cell lung cancer (NSCLC) has improved the prognosis in patients with tumors that express the appropriate molecular targets for the inhibitory agents [2]. However, most advanced lung cancer patients do not have molecular aberrations targeted by the available agents, thus indicating the need for discovering novel agents or establishing new concepts for molecular targeted therapy.

Abbreviations: ALK, anaplastic lymphoma kinase; CTLs, cytotoxic T lymphocytes; DLBCL, diffuse large B-cell lymphoma; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; mAb, monoclonal antibody; NSCLC, non-small cell lung cancer; non-SQC, non-squamous cell lung cancernon; PD-1, programmed cell death-1; PD-L1, programmed cell death ligand-1; R-CHOP, rituximabcyclophosphamide anthracycline vincristine and prednisone; RCC, renal cell carcinoma; RA, rheumatoid arthritis; PD-L1, soluble form of PD-L1; SQC, squamous cell lung cancer.

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Table 1
Baseline demographic and clinical characteristics of patients.

Patients characteristics	Number of patients (n = 96)	(%)
Age		
Median [year, range]	68.5	–
<75	[29–86]	75.0
≥75	72	25.0
	24	
Sex		
Male	54	56.3
Female	42	43.7
PS		
0–1	54	56.3
≥2	42	43.7
Histological subtypes		
Non-small cell carcinoma	81	84.4
Adenocarcinoma	73	76.1
Squamous cell carcinoma	7	7.3
Large-cell carcinoma	1	1.0
Small-cell carcinoma	15	15.6
Genetic status in adenocarcinoma	73	100.0
EGFR-wt, ALK rearrangement	51	69.9
negative	19	26.0
EGFR-mutation	3	4.1
ALK rearrangement		
Clinical stage		
IIIB	6	6.3
IV	75	78.1
M1a (without distance metastasis)	9	9.5
M1b (metastasis)	66	68.6
recurrence	15	15.6
Smoking history		
No/light (Brinkmann index < 400)	36	37.5
Previous heavy smoker	60	62.5
Previous history of radiotherapy		
Yes	45	46.9
No	51	53.1
Lines of chemotherapy		
0	65	67.7
≥1	31	32.3
Use of steroid		
Yes	9	9.4
No	87	90.6

Laboratory Data	Median, [range]
White blood cell counts (/μL)	7400 [1900–164000]
Absolute neutrophil counts (/μL)	5170 [810–29290]
Lymphocyte counts (/μL)	125 [10.2–3600]
Albumin (g/mL)	3.55 [1.3–4.9]
Lactate dehydrogenase (IU/L)	240 [133–2146]
C-reactive protein (mg/dL)	0.9 [0.03–25.96]
Soluble form of programmed cell death-1 (ng/ml)	6.95 [2.2–20]

n, number; PS, performance status; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase.

Immunotherapy based on immune checkpoint blockade has opened a new era in cancer treatment [3]. Antibody-mediated blockade of the interaction between programmed cell death-1 (PD-1) on activated cytotoxic T lymphocytes (CTLs) and programmed cell death ligand 1 (PD-L1) on tumor cells, which inactivates the tumoricidal activity of CTLs thus allows tumor cell immune evasion, has exhibited significant clinical efficacy in several types of cancer, including advanced NSCLC [4]. Nivolumab, which is a humanized monoclonal antibody (mAb) to human PD-1, has become a standard second-line treatment for both squamous cell lung cancer (SQC) [5] and non-squamous cell lung cancer (non-SQC) [6]. Pembrolizumab, another type of mAb to human PD-1, has also exhibited significant antitumor activity to NSCLC [7]. However, despite occasional marked tumor regression by anti-PD-1 mAb treatment, the response rate of anti-PD-1 mAb therapy in lung cancers is limited at present. PD-L1 expression in tumor tissue could predict the effectiveness of anti-PD-1 mAb therapy [8], but the existence of a number of exceptional cases has resulted in great controversy [9].

Accordingly, the identification of certain biomarkers that predict the clinical efficacy of anti-PD-1 mAb therapy is urgently required. Furthermore, establishing effective combined therapies with immune checkpoint blockade therapy is needed for improved clinical benefit [10].

It has been suggested that soluble form of PD-L1 (sPD-L1) is involved in tumor-associated immune suppression and the resultant poor prognosis [11,12]. A phase III trial of rituximab, cyclophosphamide, anthracycline, vincristine, and prednisone (R-CHOP) combination chemotherapy in patients with CD20 positive diffuse large B-cell lymphoma (DLBCL) revealed that a sPD-L1 plasma concentration ≥1.52 ng/ml was a predictor of poor prognosis and that 30% of the patient cohort had high sPD-L1 plasma levels [12]. In patients with clear cell renal cell carcinoma (RCC), PD-L1 expression in tumor tissue indicates poor prognosis [13,14] and elevated sPD-L1 serum levels eliciting immune suppressive activity are associated with the poor prognosis of RCC [11]. In addition, sPD-L1 was reported to be associated with clinical characteristics of NSCLC [15]. This study prospectively investigated sPD-L1 plasma levels in advanced lung cancer patients and investigated the association between the plasma sPD-L1 levels and the clinicopathological features.

2. Patients and methods

2.1. Patients

Blood samples and clinical information were prospectively collected from patients who had been histologically or cytologically diagnosed as advanced lung cancer or postsurgical recurrent lung cancer at the Tokyo Metropolitan Cancer and Infectious diseases Center Komagome Hospital (Tokyo, Japan) between August 2014 and March 2016.

The study protocol was approved by the Ethics Committee of the Tokyo Metropolitan Cancer and Infectious diseases Center Komagome Hospital (#1469) and The Jikei University School of Medicine (26-212 7717) and conducted in accordance with the Declaration of Helsinki and the REMARK guidelines [16]. The study was registered with UMIN Clinical Trials Registry (ID: UMIN 000014760).

2.2. Sample collection, procedure, and restoration

Plasma was collected from 96 patients with advanced lung cancer before the initiation of any line of chemotherapy or undergoing best supportive care at least three or four weeks after the last chemotherapy. Blood was collected into tubes containing potassium EDTA (5 mL, Terumo Venogect II, Tokyo, Japan) and centrifuged at 1000 rpm at 4 °C for 10 min within 30 min after collection. Plasma samples were stored in 1000 μL aliquots at −80 °C.

2.3. Analysis of sPD-L1

The plasma sPD-L1 concentrations were measured using an enzyme-linked immunosorbent assay kit for programmed cell death protein 1 ligand 1 (Cloud-Clone Corp. Houston, TX, USA) according to the manufacturer's protocol. The minimum detectable concentration of sPD-L1 was 0.117 ng/ml, and the quantitative range was 0.312–20 ng/ml. Each sample was analyzed in duplicate.

2.4. Patient data acquisition

The following clinical factors of lung cancer patients were examined: age, sex, tumor stage (UICC classification 7th edi-