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Case Report

Lack of Response to Vemurafenib in Melanoma Carrying BRAF K601E Mutation

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Abstract
Vemurafenib has been developed to target common BRAF mutation V600E. It also exerts activity towards some but not all rare BRAF substitutions. Proper cataloguing of drug-sensitive and -insensitive rare mutations remains a challenge, due to low occurrence of these events and inability of commercial PCR-based diagnostic kits to detect the full spectrum of BRAF gene lesions. We considered the results of BRAF exon 15 testing in 1872 consecutive melanoma patients. BRAF mutation was identified in 1,090 (58.2%) cases. While drug-sensitive codon 600 substitutions constituted the majority of BRAF gene lesions (V600E: 962 [51.4%]; V600K: 86 [4.6%]; V600R: 17 [0.9%]), the fourth common BRAF allele was K601E accounting for 9 (0.5%) melanoma cases. The data on BRAF inhibitor sensitivity of tumors with K601E substitution are scarce. We administered single-agent vemurafenib to a melanoma patient carrying BRAF K601E mutation as the first-line treatment. Unfortunately, this therapy did not result in a tumor response. Taken together with already published data, this report indicates lack of benefit from conventional BRAF inhibitors in patients with BRAF K601E mutated melanoma.

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Introduction

Approximately a half of cutaneous melanomas carry activating mutations in BRAF oncogene. BRAF V600E substitution accounts for more than 90% of these mutations. Several $BRAF^{V600E}$ inhibitors (vemurafenib, dabrafenib, encorafenib) have been developed and approved for clinical use. In addition to BRAF V600E, these inhibitors exert some activity towards some rare BRAF mutations, particularly V600K [1]. However, proper cataloguing of drug sensitivity for uncommon BRAF substitutions remains a challenge, due to rarity of these events and inability of commercial PCR-based diagnostic kits to detect the full spectrum of BRAF activating events.

BRAF K601E is a recurrent mutation in melanoma, thyroid, lung and colorectal cancers (BRAF Gene. Catalogue of Somatic Mutations in Cancer. https://cancer.sanger.ac.uk/cosmic/gene/analysis?ln = BRAF. Accessed December 26, 2018). Its frequency in melanoma approaches to approximately 1% [2]. It demonstrates some sensitivity to vemurafenib treatment in vitro, although the extent of BRAF inhibition is lower as compared to BRAF V600E mutated protein [3]. Clinical data on the efficacy of BRAF inhibitors towards melanoma carrying BRAF K601E allele are limited to 4 patients. Falchook et al. [4] reported the results of phase I dabrafenib trial; they did not observe objective responses in two patients with BRAF K601E mutated melanomas, however one of these subjects had progression-free survival (PFS) of 4.2 months. Hallmeyer et al. [1] described two instances of melanomas carrying BRAF K601E allele. Use of vemurafenib did not result in clinical responses; the duration of PFS was not specified [1].

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We performed an analysis of melanomas, which were referred to the N.N. Petrov Institute of Oncology (St.-Petersburg, Russia) for BRAF gene testing from February, 2015 to November, 2018. BRAF mutation status was investigated in 1872 consecutive melanoma cases. BRAF exon 15 alterations were analyzed by combination of allele-specific PCR and DNA sequencing as described in [5]. BRAF gene lesions were identified in 1090 (58.2%) cases, including 962 p.V600E, 86 p.V600K, 17 p.V600R, 9 p.K601E, 3 p.L597Q, 2 p.L597S, 2 p.599_V600insT as well as single instances of p.D594G, p.D594N, p.A598_T599insV, p.A598A, p.T599_V600insTT, p.T599_V600insDFGLAT, p.V600_S602>DT, p.V600_W604>E and p.V600_W604>R mutations. The frequency of BRAF K601E substitution in this data set approached to 0.5%.

Here we describe a patient with metastatic BRAF K601E mutated melanoma, who received vemurafenib as a first-line treatment. A 71-year-old male patient underwent wide excision of the back skin tumor on September 12, 2017. Pathological examination revealed ulcerated melanoma with a small amount of pigment, Clark level III, Breslow depth 13 mm. The disease was staged as T4bN0M0 (IIc). Evidences for local recurrence and metastatic involvement of left axillary lymph nodes emerged in October 2017. Surgical resection of the relapsed tumor and affected lymph nodes was undertaken in January 2018. Morphological analysis identified metastases in 6 out of 13 lymph nodes. Follow-up PET-CT examination was performed in April 27, 2018 and revealed new lesions in right axillary lymph nodes, soft tissues of the back as well as multiple metastatic foci in lungs (Fig. 1). Sequencing of exon 15 of BRAF oncogene revealed K601E substitution. Given some preclinical data and limited clinical experience reported in the literature [1, 3, 4], we considered the use of single-agent vemurafenib as an option. We were aware of the fact that even in overtly BRAF inhibitor-sensitive

melanomas the best clinical results can be obtained by combining BRAF antagonists with MEK inhibitors. However, we reasoned that the use of the doublet in this particular patient would be justified only if we first obtain for him the evidence for single-agent vemurafenib activity. Vemurafenib treatment (960 mg, twice daily, starting on May 3, 2018) was accompanied by skin toxicity (grade 2), hearing loss (grade 2) and fatigue (grade 3). Treatment was interrupted for 7 days to resolve the adverse events and then continued with 75% of the initial dose.

Follow-up PET-CT examinations performed on July 2, 2018 and on August 10, 2018 revealed the disease stabilization by RECIST, thus justifying the continuation of vemurafenib treatment (Fig. 1). However, in the end of August 2018 the patient noticed dysarthria and unsteady gait. Brain MRI revealed multiple metastatic lesions in the brain. Vemurafenib therapy was discontinued and the patient was administered to receive nivolumab. Use of immune checkpoint inhibitor failed to stop the disease progression and the patient died in October 2018.

Discussion

The major drawback of the clinical management of this patient is a failure to arrange the experimental use of MEK inhibitors. Several melanoma patients with BRAF K601E substitution are described in the literature, and some of them benefited from MEK-targeted drugs [6–9]. Furthermore, a recent report, which was released after the treatment failure in this patient, demonstrated potential utility of combined use of dabrafenib and trametinib for the management of BRAF K601E mutated melanoma both in vitro and in a single clinical case [10]. Nevertheless, there are some arguments discouraging the use of drug combinations without proper reference to their single-agent activity and clear evidences for synergistic effect [11]. Taken together with already published data, this report indicates lack of benefit from conventional BRAF inhibitors in patients with BRAF K601E mutated melanoma.

Statement of Ethics

Written informed consent for publication was obtained from the patient.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

VVE, MMK, EVA treated the patients. SNA and MMH performed BRAF analysis. FVM, VMM and ENI designed the study and prepared the manuscript. All authors read and approved the final manuscript.

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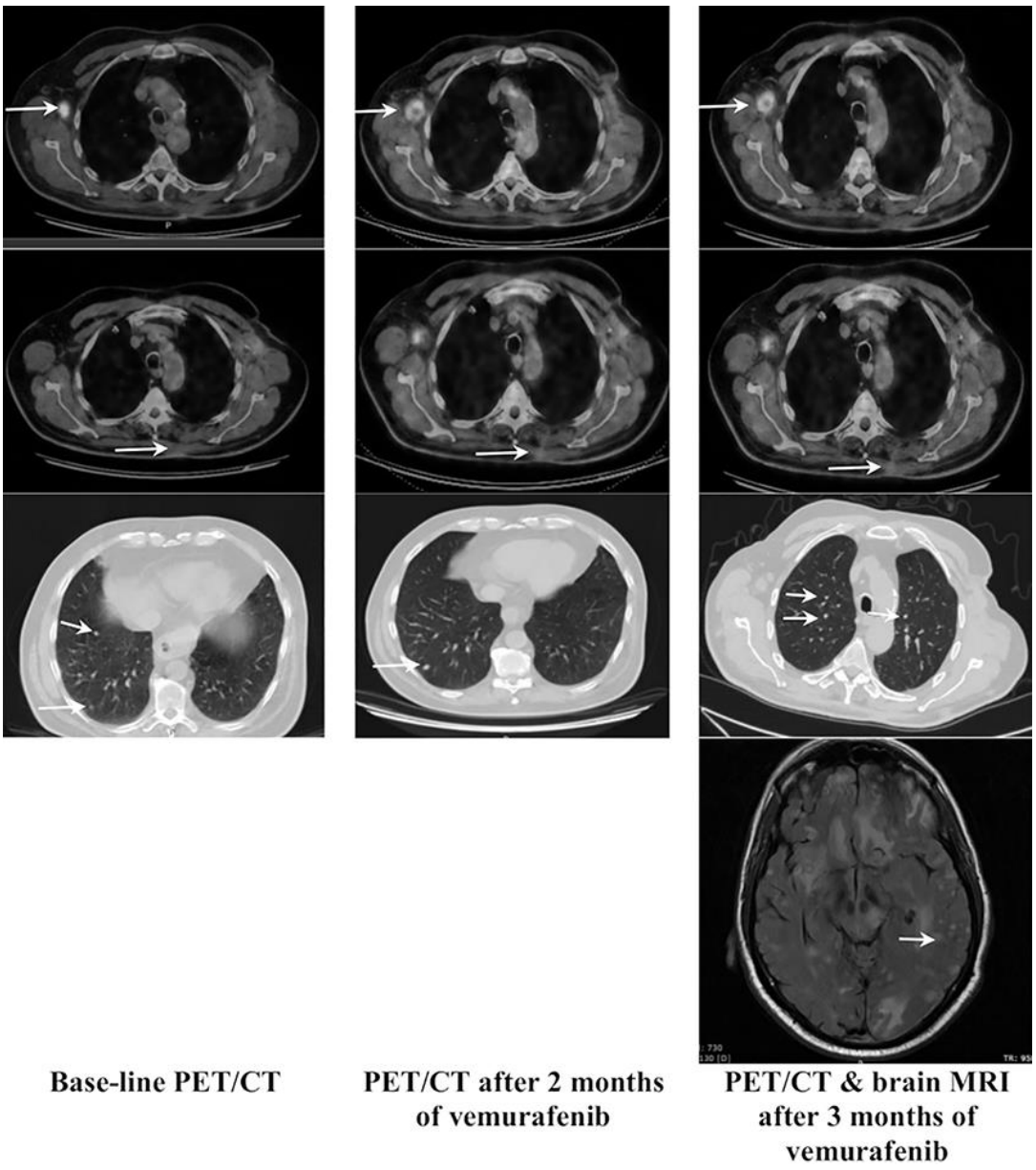

Fig. 1. Consecutive whole body 18F-FDG PET/CT and brain MRI of the patient with BRAF K601E melanoma during monotherapy with vemurafenib.