CANCER DIAGNOSIS & PROGNOSIS
2: 324-329 (2022) doi: 10.21873/cdp.10112

Association of Tumor PD-L1 Expression With Time on Treatment Using EGFR-TKIs in Patients With EGFR-Mutant Non-small Cell Lung Cancer

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Abstract. *Background/Aim: The association between tumor PD-L1 expression and the rate of acquisition of the T790M mutation during treatment with first-/second-generation epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) is a matter of study. This retrospective study was conducted to evaluate the association of tumor PD-L1 expression with the time on treatment under EGFR-TKIs in patients with EGFR-mutant non-small cell lung cancer (NSCLC), treated with first-/second-generation EGFR-TKIs. Patients and Methods: We conducted a retrospective review of the medical charts of patients with EGFR-mutant NSCLC treated with first- /second-generation EGFR-TKIs. Time on treatment with EGFR-TKIs was defined as the sum of progression-free survival period (PFS) from the start of treatment with first- /second-generation EGFR-TKIs and the PFS from the start of osimertinib treatment after acquisition of the T790M mutation. Tumor PD-L1 expression was evaluated using the 22C3 antibody. Results: Data of a total of 49 patients were analyzed, including 20 patients with negative tumor PD-L1 expression (tumor proportion score <1%) and 29 patients with positive tumor PD-L1 expression (tumor proportion score ≥1%). In the negative tumor PD-L1 expression group, the T790M mutation was detected in 12 (75%) of the 16 patients. In the positive tumor PD-L1 expression group, the T790M mutation was detected 6 (31.6%) out of the 19 patients in whom it was tested. The median (95% confidence interval) time on treatment with EGFR-TKIs was 21.7 (12.9-24.8) months and 12.3 (5.6-22.2) months in the negative and positive tumor PD-L1 expression groups, respectively. Analysis using a Cox proportional hazards model identified performance status and presence/absence of tumor PD-L1 expression as significantly associated with the time on treatment with EGFR-TKIs. Conclusion: EGFR-mutant NSCLC patients with negative tumor PD-L1 expression showed a higher rate of acquisition of the T790M mutation and implementation rate of osimertinib therapy, leading to a longer time on treatment with EGFR-TKI.*

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Key Words: Epidermal growth factor receptor, lung cancer, T790M, prognosis, programmed death ligand-1.

Clinical trials have shown that EGFR-mutant non-small cell lung cancer (NSCLC) patients treated with epidermal growth factor-tyrosine kinase inhibitors (EGFR-TKIs) show significantly longer progression-free survival periods (PFS) compared to those treated with cytotoxic agents (1, 2); an observational study also showed significantly longer overall survival periods in EGFR-mutant NSCLC patients treated with EGFR-TKIs than in those not treated with EGFR-TKIs (3). However, patients receiving treatment with EGFR-TKIs eventually develop resistance to EGFR-TKIs, and acquisition of the EGFR exon 20 T790M mutation is one of the main mechanisms of development of resistance to EGFR-TKIs in patients receiving first-generation EGFR-TKIs (4).

It has been shown that osimertinib, a third-generation EGFR-TKI, can overcome the EGFR-TKI resistance that develops with the acquisition of the T79M mutation and confer long survivals in patients with EGFR-mutant NSCLC

(5). On the other hand, osimertinib is also an important treatment choice for previously untreated patients with EGFR-mutant NSCLC, as it yields a longer overall survival compared to first-generation EGFR-TKIs (6). Although sequential therapy with osimertinib after acquisition of the T790M mutation conferred a relatively long survival (7), no methods have been established yet for predicting acquisition of the T790M mutation.

Programmed death ligand-1 (PD-L1) is an immune checkpoint molecule involved in inactivating T cells. Recent studies have reported the existence of an association between tumor PD-L1 expression and the rate of acquisition of the T790M mutation during treatment with first-/second-generation EGFR-TKIs, and tumors with negative or low expression levels of PD-L1 showed a higher acquisition rate of the T790M mutation (8-10). Therefore, the tumor PD-L1 expression status might be associated with the clinical outcome in patients with EGFR-mutant NSCLC via influencing the acquisition rate of the T790M mutation. This retrospective study was conducted to evaluate the associations of the tumor PD-L1 expression status and acquisition rate of the T790M mutation with the time on treatment with EGFR-TKIs.

Patients and Methods

Patient samples. The present study was conducted with the approval of the Ethics Committee of the University of Toyama (approval number: R2019103). The need to obtain informed consent from the subjects was waived due to the retrospective nature of the study; therefore, only information about the study was disclosed to the subjects.

We reviewed the medical charts of the subjects and analyzed the patient data. The study inclusion criterion was patients with cytologically or histologically diagnosed EGFR-mutant NSCLC who had received treatment with first-/second-generation EGFR-TKIs (gefitinib, erlotinib, or afatinib) between 2007 and 2021. Patients who had received combined first- generation EGFR-TKI plus vascular endothelial growth factor (VEGF) inhibitor therapy and patients with recurrent disease after surgical resection, radiation, or chemoradiation were also included. Patients with uncommon EGFR mutations and patients in whom any necessary information, including on the tumor PD-L1 expression status, was not available were excluded. Patient background characteristics, such as the age, performance status (PS), and presence/absence of brain metastasis were evaluated at the time of initiation of EGFR-TKI therapy. The EGFR mutation of exon 19 deletion and insertion was addressed as exon 19 deletion. The tumor PD-L1 expression status was evaluated by determining the tumor proportion score (TPS) using the 22C3 antibody. Presence of the T790M mutation was evaluated by Cobas ver. 2 polymerase chain reaction testing in histopathological specimens, plasma, pleural fluid, or cerebrospinal fluid.

Statistical analysis. The primary endpoint was the time on treatment with EGFR-TKIs, which was defined as the sum of the progression-free survival period (PFS) from the start of treatment with first-/second-generation EGFR-TKIs and the PFS from the start of osimertinib treatment after acquisition of the T790M mutation. PFS was calculated from the initiation of treatment with EGFR-TKIs until progressive disease was identified according to the Response Evaluation Criteria in Solid Tumors version 1.1 and/or clinical judgement of disease progression (hereinafter referred to as "progression"). If the treatment was changed because of the emergence of adverse events in the absence of progression, PFS was censored at the initiation of the subsequent treatment. However, change of the treatment among first-/second-generation EGFR-TKIs in the absence of progression was regarded as a series of the treatment, and the data were not censored for calculation of the PFS.

Patients were divided according to categorical variables or the median levels. Survival curves were drawn by the Kaplan-Meier method. Log-rank test was performed to compare the times on treatment with EGFR-TKIs. A Cox proportional hazards model was performed to analyze the association between the tumor PD-L1 expression status and the time on treatment with EGFR-TKIs, after adjusting for variables that were found to show significant associations ($p<0.05$) in the log-rank test. Statistical analysis was performed using JMP ver. 15.0.0 (SAS, Cary, NC, USA).

Results

Table I shows the patient characteristics. Data of a total of 49 patients were analyzed. Nine patients had a history of surgical resection and 4 patients had a history of radiotherapy (chemoradiation: 3 patients, stereotactic radiotherapy: 1 patient). EGFR-TKI therapy was initiated as the first-line treatment in 44 patients and as second- or further-line treatment after primary treatment in 5 patients. Five patients received combined first-generation EGFR-TKI plus VEGF inhibitor therapy (erlotinib plus bevacizumab therapy). The PD-L1 TPS was <1% (PD-L1-negative) in 20 patients and ≥1% (PD-L1-positive) in 29 patients. The proportion of females, patients with PS of ≥1, and patients with a history of radiation therapy was higher in the negative tumor PD-L1 expression group, and the proportion of patients with non-adenocarcinoma histology was higher in the positive tumor PD-L1 expression group.

Acquisition rate of the T790M mutation. In the PD-L1-negative group, disease progression was confirmed in 16 of 20 patients during treatment with first-/second-generation EGFR-TKIs. Of the 16 patients, 12 (75%) were found to have acquired the T790M mutation. In the positive tumor PD-L1 expression group, progression was confirmed in 22 of 29 patients during treatment with first-/second-generation EGFR-TKIs. Of these, PCR testing for the T790M mutation was performed in 19 patients, and 6 of the 19 (31.6%) patients were found to have acquired the T790M mutation ($p=0.018$, Fisher's exact test). All 18 patients identified to be positive for the T790M mutation received osimertinib therapy.

PFS and time on treatment with EGFR-TKIs. The median (95% confidence interval [CI]) PFS after the start of treatment with first-/second-generation EGFR-TKIs was 11.2

Table I. *Patient characteristics*.

		Whole 49	PD-L1<1% 20	PD-L1≥1% 29	*p*-Value
Age (years)	<75	37 (75.5%)	15 (75.0%)	22 (75.9%)	1.000
	≥75	12 (24.5%)	5 (25.0%)	7 (24.1%)	
Sex	Male	22 (44.9%)	7 (35.0%)	15 (51.7%)	0.381
	Female	27 (55.1%)	13 (65.0%)	14 (48.3%)	
PS	0	21 (42.9%)	7 (35.0%)	14 (48.3%)	0.394
	≥1	28 (57.1%)	13 (65.0%)	15 (51.7%)	
Histology	Adenocarcinoma	46 (93.9%)	20 (100%)	26 (89.7%)	0.260
	Others	3 (6.1%)	0	3 (10.3%)	
EGFR mutation	del 19	21 (42.9%)	8 (40.0%)	13 (44.8%)	0.777
	L858R	28 (57.1%)	12 (60.0%)	16 (55.2%)	
Brain metastasis	Local therapy (–)	3 (6.1%)	0	3 (10.3%)	0.354
	Local therapy (+)	14 (28.6%)	7 (35.0%)	7 (24.1%)	
	No metastasis	32 (65.3%)	13 (65.0%)	19 (65.5%)	
History of RT	Yes	4 (8.2%)	3 (15.0%)	1 (3.4%)	0.291
	No	45 (91.8%)	17 (85.0%)	28 (96.6%)	
History of surgery	Yes	9 (18.4%)	3 (15.0%)	6 (20.7%)	0.720
	No	40 (81.6%)	17 (85.0%)	23 (79.3%)	
EGFR-TKI treatment line	1	44 (89.8%)	18 (90.0%)	26 (89.7%)	1.000
	≥2	5 (10.2%)	2 (10.0%)	3 (10.3%)	
VEGF inhibitor	Yes	5 (10.2%)	3 (15.0%)	2 (6.9%)	0.387
	No	44 (89.8%)	17 (85.0%)	27 (93.1%)	

EGFR-TKI, Epidermal growth factor receptor-tyrosine kinase; PD-L1, programmed death ligand-1; PS, performance status; RT, radiotherapy; VEGF, vascular endothelial growth factor.

(9.1-13.2) months in the 49 patients, and the median (95% CI) PFS after the start of osimertinib treatment was 9.5 (4.9-15.8) months in the 18 patients who were detected to have acquired the T790M mutation.

The median (95% CI) of time on treatment with EGFR-TKIs was 21.7 (12.9-24.8) months in the 20 patients with negative tumor PD-L1 expression, and 12.3 (5.6-22.2) months in the 29 patients with positive tumor PD-L1 expression (Figure 1, p=0.107, log-rank test). The median (95% CI) time on treatment with EGFR-TKIs was 24.8 (19.6-30.3) months in the 18 patients who were found to be positive for the T790M mutation.

Analysis by the log-rank test showed that the PS and tumor histology were significantly associated with the time on treatment with EGFR-TKIs (Table II). Analysis using a Cox proportional hazards model with adjustments for the PS and tumor histology conducted to assess the association between tumor PD-L1 expression status and time on treatment with EGFR-TKIs identified the PS and tumor PD-L1 expression status as being significantly associated with the time on treatment with EGFR-TKIs (Table III).

Discussion

The present study showed that EGFR-mutant NSCLC patients with negative tumor PD-L1 expression showed a higher rate of acquisition of the T790M mutation during treatment with first-/second-generation EGFR-TKIs, consistent with previous reports (8-10). Furthermore, time on treatment with EGFR-TKIs was longer in patients with negative tumor PD-L1 expression. PFS after the start of first-/second-generation EGFR-TKIs and from the start of osimertinib treatment after acquisition of the T790M mutation observed in the present study were similar to those reported from previous clinical trials (1, 2, 5).

While the mechanisms underlying the association between the tumor PD-L1 expression status and acquisition of the T790M mutation remain unclear, involvement of the dependence of cell proliferation on EGFR signaling has been proposed. It has been suggested that low tumor PD-L1 expression might be associated with a less immunogenic nature of EGFR-mutant NSCLC and a higher likelihood of acquisition of resistance in the EGFR pathways. On the other hand, it has been reported that many oncogenes mediate tumor PD-L1 expression. Thus, high tumor PD-L1 expression in EGFR-mutant NSCLC might be a result of both EGFR mutation and other oncogene alterations, so that acquisition of resistance could also occur independently of EGFR signaling (9).

As mentioned above, it was suggested that tumor PD-L1 expression might be associated with the dependence of cell proliferation on EGFR signaling (9). Furthermore, it has been reported that poor tumor cell differentiation, advanced

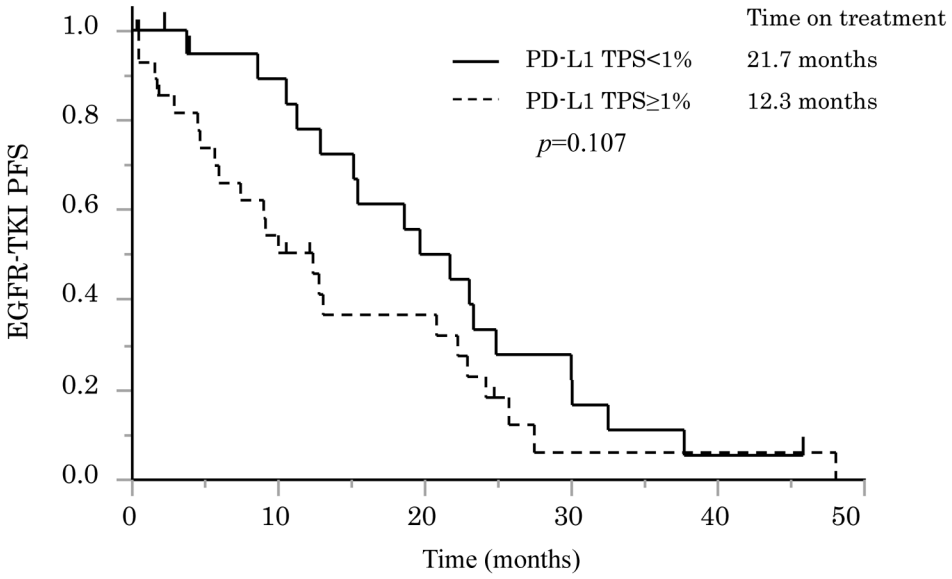

Figure 1. *Kaplan-Meier curve to determine the time on treatment with EGFR-TKIs, defined as the sum of the PFS after the start of treatment with first-/second-generation EGFR-TKIs and the PFS from the start of osimertinib treatment after acquisition of the T790M mutation. Solid line: patient group with negative tumor PD-L1 expression (tumor proportion score <1%); dashed line: patient group with positive tumor PD-L1 expression (tumor proportion score ≥1%). EGFR-TKI, Epidermal growth factor receptor-tyrosine kinase; PD-L1, programmed death ligand-1; PFS, progression-free survival.*

TNM stage, and shorter survival were associated with higher PD-L1 expression (11). These suggest that tumor PD-L1 expression may be a clinical biomarker. On the other hand, a previous study investigating the association between inflammatory parameters and tumor PD-L1 expression found no significant association between them (12).

If a high T790M mutation acquisition rate could be achieved in patients with EGFR-mutant NSCLC with negative tumor PD-L1 expression, sequential therapy with first-/second-generation EGFR-TKIs plus osimertinib might confer prolonged survival. However, first-line treatment with osimertinib might be also recommended in patients with negative tumor PD-L1 expression, due to the cell proliferation dependence on EGFR signaling and a high acquisition rate of the T790M mutation (9). In fact, the PFS after the start of osimertinib treatment was longer in patients with negative tumor PD-L1 expression than in patients with positive tumor PD-L1 expression (13, 14). It cannot be concluded from the present study if sequential therapy with first-/second-generation EGFR-TKI plus osimertinib therapy may be superior to first-line osimertinib therapy in tumor PD-L1-negative EGFR-mutant NSCLC patients.

It has been reported that combined first-generation EGFR-TKI plus VEGF inhibitor therapy yields a longer PFS compared to EGFR-TKI monotherapy (15). However, in our study, the PFS was similar between the 5 patients who received the combination therapy and the patient group that received EGFR-TKI monotherapy. Although it is difficult to specify the precise reason for the relatively short PFS in the patients who received the combination therapy, it is possible that patients with poor prognostic factors were selected. Combined EGFR-TKI plus VEGF inhibitor therapy has been proposed as a possible treatment option for patients with higher tumor PD-L1 expression levels (9), because the proliferative activities of tumors with higher tumor PD-L1 expression levels might depend not only on EGFR signaling, but also on other oncogene alterations.

There are several limitations in the present study. Because of the retrospective nature of the study, bias was inevitable and could have affected the results of the statistical analysis. Second, it remains unclear if the findings of this study can be generalized, because the sample size was small. It is considered that the time on treatment with EGFR-TKIs in patients treated with first-/second- generation EGFR-TKIs depends on the acquisition rate of the T790M mutation, which has been reported to be in the range of 50-75% (8-10). Furthermore, we did not conduct analysis for the overall survival, because the patients received EGFR-TKIs as second or further line of treatment were included. On the other hand, the strength of our study is that the association between tumor PD-L1 expression and clinical outcome (time on treatment with EGFR-TKIs) was evaluated, in addition to the association between PD-L1 expression and T790M acquisition rate shown in the previous studies.

In summary, the acquisition rate of the T790M mutation and implementation rate of osimertinib therapy was higher

Table II. *Log-rank test for determining the associations between clinical parameters and PFS after EGFR-TKI therapy.*

		PFS	95% CI	*p*-Value
Age (years)	<75	15.1	9.1-22.2	0.769
	≥75	21.7	1.5-30.0	
Sex	Male	11.4	5.9-20.8	0.080
	Female	21.7	11.2-27.5	
PS	0	22.9	12.3-27.5	0.016
	≥1	11.2	7.4-18.6	
Histology	Adenocarcinoma	18.6	11.2-22.9	0.020
	Others	9.1	2.9-10.0	
EGFR	del 19	19.6	10.5-24.1	0.525
	L858R	12.8	7.4-23.0	
PD-L1 TPS	<1%	21.7	12.9-24.8	0.107
	≥1%	12.3	5.6-22.2	
Brain metastasis	Local therapy (–)	7.4	5.6-NE	0.436
	Local therapy (+)	15.1	5.9-23.0	
	No metastasis	18.6	11.2-23.3	
History of RT	Yes	19.1	3.7-27.5	0.787
	No	13.0	10.0-22.9	
History of surgery	Yes	13.0	4.5-27.5	0.726
	No	15.4	9.1-22.2	
EGFR-TKI treatment line	1	13.0	9.1-22.2	0.657
	≥2	19.2	10.0-NE	
VEGF inhibitor	Yes	15.1	8.6-32.5	0.881
	No	15.4	10.5-22.2	

CI, Confidence interval; EGFR-TKI, epidermal growth factor receptor-tyrosine kinase; PD-L1, programmed death ligand-1; PFS, progression free survival; PS, performance status; RT, radiotherapy; TPS, tumor proportion score; VEGF, vascular endothelial growth factor.

Table III. *Analysis using a Cox proportional hazards model.*

		HR	95% CI	*p*-Value
PS	0	0.33	0.15-0.72	0.005
	≥1	1.00		
Histology	Adenocarcinoma	0.54	0.14-2.05	0.367
	Others	1.00		
PD-L1 TPS	<1%	0.42	0.20-0.88	0.022
	≥1%	1.00		

CI, Confidence interval; HR, hazard ratio; PD-L1, programmed death ligand-1; PS, performance status; TPS, tumor proportion score.

in EGFR-mutant NSCLC patients with negative tumor PD-L1 expression treated with first-/second-generation EGFR-TKIs, and this patient group showed longer time on treatment with EGFR-TKI in the present study.

Conflicts of Interest

The Authors declare that they have no competing interests in relation to this work.

Authors' Contributions

MI contributed to the conception and design of the work, and to the data analysis. Data were collected by MI, MM, IM, KH, ZS, KT (Kotaro Tokui), CT, SO, KK, SI, TM, RH, and SM. The data were interpreted and manuscript was revised by MI, MM, IM, KH, ZS, KT (Kotaro Tokui), CT, SO, KK, SI, TM, RH, SM, and KT (Kazuyuki Tobe).

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Received February 4, 2022
Revised March 3, 2022
Accepted March 28, 2022