frontiers | Frontiers in Oncology

TYPE Case Report
PUBLISHED 23 April 2024
DOI 10.3389/fonc.2024.1387388

Case report: Dual dabrafenib and trametinib therapy for treating BRAF V600E mutated lung adenocarcinoma with BRCA2 germline mutation post multiline progression

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RECEIVED 17 February 2024
ACCEPTED 09 April 2024
PUBLISHED 23 April 2024

CITATION
Zhang H, Cong X, Yin J, Chen C and Liu Z (2024) Case report: Dual dabrafenib and trametinib therapy for treating BRAF V600E mutated lung adenocarcinoma with BRCA2 germline mutation post multiline progression. *Front. Oncol.* 14:1387388. doi: 10.3389/fonc.2024.1387388

The v-raf murine sarcoma viral oncogenic homolog B1 (BRAF) V600E is a rare mutation that functions as an oncogenic driver in patients with non-small cell lung cancer (NSCLC) leading to the overactivation of the RAS-RAF-MEK-ERK (MAPK) pathway and the subsequent uncontrolled cell proliferation. Understanding the mechanism behind BRAF mutation, its inhibition, and relationship to the upstream and downstream effector is essential for advancing treatment strategies for NSCLC patients with the BRAF V600E mutation. Next-generation sequencing studies have identified the presence of breast cancer susceptibility gene 1/2 (BRCA1/2) mutations in NSCLC patients, which are pathogenic variants associated with breast, ovarian, and prostate cancers. Although poly ADP-ribose polymerase (PARP) inhibitors are currently an approved treatment option for malignant tumors linked to BRCA1/2 pathogenic variants, the therapeutic potential of PARP inhibitors in NSCLC remains unclear. The development of genetic testing provides a platform for investigating the pathophysiological mechanisms of genetic mutations above. Here, we report a novel case of a middle-aged non-smoking female diagnosed with BRAF V600E and BRCA2 germline mutated lung adenocarcinoma, who had previously undergone a diverse array of cancer-targeted therapies, including PARP inhibitor, before the identification of the BRAF V600E mutation. Following this, a combination of dabrafenib and trametinib was administered and induced a rapid and positive response within two months. Our case not only highlights the importance of dynamic and repetitive genetic testing in managing patients, but contributes to the growing body of clinical evidence supporting the efficacy of BRAF/MEK co-inhibition in patients harboring a BRAF V600E mutation and provokes thinking for further research into the impact of PARP inhibitors in BRCA1/2-mutated NSCLC.

KEYWORDS

dabrafenib, trametinib, BRAF V600E mutation, BRCA2 germline mutation, lung adenocarcinoma

1 Introduction

The pathway of RAS-RAF-MEK-ERK transmits signals through sequential activation, enabling the transduction of signals from the cell surface into the intracellular space, where it plays a pivotal role in regulating multiple crucial physiological processes such as cellular proliferation and survival programs (1). RAS protein family, including KRAS, HRAS and NRAS, functions as a molecular switch by cycling between active guanosine triphosphate (GTP) - bound states and inactive guanosine diphosphate (GDP) - bound states (2). Aberrant activation of RAS protein leads to the development of cancer. Among RAS protein family, KRAS mutations are the most common type in NSCLC cases, which are generally mutually exclusive with other major driver mutations such as EGFR, BRAF and ALK (3). The first downstream effectors activated by RAS belong to the RAF family which comprises ARAF, BRAF and CRAF. Among them, BRAF is a proto-oncogene, encoding a serine/threonine protein kinase which is the most active isoform of the RAF family. Mutation of BRAF is present in approximately 7-8% of all solid tumors (4), and it is present in approximately 4% of all NSCLC cases (5), with about 50% classified as class I mutations, specifically the BRAF V600E mutation (6). BRAF V600E mutation tends to manifest in mild or never-smoking women and has been associated with non-mucinous adenocarcinoma with a microgrowth pattern and strong TTF-1 expression, whereas non V600E mutation tends to exhibit a mucus component and a higher prevalence in male smokers (5, 6). Extensive research into the mechanisms of BRAF mutation has led to significant advancements in the field of targeted therapy for BRAF V600E (7). Consequently, the detection of BRAF mutations in the diagnosis process has become a routine test to identify patients eligible for precision cancer treatment. MEK1/2 are phosphorylated and activated by its upstream RAF kinases. Previous studies have indicated that KRAS or BRAF mutations are sensitive to MEK inhibitors (8). Besides, the resistance of BRAF V600 mutants to BRAF inhibitors may be caused by activating mutations of NRAS or KRAS or upregulation of receptor tyrosine kinases, which conferred sensitivity to MEK inhibition (9, 10). Therefore, the dual pharmacological inhibition of BRAF and downstream MEK has demonstrated a significant improvement in the response rate (11), leading to its establishment as the preferred first-line or back-line treatment for BRAF V600E-positive NSCLC patients (7).

BRCA1/2 are tumor suppressor genes with a pivotal role in homologous recombination (HR) - mediated DNA double - strand - break repair, and PARP inhibitors are specific drugs that target defects in the HR pathway. PARP inhibitors have shown remarkable effectiveness in treating ovarian, breast, and prostate cancer with HR defects, especially those associated with BRCA1/2 mutations. In the context of NSCLC, next-generation sequencing studies have identified the presence of BRCA1 and BRCA2 mutations in around 3% and 4.5% of the cases, respectively (12), providing a promising opportunity for targeted therapy with PARP inhibitors. However, research about PARP inhibitors is still limited, and the efficacy of PARP inhibitors in the treatment of NSCLC is still unclear.

In this report, we present a case of a lung adenocarcinoma patient with BRAF V600E and BRCA2 germline mutations. Prior to gene mutations discovery, the patient had already undergone an array of treatments, including cytotoxic chemotherapy, radiotherapy, immunotherapy, anti-angiogenic therapy, and Tyrosine Kinase Inhibitors (TKIs) therapy. The presence of germline BRCA2 mutation gave clues to treatment with olaparib while the effect was not unsatisfactory. The BRAF V600E mutation was detected during the patient's third genetic assessment and the following administration of dabrafenib and trametinib dual therapy led to a rapid and striking reduction in tumor size. This case serves as a valuable therapeutic reference for patients with lung adenocarcinoma who have previously received extensive treatment and emphasizes the significance of ongoing and dynamic monitoring of genetic status.

2 Case report

A 48-year-old non-smoking female with no significant past medical history presented to her primary care doctor in July 2019 for three months of mild cough without blood in the sputum, and weight loss of more than five percent of body weight for the prior six months. She denied fever, chest tightness, or chest pain. The computed tomography (CT) of the chest revealed a dense mass in the superior lobe of the lung that measured approximately 2.1×3.0 cm in size, exhibiting lobules and burrs visible at the edge and pulling the pleura nearby. This mass was considered as left peripheral lung cancer with mediastinal and left hilar lymph node metastasis. And there were multiple ground glass nodules in both lungs, about 0.5-1.2 cm in diameter, with the larger ones being considered space-occupying lesions (Figure 1A).

The result of percutaneous lung puncture biopsy supported primary adenocarcinoma of the lung and immunohistochemistry analysis revealed positive staining for CKpan, EMA, KI-67 (approx. 10%), TTF-1, CK7, NapsinA, and negative staining for Ventana ALKD5F3. Due to limited lung biopsy samples, only EGFR gene testing was performed, and no mutation was found. Given the presence of metastatic lesions in the different left lobes, as well as mediastinal and ipsilateral hilar lymph node metastasis and contralateral lobe metastasis, she was diagnosed with stage IVA lung adenocarcinoma (cT4N2M1a).

The first-line treatment, consisting of pemetrexed + carboplatin + bevacizumab, was administered for 6 courses starting on August 22, 2019, and the treatment response was assessed as stable disease (SD) according to response evaluation criteria in solid tumors (RECIST). After maintenance treatment with pemetrexed + bevacizumab for 2 courses on January 9, 2020, the lesion in the superior lobe of the left lung and the enlarged lymph nodes of the left hilum were treated with radiation therapy from March 3 to April 20. After the radiation therapy, the CT scan reported that the lesion size was about 1.7×1.3 cm (Figure 1B).

The second-line treatment started on July 31, 2020, during which she complained of continuous dizziness and memory loss. The detection of an abnormal enhancement in the left frontal lobe and the posterior horn of the lateral ventricle on a brain magnetic