Case Report

Ineffective target therapy in non-small cell lung cancer harboring BRAF G466R mutation: a case report and biological rationale

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Background: The discovery of BRAF mutations occurrence in non-small cell lung cancer (NSCLC) is enriching the knowledge of molecular biology of oncogene addicted disease. Their overall prevalence amounts until 3–5%, being the V600E the most frequent, and accounting for 1–2% of cases. The combination of Dabrafenib and Trametinib guarantees clinical responses in first and second line setting for V600E positive NSCLC and it offers a therapeutic opportunity for BRAF positive disease that is usually insensitive to platinum-based chemotherapy. Conversely, data regarding non-V600E mutations are limited. They represent a heterogeneous subgroup, and the mutational specificity correlates with sensitivity to BRAF inhibition.

Case Description: We report the case of a patient treated at our center in third line setting for a metastatic chemotherapy resistant BRAF non-V600E NSCLC with the oral tyrosine kinase inhibitors (TKIs) Dabrafenib and Trametinib. The patient did not experience any benefit, and we hypothesize that BRAF G466R did not represent a therapeutic target. The biological implications of non-V600E BRAF mutations in the field of NSCLC are not fully described: BRAF promotes cell proliferations in some cases, and it does not in others. There is some evidence that a subset of BRAF mutations is not driver of cancer cells growth, and their inhibition does not exert antitumoral effect. The literature reports clinical outcomes of patients receiving oral TKIs for "uncommon" oncogene mutations, especially epidermal growth factor receptor (EGFR). Conversely, the investigation of the TKIs efficacy for V600E and non-V600E BRAF disease is limited by the rarity and the heterogeneity of BRAF mutations. Recent studies recently provided some robust evidence supporting the treatment with Dabrafenib and Trametinib for V600E positive cancer, but their effectiveness for non-V600E mutations is far from being examined.

Conclusions: The present case report suggests that the clinicians should first analyze the biological significance of specific BRAF mutations before considering the combination TKI strategy for NSCLC treatment.

Keywords: Oncogene addicted non-small cell lung cancer (oncogene addicted NSCLC); uncommon BRAF mutation; tyrosine kinase inhibitor (TKI); prediction; case report

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Introduction

BRAF represents a novel target for oncogene addicted non-small cell lung cancer (NSCLC). It belongs to the RAF kinase family and it regulates cell growth and differentiation via the mitogen-activated protein kinase (1). Its mutation is rare, occurring in about 3% of NSCLC (2), and it is mutually exclusive with epidermal growth factor receptor (EGFR) mutations and ALK rearrangements. It is relatively more frequent in Caucasian rather than Asiatic population (3). The substitution of valine for glutamic acid in exon 15, i.e., V600E, represents the most frequent BRAF mutation; it induces an oncogene-driven constitutive activation of BRAF kinases paving the way to ERK pathway's hyperactivation and subsequent cell proliferation. 50% of BRAF mutations are non-V600E, among which the G469A and the G594G are the most common (4).

BRAF V600E occurs more frequently in female nonsmoker patients; conversely non V600E mutations are common in male smokers (5). BRAF V600E positive NSCLC is associated with more aggressive biological features such as non-mucinous and micropapillary histology and acinar or solid growth (6).

We report the case of a 58-year-old woman affected by metastatic lung adenocarcinoma harboring BRAF G466R mutation and treated with combination of the BRAF inhibitor (BRAFi) Dabrafenib and the MEK inhibitor (MEKi) Trametinib in third line setting. The patient did not benefit from the treatment experiencing precocious disease progression. We present the following case in accordance with the CARE reporting checklist (available at https://pcm.amegroups.com/article/view/10.21037/pcm-21-24/rc).

Case presentation

The patient, never smoker, addressed to our center in July 2019 due to diagnosis of lung adenocarcinoma with mediastinal nodal, skeletal, and hepatic metastases. The clinical tumor-node-metastasis (TNM) status was T4N3M1 according to the eight editions of the International Association for the Study of Lung Cancer (IASLC). The patient did not suffer from relevant comorbidities, with the exception of essential hypertension upon pharmacological treatment.

ALK, EGFR and Ros1 status was wild type; immunohistochemical PD-L1 expression was 0%.

The patient started first line treatment with every 3 weeks administration of Cisplatin 75 mg/m^2 and Pemetrexed 500 mg/m^2 in August 2019.

Due to smoking habit absence, we tested EGFR status again by liquid biopsy in August 2019, but we did not detect any actionable mutation.

The patient received radiation therapy on dorsal vertebral metastases (D9–11) with antalgic extent in September 2019 (single dose 8 Gy for each site) and on left hip joint in October 2019 (total dose of 20 Gy, 400 cGy per day).

The first CT scan of October 2019 showed a platinum refractory systemic disease progression and *de novo* brain metastasization, thus the patient started second line treatment with weekly Docetaxel 30 mg/m^2 plus Nintedanib 400 mg per day.

Whole brain radiation treatment was carried out in December 2019, for a total dose of 30 Gy (300 cGy per day).

In December 2019, the Next Generation Sequencing (NGS) of tumoral DNA (Foundation One®) revealed NF1 I70fs*15 and BRAF G466R (c.1396G>A; p.Gly466Arg) mutations.

In January 2020, the patient experienced stable disease as best response to the second line chemotherapy; the brain magnetic resonance showed light dimensional response to radiation treatment.

In April 2020, the CT scan revealed numerical pulmonary and dimensional hepatic progression. Considering the absence of smoking habitude and the poor response to previous chemotherapy-based regimens, we assumed that the disease could be oncogene driven.

Then, the patient started third line treatment with the oral tyrosine kinase inhibitors (TKIs) Dabrafenib and Trametinib on 29th April 2020.

Despite 50% dose reduction in May 2020, cause of Grade 3 nausea and Grade 2 epigastralgia, the patient reported further Grade 1 skin toxicity, Grade 2 asthenia, disabling pyrexia and recurring epigastralgia. The high burden of disease might have enhanced the treatment-induced toxicity.

The restaging CT scan of July 2020 showed hepatic and nodal progressive disease and the patient started further treatment with Atezolizumab. She died on 13th August 2020.

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). Informed consent was obtained from the patient's relatives. 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 positive NSCLC is usually poorly responsive to platinum based chemotherapy in comparison with wild type disease (7,8).

The first demonstration of the efficacy of BRAF inhibition in this subset of patient derives from the study of Hyman *et al.* Vemurafenib was tested in basket a phase 2 trial including several nonmelanoma V600E positive cancers. The median progression free survival (PFS) was 7.3 months and the response rate was 42% (9).

Planchard *et al.* investigated the clinical activity of Dabrafenib in a phase 2, nonrandomized trial for previously treated and untreated patients affected by metastatic BRAF V600E mutated NSCLC. Most patients (78 out of 84) had already received at least one prior treatment. Thirty-five out of 84 enrolled patients experienced serious adverse events. The overall response was 33% and the median PFS was 5.5 months in the pre-treated cohort. Similarly to other TKI-based regimens, Dabrafenib assured a substantial and precocious tumor shrinkage, in fact, 73% of responses occurred within 6 weeks since beginning of treatment (10).

A consistent benefit from combination of Dabrafenib and Trametinib in first line setting was enlightened by Planchard *et al.* Overall response rate and median PFS of Dabrafenib and Trametinib in first line setting were 23% and 10.9 months. Sixty-nine percent of patients enrolled reported at least one grade 3 or 4 adverse event (11).

Real life data suggest that anti-BRAF TKI-based regimens are not strictly comparable to other oncogene addicted diseases, i.e., EGFR, ALK and Ros1, in terms of duration of response. The TTF with BRAFis was 7.3 months in the analysis by Wiesweg *et al.* (12).

Current knowledge regarding the outcomes of BRAF positive NSCLC upon immunotherapy derives from retrospective studies, whose main limitation is the categorization into V600E and non-V600E.

Differently from other oncogene addicted NSCLC, BRAF mutated NSCLC usually benefits from immune checkpoints inhibitors (ICI) and global outcomes are similar to the wild-type population.

The retrospective analysis by Dudnik *et al.* pointed out objective response rates to immunotherapy as first, second or third line of treatment of 25% and 33%, and median PFS of 3.7 and 4.1 months in V600E and non-V600E cohorts, respectively. Both BRAF mutation type and PD-L1 expression were not associated with clinical outcomes, but notably median overall survival (OS) was significantly higher in the 22 patients treated with ICI, despite the low number of cases included in the analysis (13). The 38 cases included in the analysis by Mazieres *et al.* confirmed sensitivity to ICI. The overall response rate and the median PFS were 28.1% and 13.6 months, but no information regarding specific BRAF mutations is available (14). A retrospective study comparing outcomes of 11 BRAF positive and 199 BRAF wild type non squamous NSCLC upon second line therapy with Nivolumab confirmed similar results. Median OS was 10.3 and 11.2 months respectively; the limited cohort size might have influenced the low response rate (9%) (15). Guisier *et al.* included 26 BRAF V600E and 18 BRAF non-V600E cases in a retrospective analysis of ICI efficacy in any line setting in a large and heterogeneous population of oncogene-addicted NSCLC. Median PFS, median OS and response rate were 5.3 and 4.9 months, 22.5 and 12 months, 26.1% and 35%, respectively (16). The IMMUNOTARGET registry includes 43 patients with BRAF positive NSCLC that received ICI in any line setting: PFS was higher in smokers versus never smokers (4.1 *vs.* 1.9 months) and in non-V600E versus V600E cohort (4.1 *vs.* 1.8 months) (17).

The study by Wiesweg *et al.* confirms the ICI-sensitivity: 14 patients with BRAF V600E and non-V600E that received ICI in any line setting experienced a response rate and a median PFS of 28.6% and 2.2 months, respectively. The benefit was comparable to the two control cohorts, i.e., K-Ras mutated NSCLC and all wild type NSCLC, and it was independent from the specific BRAF mutation (12).

Only a limited number of studies evaluated efficacy of anti-BRAF TKI for non-V600E positive NSCLC. In a retrospective analysis by Dudnik *et al.*, BRAFi ± MEKi guaranteed an objective response rate (ORR) of 33%, a median PFS and an OS of 3.6 and 7.1 months in 7 non-V600E patients. Toxicities rates were similar among the subgroups (A1: V600E, BRAFi; A2: V600E, BRAFi + MEKi; A3: V600E, no BRAFi; B1: non-V600E, BRAFi ± MEKi; B2: non-V600E, no BRAFi). G469A and L597R mutations correlated with favorable response (18).

Mu *et al.* included 2 non-V600E positive in a retrospective series: the T599dup and the K601E mutated cases experienced stable disease and progressive disease as best response, while the patient with G466R did not received TKI (19).

BRAF mutations family includes about 200 variants described in human cancers and classified into three different classes depending on the mechanisms of action. Class 1 mutations account for the "typical" V600E

mutation; they are RAS-independent, and they induce sensitive to BRAFi active monomers. Class 2 mutations are RAS-independent; they stimulate cell growth via constitutive dimers, and they are sensitive to BRAFi and MEKi. Class 3 mutations do not enhance kinase activity, but they show high affinity to RAS-GTP activating CRAF and ERK signaling. In this case, concomitant mutations, involving more often RAS and NF1, are usually needed to promote cell proliferation. The inhibition of BRAF pathways may not exert clinical response in this subgroup of patients, and therapeutic strategies could be hypothesized according to the concurrent mutations: ERK inhibitors represent a potential target for RAS/NF1 positive class 3 BRAF mutant cancers, especially melanoma. Epithelial class 3 BRAF positive cancers, including NSCLC, are more likely to hyper-stimulate RAS trough other mechanisms, first receptor tyrosine kinases (RTKs). Clinical characteristic of G466R BRAF positive NSCLC are unknown, but the class 3 includes several similar mutations, such as G466V, G466E and G466A (20).

Despite our patient being diagnosed with NSCLC, the concomitant presence of NF1 mutation is coherent with the low responsiveness of a class 3 mutation to the combination of BRAFi and MEKi. To our knowledge, the present report describes for the first time the outcome of G466R BRAF positive NSCLC upon BRAFi and MEKi, since the only previously reported case had received ICI-based treatment (19).

We clarify that the treatment was intended as salvage therapy after the standard chemotherapy-based regimens.

Substantial data concerning with BRAFi ± MEKi efficacy for non-V600E BRAF positive NSCLC are still lacking. We conclude that the clinicians should investigate the biological relevance of non-V600E BRAF mutations, since class 2 mutations could be sensitive to TKI treatment, as confirmed by retrospective studies, while class 3 could not. Particular attention should be in addition paid to concomitant molecular mutations.

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