Case Report

Efficacy of pembrolizumab in lung adenocarcinoma harboring non-V600E BRAF mutation: a case report

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Abstract: Small percentage of non-small cell lung cancer (NSCLC) patients, ranging 2–4% present BRAF mutations whom classification is easily accounted as V600E/non-V600E variant. There is a growing interest linked to different functional classes of BRAF mutations, which include class I (V600E mutations), class II mutations (kinase-activating non-V600E mutations), and class III mutations (kinase-impaired non-V600E mutations that increase ERK signaling or RAS activity), with a more aggressive behavior in non-V600E mutant NSCLC. V600E positive mutation patients are susceptible to target therapies, as the combination dabrafenib and trametinib in first- and second-line setting; meanwhile the others have an unknown clinical significance and there is no standard of therapy. Higher levels of programmed death-ligand 1 (PD-L1) expression are associated with presence of BRAF mutation. Furthermore, there is little evidence on the efficacy of immune checkpoint inhibitors (ICIs): in contrast to EGFR mutated or ALK rearranged tumors, ICIs have favorable activity both in V600E than non-V600E mutated BRAF variant. We identified a biological rationale for the use of immunotherapy in patients harboring uncommon BRAF mutations. We report a case of a G466E BRAF-mutated lung adenocarcinoma successfully treated with pembrolizumab. Besides, our case adds to the limited literature on NSCLC harboring BRAF mutations, showing the importance of analyze the biological significance of specific BRAF mutation before starting a treatment.

Keywords: BRAF mutation; lung adenocarcinoma; case report; immunotherapy; pembrolizumab

Received: 20 June 2021; Accepted: 12 October 2021; Published: 30 March 2022.
doi: 10.21037/pcm-21-22
View this article at: https://dx.doi.org/10.21037/pcm-21-22

Introduction

V-raf murine sarcoma oncogene homolog B1 (BRAF-1) belongs to serine/threonine kinase family, though included in RAS/MAPK pathway for cell adhesion and spreading through mitogen activated kinases and extracellular signal-regulated protein kinase phosphorylation (i.e., MEK1/2, ERK1/2) (1).

BRAF inducing mutations constitutively maintain downstream kinase activity and pathway thus promoting cell proliferation and survival, as an oncogenic driver (1).

In relation to biochemical behavior V600E substitution in exon 15 highly increase BRAF activity and occur in almost 50% of cases, instead of non-V600E ones (distributed in exon 11 and 15) which show variable degrees of direct activation on MEK1/2: these kinds of mutation elicit downstream pathway through the trans-activation of Raf-1 proto-oncogene, serine/threonine kinase (CRAF) (2).

While non-V600E BRAF point mutations are associated with current or former smoking habit, sex-female and never smoking status set up a frequent profile for V600E variant finding (3).

Nevertheless, BRAF role in non-small cell lung cancer (NSCLC) prognosis is unclear, some studies emphasize a shorter progression-free survival (PFS) to platinum-based chemotherapy in patients with V600E mutated

tumors, compared to those with non-V600E mutations (2). However, tumors harboring V600E BRAF mutations have larger benefit from targeted therapy: Double therapy association with BRAF and MEK inhibitors represents a new therapy with clinically meaningful antitumor activity and a manageable safety profile in naive patients, achieving objective response rate (ORR) of 64% and median PFS of 9.7 months (4). In contrast, most non-V600E BRAF mutations do not respond to BRAF inhibition (5). Therefore, targeted therapies are currently only approved for V600E mutations.

A new preclinical framework has reclassified BRAF mutations, including V600 and non-V600, into three functional classes based on kinase activity and signaling mechanism. It remains to establish whether BRAF functional class influences clinicopathologic characteristics and clinical outcomes (6).

Due to the low frequency of BRAF-mutant NSCLCs, the immunological characteristics and the efficacy of immune checkpoint inhibitors (ICIs) have not been extensively studied (7).

A real-world study supports the hypothesis that ICIs may have an efficacy in BRAF-mutant NSCLC patients similar to that observed in the overall NSCLC population (8).

The present case report aims at describing features and outcomes of G466E BRAF-mutated NSCLC patient treated with pembrolizumab.

This case adds to the limited current published literature on NSCLC harboring non-V600E BRAF mutations and suggests that immunotherapy is a reasonable treatment option.

We present the following case in accordance with the CARE reporting checklist (available at https://pcm.amegroups.com/article/view/10.21037/pcm-21-22/rc).

Cases presentation

The patient is a 79 years old male who performed diagnostic investigations in December 2019 due to recurrent dorsal pain. Spine magnetic resonance imaging (MRI) showed multiple pathological secondary lesions on the spine. A subsequent full body computed tomography (CT) revealed the presence of a solid lung mass in the lower left lobe (LLL) larger than 6 cm and pleural effusion, and bone metastases.

In April 2020, he underwent to pleural biopsy and talc-procedure on pleural leaflets. The diagnosis was lung adenocarcinoma. Programmed death-ligand 1 (PD-L1) immunohistochemistry (IHC) expression was 60%, and molecular tests excluded the presence of driver mutations on *EGFR*, *ALK* and *ROS-1* genes. Comprehensive molecular profiling by next generation sequencing (NGS) identified the G466E BRAF mutation. Other cancer-related alterations founded were NF1 (Y2285fs*5; Y2640fs*3), TP53 (D281Y). The tumor resulted microsatellite-stable and tumor mutational burden (TMB) was 5.04 mutations-per-megabase.

A positron emission tomography (PET) CT scan performed in August 2020 confirmed IV stage disease: pleural, mediastinal nodal, adrenal and several bones metastases. Then, the patient started first line immunotherapy with pembrolizumab. Three months later, the PET CT scan showed impressive response of disease: metabolic and dimensional reductions of lung and pleural lesions, complete metabolic response of disease on mediastinal nodes, adrenal and bone metastases (*Figure 1*). Thus, the patient continued therapy with pembrolizumab.

In February 2021, PET CT scan revealed a modest increase of the uptake on pleura, mediastinal lymph node and fourth-lumbar vertebra. However, in view of clinical benefit and radiological response achieved in all other sites of disease, he continued pembrolizumab treatment. The last PET CT performed 2 months later showed bone complete metabolic response and further partial metabolic response on lung, pleural and adrenal disease.

The patient is currently receiving treatment with pembrolizumab, maintaining clinical benefit and good safety profile.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal. Local ethics committee approval was not required due to non-experimental content of the manuscript.

Discussion

BRAF mutation is one of oncogenic driver mutations in NSCLC, which phosphorylates the downstream effectors MEK and ERK to promote cell proliferation and survival.

MAP Kinase pathway alteration is involved in several tumor types, thus allowing MEK inhibitors or pan-RAF inhibitors to target BRAF mutation in lung cancer. Moreover, MAPK-BRAF linked activation (including non-

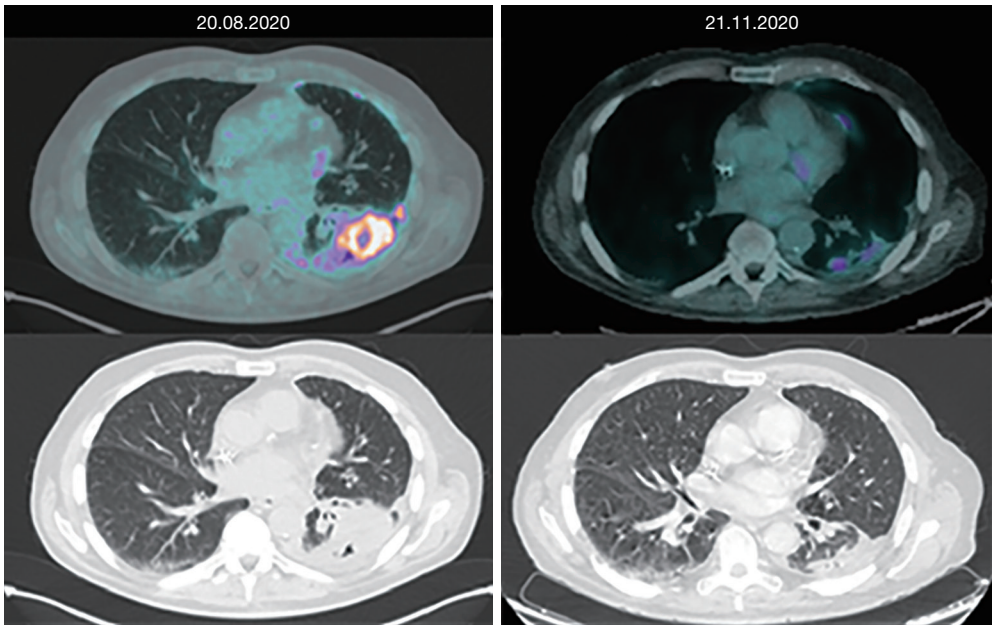

Figure 1 Comparison between baseline and first PET CT scan during treatment with pembrolizumab: metabolic and morphologic response on primary lung cancer. PET, positron emission tomography; CT, computed tomography.

V600E variants) may be sensitive to specific signaling nodes of MEK and ERK (9).

Not yet provided a complete BRAF mutation list; only few papers referred other mutations in exon 11 and 15 (10).

According to classification system BRAF mutations are classified in three classes, G466E BRAF belonging to class III.

The clinical significance of class II–III mutation found in NSCLC remains unclear and may be associated with other upstream MAPK alterations, such as RAS mutation or neurofibromatosis gene (NF1) loss (11) or loss of function.

Changing of pathway by class III of alterations specifically maintain signals through dimerization with wild-type C-RAF. Upstream activation to increase ERK signaling is also requested, and obtained either through genomic alterations indeed (RAS mutations or NF1 loss) or through receptor tyrosine kinase (RTK) signaling. This upstream signaling will counter the ERK-mediated negative feedback on RAS proteins.

Class III BRAF mutations differentiate from class I and II ones for feedback of high RAS-GTP levels (12).

BRAF/MEK inhibition in non-V600E mutations mostly counts in melanoma patients according to clinical practice and case reports (13). Vemurafenib activity (a BRAF inhibitor) in patients with NSCLC harboring non-V600E and V600E BRAF mutations is slightly described in literature (14). High RAS levels present in cell-lines with this class of BRAF mutations should justify some more investigation on the combination of a MEK inhibitor plus a RTK inhibitor (such as EGFR) (15,16). Other way of investigation point towards ICIs still based on retrospective data and case reports. Rittberg *et al.* reported a case of a rare BRAF G469A mutated NSCLC successfully treated with nivolumab (17). Dudnik *et al.* retrospectively investigated the PD-L1 expression, the TMB, the microsatellite instability status, and the response to ICIs in BRAF-mutant NSCLC patients. BRAF mutations were associated with high level of PD-L1 expression, low/intermediate TMB and microsatellite-stable status. ICIs showed favorable activity in both BRAF V600E and BRAF non-V600E mutant NSCLC, with an ORR of 25% and 33%, respectively (18). Similarly, Guisier *et al.* suggest that the efficacy of ICIs in patients with actionable mutations and in unselected population is similar (19). The Authors emphasize that among 44 BRAF-mutated patients (of whom 26 were V600E mutated) the ORR was approximately 30% (33% for non-V600E, 26% for V600E mutated patients).

BRAF-mutations could more closely mirror the impact of KRAS mutations than EGFR or ALK alterations in NSCLC. Indeed, given BRAF's association with smoking,

PD-L1 expression and a higher mutational burden, there is a biological rationale for a higher sensitivity to ICIs compared to other oncogenic drivers (20).

We present an example of good tolerance and response to immunotherapy in a non-V600E mutated patient. This case shows once again the importance of driver mutations, in order to identify the most accurate therapeutic strategy, although not always possible due to lacking evidences. Indeed, due to increased sensitivity of NGS, more mutations of unknown significance are identified in clinical practice. Moreover, immunotherapy in NSCLC patients with driver mutations has quite low level of evidence of support yet, being rigorous judgment on benefit-harm balance still needed for clinical decision.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Precision Cancer Medicine*, for the series "Uncommon Mutations in Non-Small Cell Lung Cancer". The article has undergone external peer review.

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://pcm.amegroups.com/article/view/10.21037/pcm-21-22/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (Available at https://pcm.amegroups.com/article/view/10.21037/pcm-21-22/coif). The series "Uncommon Mutations in Non-Small Cell Lung Cancer" was commissioned by the editorial office without any funding or sponsorship. MR served as the unpaid Guest Editor of the series. MR serves as an unpaid editorial board member of *Precision Cancer Medicine* from August 2020 to July 2022. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal. Local ethics committee approval was not required due to non-experimental content of the manuscript.

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doi: 10.21037/pcm-21-22
Cite this article as: Di Fazio GR, Citarella F, Dell'Aquila E, Russano M, Galletti A, Santo V, Vincenzi B, Tonini G, Santini D. Efficacy of pembrolizumab in lung adenocarcinoma harboring non-V600E BRAF mutation: a case report. Precis Cancer Med 2022;5:10.