Case Report

KRAS G12V mutation as an acquired resistance mechanism after treatment with dabrafenib and trametinib in non-small cell lung cancer harbouring the BRAF V600E mutation: a case report

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Background: Molecularly targeted therapies for non-small cell lung cancer (NSCLC) have developing remarkable progress. Nevertheless, several molecularly targeted therapies are associated with initial dramatic responses followed by acquired resistance due to spontaneous mutations or activation of signaling pathways. Identifying the mechanisms of acquired resistance is important for improving the outcomes of patients with NSCLC treated with targeted therapy. BRAF (a serine-threonine kinase that belongs to the RAF kinase family which interacts directly with the MEK-ERK signaling cascade) mutations are the rare which have been reported in 3–4% of NSCLC, with the BRAF V600 mutation representing about half of all BRAF mutations. The combination of dabrafenib and trametinib therapy was recently introduced for the treatment of BRAF V600E-mutated NSCLC, and few reports have addressed the mechanism of acquired resistance to combined dabrafenib and trametinib therapy for NSCLC. However, the mechanism of resistance to combined dabrafenib and trametinib therapy has not yet been described adequately.

Case Description: We present a patient with BRAF V600E-mutated stage IV NSCLC, adenocarcinoma subtype, in whom a KRAS G12V mutation was identified by plasma sequencing after the administration of combined dabrafenib and trametinib therapy for about three years.

Conclusions: The optimal approach to overcoming this resistance remains uncertain, and further efforts to develop novel treatment strategies and drug combinations are needed to overcome acquired resistance.

Keywords: BRAF V600E; acquired resistance; dabrafenib; trametinib; case report

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Introduction

Recently, molecular-targeted therapies for non-small cell lung cancer (NSCLC) have made remarkable progress. One of the oncogenic drivers in NSCLC is mutated BRAF, a serine-threonine kinase that belongs to the RAF kinase family and that interacts directly with the MEK-ERK signaling cascade. BRAF mutations have been reported in 3–4% of NSCLC patients (1,2), with the BRAF V600 mutation representing about half of all BRAF mutations (3).

Combined treatment with the BRAF inhibitor dabrafenib and the MEK inhibitor trametinib in patients with metastatic BRAF V600E-mutated NSCLC reportedly resulted in an overall response rate (ORR) of 64%, a progression-free survival (PFS) period of 10.9 months and an ORR of 63% in a first-line setting, and a PFS of 9.7 months in subsequent-line settings (4,5); as a result, combined treatment with dabrafenib and trametinib

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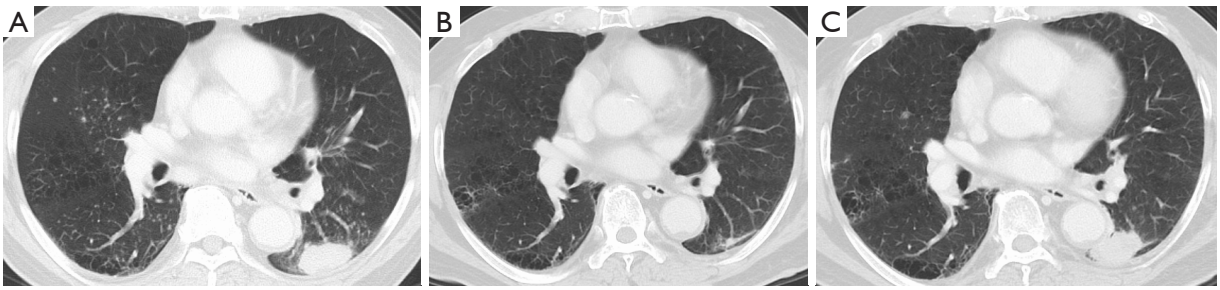

Figure 1 Computed tomography (CT) images showing the initial response to combined dabrafenib and trametinib treatment and the subsequent progression. The CT scans were obtained before treatment (A) and 3 months (B) and 27 months (C) after the start of treatment. A dominant consolidated mass in the left lower lobe and multiple metastatic nodules in the right lower lobe are visible in the baseline image. A partial response was confirmed by the volume reduction in the dominant mass and the loss of multiple metastatic nodules after 3 months of therapy. CT scans performed after 27 months of therapy show disease progression of the primary dominant mass in the left lower lobe and the appearance of new lung nodules in the right lower lobe.

is the current standard of treatment for such patients. Similar to the situation for metastatic EGFR-mutated NSCLC, however, the response duration is limited, and the acquisition of resistance is expected.

Resistance mechanisms to dabrafenib monotherapy or combined dabrafenib and trametinib therapy have been reported in several patients with BRAF V600E-mutated NSCLC; these mechanisms appear to involve MEK1 K57, KRAS G12D, KRAS G12V, KRAS Q61R, NRAS Q61K, and NRAS Q61R mutations (6-9). However, the mechanism of resistance to combined dabrafenib and trametinib therapy in patients with NSCLC has not yet been described adequately.

Here, we describe an acquired resistance mechanism involving KRAS G12V in a patient with BRAF V600E-mutated NSCLC who was treated with a combination of dabrafenib and trametinib. We present the following case in accordance with the CARE reporting checklist (available at https://pcm.amegroups.com/article/view/10.21037/pcm-21-55/rc).

Case presentation

The patient was a 70-year-old Asian male who was a former smoker and has been diagnosed with stage IV NSCLC, adenocarcinoma subtype. Of the left lung since 2018 with metastases to multiple mediastinal lymph nodes and a separate nodule in the counter lateral lung. An endobronchial ultrasound-guided transbronchial needle aspiration biopsy of the left hilar node revealed adenocarcinoma. Initial molecular testing was negative for epidermal growth factor mutations, anaplastic lymphoma kinase (ALK) and ROS1 rearrangements. Subsequent, tissue-based next generation sequencing (NGS) with Oncomine Dx Target Test CDx revealed BRAF V600E mutation, and FoundationOne Liquid by clinical trial setting also showed BRAF V600E and TP53 I255S mutations. He was treated with dabrafenib and trametinib combination therapy and achieved a response, with reduction in size of the left lower lobe primary, mediastinal nodes and multiple lung metastases. In January 2021, he experienced disease progression of the primary lung tumor and multiple new lung nodules in the right lobe (*Figure 1*). Plasma sequencing (Guardant360® CDx) revealed the acquisition of the KRAS G12V mutation (0.3% of variant allele frequency) in addition to the original BRAF V600E and TP53 I255S mutations (0.2% for both of variant allele frequency). No other genomic mechanism of resistance to dabrafenib and trametinib was identified. Upon disease progression, the patient has been treated with carboplatin and pemetrexed. The response for carboplatin and pemetrexed was partial response with the primary tumour shrinkage.

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.

Discussion

The number of NSCLC patients harbouring BRAF V600E

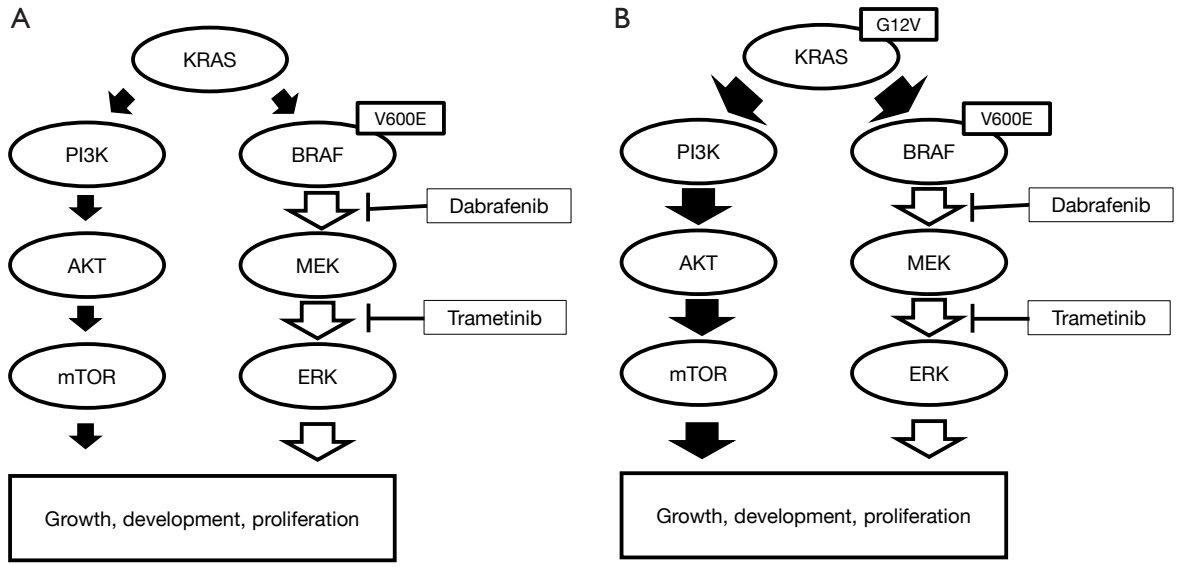

Figure 2 Model of resistance to combined dabrafenib and trametinib therapy arising from activating mutations in the *KRAS* gene in NSCLC. (A) The MAPK pathway is shown. The BRAF V600E mutation leads to constitutive activity, which activates the downstream pathway components of MEK and ERK that regulate cell growth, development, and proliferation. Dabrafenib and trametinib treatment inhibits the MAPK pathway. (B) The KRAS G12V mutation, which is induced by combined dabrafenib and trametinib treatment, activates the PI3K/AKT/mTOR pathway and likely causes disease progression. NSCLC, nonsmall cell lung cancer; MAPK, mitogen-activated protein kinase.

mutation is relatively small, and only a few cases report on acquired resistance mechanisms have been reported. The identification of recurrent molecular aberrations will lead to the development of new therapeutic strategies for this patient population.

Similar to other advanced NSCLC harbouring actionable mutations treated with targeted agents, resistance almost invariably develop. Multiple mechanisms of resistance to combined BRAF and MEK inhibitors have been reported in BRAF mutant melanoma. These include secondary mutations of the RAS/RAF/MAPK pathway such as BRAF amplification, BRAF splicing variants and gain-of-function mutations in KRAS and NRAS (10). KRAS is upstream from BRAF, and its activation may lead to activation of the PI3K/AKT/mTOR pathway, leading to tumour progression.

In the presently reported patient, secondary KRAS G12V mutation was identified as mechanism of resistance to combination therapy with dabrafenib and trametinib in our BRAF V600E mutation positive NSCLC patients. Seven cases with acquired resistance to dabrafenib monotherapy or combined dabrafenib and trametinib therapy have been reported (6-9), one of which involved the KRAS G12V mutation. In the literature review, the increased expression level of cyclin-dependent kinase (CDK) 4 and CDKN2 deletion or nonsense mutations have been reported as the resistance mechanisms of non-RAS/RAF/MAPK aberrations (9,11). The present case suggests that the KRAS G12V mutation was present in a minute subclone and that the combination therapy caused the selective outgrowth of the KRAS G12V-positive subclone, leading to tumor progression through the activation of the PI3K/AKT/mTOR pathway (*Figure 2*). A limitation of our case was that we could not perform molecular analysis by tumor tissue-based assay at resistance. Plasma-based NGS assays cannot rule out the clonal hematopoiesis of indeterminate potential. However, our patient had no KRAS mutation in plasma-based NGS assays before treatment, but plasma-based NGS assays at resistance detected KRAS mutation. For that, we suggest that this KRAS mutation at resistance would be not related to clonal hematopoiesis.

To summarize, we have identified a mechanism of resistance to combined dabrafenib and trametinib therapy involving a KRAS G12V mutation in a patient harboring the BRAF V600E mutation. The optimal approach to

overcoming this resistance remains unclear, and further efforts to develop novel treatment strategies and drug combinations are needed to overcome drug resistance.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://pcm.amegroups.com/article/view/10.21037/pcm-21-55/rc

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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.

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