Respiratory Medicine Case Reports 30 (2020) 101071

Contents lists available at ScienceDirect

Respiratory Medicine Case Reports

journal homepage: http://www.elsevier.com/locate/rmcr

Case report

Five cases of *BRAF* V600E-mutant lung adenocarcinoma with high expression of programmed death ligand 1

Takuma Katano [a], Tsuneyuki Oda [a,*], Akimasa Sekine [a], Midori Sato [a], Takafumi Yamaya [a], Yozo Sato [a], Koji Okudela [b], Eri Hagiwara [a], Takashi Ogura [a]

[a] Department of Respiratory Medicine, Kanagawa Cardiovascular and Respiratory Center, Yokohama, Japan
[b] Department of Pathobiology, Yokohama City University Graduate School of Medicine, Yokohama, Japan

ARTICLE INFO

Keywords:
BRAF
Lung cancer
Pemetrexed
Programmed death ligand 1
Tumor proportion score
Immune checkpoint inhibitors

ABSTRACT

We reported consecutive five patients with *BRAF* V600E-mutant recurrent or advanced non-small cell lung cancer who were identified between April 2016 and June 2019.

All five patients had high programmed death ligand 1 (PD-L1) tumor proportion scores (50, 55, 75, 95 and 100%). Four of the five patients received regimens including pembrolizumab. Of them, one patient experienced a partial response, but two patients experienced progressive disease and one patient was not evaluable. Three of the four patients received regimens including pemetrexed were able to continue long-term treatment.

The presence of a *BRAF* mutation may be associated with higher levels of PD-L1 expression. The effect of immune checkpoint inhibitors therapy in patients with *BRAF* mutation was similar to the previous reports in patients with previously treated advanced non-small cell lung cancer with PD-L1 tumor proportion score ≥50%. Chemotherapy regimens including pemetrexed may have a positive effect in patients with *BRAF* V600E-mutant lung adenocarcinoma. Accumulation of additional Case series is necessary to confirm our results.

1. Introduction

BRAF is a serine-threonine kinase belonging to the RAF kinase family and an oncogenic driver in non-small cell lung cancer (NSCLC) [1]. *BRAF* mutations are identified in approximately 2% of NSCLC [2,3]. The *BRAF* V600E mutation, which substitute glutamic acid for valine at position 600 within exon 15, comprises roughly half of these cases [4]. The ability to detect *BRAF* mutations has improved with next-generation sequencing. Therefore, it is more likely that patients with *BRAF*-mutated lung cancer will be identified.

Recently, the emergence of immune checkpoint inhibitors (ICIs) has led to changes in management of NSCLC. Programmed death ligand 1 (PD-L1) tumor proportion score (TPS) determined by immunohistochemistry, an important predictive biomarker for response to ICIs, is used for selecting first-line treatment in advanced NSCLC. However, the correlation between *BRAF* V600E mutation and level of PD-L1 expression and the efficacy of ICIs are unknown. Here we report consecutive five cases of *BRAF* V600E-mutant lung adenocarcinoma between April 2016 and June 2019 for which we evaluated PD-L1 expression and the response to ICIs therapy.

1.1. Case reports

We describe the treatment history and outcomes of five patients with *BRAF* V600E-mutant lung adenocarcinoma, which are summarized in Table 1.

Case 1. A 61-year-old man with a nodular shadow in his right upper lung field was referred to our hospital in April 2016. He had a smoking history of 60 pack-years. He was diagnosed as having cT4N2M1a stage IVA adenocarcinoma. He received four cycles of cisplatin and pemetrexed as first-line treatment, and partial response was achieved. Subsequently he was treated with eight cycles of pemetrexed maintenance therapy. He received pembrolizumab as second-line treatment, because PD-L1 was highly expressed at TPS 50%. However, he had a progressive disease and discontinued pembrolizumab after only three cycles. A total of 11 cycles of docetaxel as third-line treatment was performed. Subsequently, he received carboplatin and weekly albumin-bound paclitaxel as fourth-line treatment, and S-1 as fifth-line treatment with minimal response. Because *BRAF* V600E mutation was newly identified

* Corresponding author. Department of Respiratory Medicine, Kanagawa Cardiovascular and Respiratory Center, 6-16-1 Tomioka-higashi, Kanazawa-ku, Yokohama, 236, Japan.
E-mail address: odatsu@kanagawa-junko.jp (T. Oda).

https://doi.org/10.1016/j.rmcr.2020.101071
Received 21 February 2020; Received in revised form 27 April 2020; Accepted 27 April 2020
Available online 1 May 2020

Abbreviations

ICIs	immune checkpoint inhibitors
NSCLC	non-small cell lung cancer
OS	overall survival
PD-L1	programmed death ligand 1
TPS	tumor proportion score

by next-generation sequencing using preserved specimens at the time of diagnosis, he recieved the combination therapy with dabrafenib and trametinib. Although he experienced a partial response and continued to take them for a total of 247 days, the disease progressed. He died of tumor progression in June 2019.

Case 2. A 61-year-old woman with a nodular shadow in her right lower lung field was referred to our hospital in October 2016. She had a smoking history of 5.5 pack-years. She was diagnosed as having cT1bN2M0 stage IIIA adenocarcinoma. She was treated with chemoradiotherapy with cisplatin and vinorelbine and received concurrent radiation (total dose, 60 Gy). However, malignant pleural effusion and a new lesion developed immediately after the completion of four cycles. She received pemetrexed as second-line treatment. Pemetrexed administered for a total of 15 cycles provided long-term disease control. Pembrolizumab was selected as third-line treatment, since PD-L1 was highly expressed at TPS 75%. However, pembrolizumab was not effective and was discontinued after only three cycles. She received four cycles of S-1 as fourth-line treatment. Since the *BRAF* V600E mutation was newly identified by next-generation sequencing using preserved specimens at the time of diagnosis, the combination therapy with dabrafenib and trametinib was initiated as fifth-line treatment. The combination therapy showed stable disease, and she continued them for 237 days. However, the disease progressed. She received carboplatin and weekly albumin-bound paclitaxel as sixth-line treatment. Three months after initiation of sixth-line treatment, she experienced a partial response and continued to recieve them.

Case 3. A 70-year-old woman with no smoking history presented with cough and dyspnea on exertion in October 2018. Chest computed tomography showed a mass in the hilum of the right lung. She was diagnosed as having cT4N3M1a stage IVA adenocarcinoma with PD-L1 TPS 100%. She received four cycles of cisplatin and pemetrexed as first-line treatment and partial response was demonstrated. She received five cycles of maintenance therapy with pemetrexed. Subsequently, the *BRAF* V600E mutation was identified by next-generation sequencing using preserved specimens at the time of diagnosis, and she was treated with dabrafenib and trametinib as second-line treatment. Four months after initiation of them, the combination therapy was effective and was continued.

Case 4. A 76-year-old man with smoking history of 46 pack-years presented with bloody sputum in May 2017. He was referred to our hospital. Chest computed tomography demonstrated a nodular shadow in his right lower lobe. A right lower lobectomy was performed, and a diagnosis of adenocarcinoma (stage IA, pT1bN0M0) was made. One year after lobectomy, the patient experienced recurrence with mediastinal lymphadenopathy, the right pleural dissemination and brain metastasis. He received stereotactic radiation therapy with a total dose of 20 Gy and pembrolizumab as first-line treatment. Since PD-L1 was highly expressed at TPS 55%, he received 15 cycles of pembrolizumab. Subsequently, a new lesion developed in his right upper lobe and he received carboplatin and weekly paclitaxel as second-line treatment. Although the *BRAF* V600E mutation was identified by next-generation sequencing using preserved specimens at the time of diagnosis, four cycles of carboplatin and weekly paclitaxel combination therapy showed

Table 1
Treatment history and outcomes of five patients with *BRAF* V600E-mutant lung adenocarcinoma.

Case number	1st-line treatment			2nd-line treatment			3rd-line treatment			4th-line treatment			5th-line treatment			6th-line treatment			OS from metastasis
	T	C	R	T	C	R	T	C	R	T	C	R	T	C	R	T	C	R	
1	CDDP + PEM +PEMB	4	PR	PEMB	3	PD	DTX	11	SD	CBDCA+ nab-PTX	3	PD	S-1	2	PD	DAB +TRA	8.2 mo	PR	38.5 mo
	PEM MAINT	7																	
2	CDDP + VNR +RT	4	PR	PEM	15	SD	PEMB	3	PD	S-1	3	SD	DAB +TRA	7.9 mo	SD	CBDCA +nab-PTX	3[a]	PR	32.2 mo[a]
3	CDDP + PEM	4	PR	DAB +TRA	4.5 mo[a]	PR													12.0 mo[a]
	PEM MAINT	5																	
4	PEMB	14	PR	CBDCA +PTX	4	PR													17.9 mo[a]
5	CDDP + PEM +PEMB	1	NE																1.4 mo

Abbreviations: T = treatment regimen, C = cycles, R = response, PR = partial response, PD = progressive disease, SD = stable disease, NE = not evaluable, OS = overall survival, CDDP = cisplatin, PEM = pemetrexed, PEM MAINT = pemetrexed maintenance therapy, VNR = vinorelbine, RT = radiotherapy, PEMB = pembrolizumab, DAB = dabrafenib, TRA = trametinib, DTX = docetaxel, CBDCA = carboplatin, nab-PTX = albumin-bound paclitaxel, mo = months.

[a] On going at the time of review. The database lock date was set at November 1, 2019.

partial response and he was followed up without treatment.

Case 5. A 72-year-old man with smoking history of 38 pack-years presented with cough and cervical lymphadenopathy. He was diagnosed as having cT4N3M1a stage IVA adenocarcinoma with PD-L1 TPS 95% in May 2019. He was treated with a combination chemotherapy with cisplatin, pemetrexed, and pembrolizumab as first-line treatment. Fifteen days later, despite tentative response, he experienced multiple cerebral infarctions as Trousseau's syndrome. Although the *BRAF* mutation was identified by next-generation sequencing preserved specimens at the time of diagnosis, he died in July 2019.

2. Discussion

We herein reported consecutive five patients who had *BRAF* V600E-mutant lung adenocarcinoma. The result of our case study indicated the following two important clinical issues. First, the presence of a *BRAF* mutation in lung adenocarcinoma may be associated with high levels of PD-L1 expression, although the responses to ICIs therapy were various. Second, a chemotherapy regimen including pemetrexed may be beneficial in treating with *BRAF* V600E-mutated NSCLC.

PD-L1 TPS ≥50% seldom overlaps with the presence of driver oncogenes such as *EGFR, ALK* and *ROS-1* [5]. In contrast, the PD-L1 TPS in *BRAF*-mutant NSCLC have been reported between 42% and 50%, which is higher than those in wild-type NSCLC [6,7]. In fact, all five patients had high PD-L1 TPS of more than 50%. The presence of a *BRAF* mutation in lung adenocarcinoma may be associated with high PD-L1 TPS.

In our study, ICIs therapy were not effective in Case 1 and 2 despite of high expression of PD-L1, while case 4 had favorable response. To our knowledge, very few reports have been published on the effect of ICIs in *BRAF* V600E-mutant NSCLC. The previous study reported the rate of complete or partial response was observed in approximately 25% for *BRAF*-mutant lung cancer [7], while the rate of complete or partial response was 33.3% in our study. Our outcomes are in line with the previous study which found that the rate of complete or partial response was 32.4% in the pembrolizumab group in patients with previously treated advanced NSCLC with PD-L1 TPS ≥50% [8]. Therefore, even in NSCLC patients with high PD-L1 expression, it is important to identify *BRAF* mutation earlier and to initiate the combination therapy with dabrafenib and trametinib, which is expected to have a better response than ICIs.

A chemotherapy regimen including pemetrexed may be a favorable treatment for patients with *BRAF* V600E-mutated lung adenocarcinoma. Our patients 1, 2 and 4 received regimens including pemetrexed for a long period. All of them experienced at least partial response during pemetrexed treatment. A previous study reported that patients with *BRAF* V600E-mutated lung adenocarcinoma achieved partial response (n = 2) and stable disease (n = 1) after pemetrexed-based chemotherapy [4]. Another study also reported that a patient with advanced *BRAF* V600E-mutant lung adenocarcinoma showed favorable outcomes following pemetrexed treatment for 8 years [9]. Patients with *BRAF*-mutant lung adenocarcinoma may be sensitive to chemotherapy regimens including pemetrexed. Pemetrexed may have contributed to a higher overall survival in this study.

3. Conclusion

The presence of a *BRAF* mutation in lung adenocarcinoma may be associated with high expression of PD-L1. However, the effect of ICIs in *BRAF*-mutant NSCLC were various in our cases. Pemetrexed may have a positive effect on patients with *BRAF*-mutant lung adenocarcinoma. Since *BRAF*-mutant lung adenocarcinoma is a rare disease, a prospective study is not practical. Accumulation of additional Case series is necessary to confirm our results.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of competing interest

None declared.

References

[1] H. Davies, G.R. Bignell, C. Cox, P. Stephens, S. Edkins, S. Clegg, et al., Mutations of the BRAF gene in human cancer, Nature 417 (2002) 949–954.
[2] F. Barlesi, J. Mazieres, J.P. Merlio, D. Debieuvre, J. Mosser, H. Lena, et al., Routine molecular profiling of patients with advanced non-small-cell lung cancer: results of a 1-year nationwide programme of the French Cooperative Thoracic Intergroup (IFCT), Lancet 387 (2016) 1415–1426.
[3] L.C. Villaruz, M.A. Socinski, S. Abberbock, L.D. Berry, B.E. Johnson, D. J. Kwiatkowski, et al., Clinicopathologic features and outcomes of patients with lung adenocarcinomas harboring BRAF mutations in the Lung Cancer Mutation Consortium, Cancer 121 (2015) 448–456.
[4] P.K. Paik, M.E. Arcila, M. Fara, C.S. Sima, V.A. Miller, M.G. Kris, et al., Clinical characteristics of patients with lung adenocarcinomas harboring BRAF mutations, J. Clin. Oncol. 29 (2011) 2046–2051.
[5] D. Rangachari, P.A. VanderLaan, M. Shea, X. Le, M.S. Huberman, S.S. Kobayashi, et al., Correlation between classic driver oncogene mutations in EGFR, ALK, or ROS1 and 22C3-PD-L1 >/=50% expression in lung adenocarcinoma, J. Thorac. Oncol. 12 (2017) 878–883.
[6] E. Dudnik, N. Peled, H. Nechushtan, M. Wollner, A. Onn, A. Agbarya, et al., BRAF mutant lung cancer: programmed death ligand 1 expression, tumor mutational burden, microsatellite instability status, and response to immune check-point inhibitors, J. Thorac. Oncol. 13 (2018) 1128–1137.
[7] J. Mazieres, A. Drilon, A. Lusque, L. Mhanna, A.B. Cortot, L. Mezquita, et al., Immune checkpoint inhibitors for patients with advanced lung cancer and oncogenic driver alterations: results from the IMMUNOTARGET registry, Ann. Oncol. 30 (2019) 1321–1328.
[8] R.S. Herbst, P. Baas, D.W. Kim, E. Felip, J.L. Pérez-Gracia, J.Y. Han, et al., Use of archival versus newly collected tumor samples for assessing PD-L1 expression and overall survival: an updated analysis of KEYNOTE-010 trial, Ann. Oncol. 30 (2019) 281–289.
[9] Y. Nakanishi, Y. Nakagawa, I. Tsujino, T. Shimizu, N. Takahashi, S. Hashimoto, et al., Favorable outcome with pemetrexed treatment for advanced BRAF-V600e-positive lung adenocarcinoma in a patient followed up over 8 years, J. Thorac. Oncol. 13 (2018) 199–202.