

Trametinib Monotherapy for the Treatment of Brain Metastasis From Non-small-cell Lung Cancer: a Case Report

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Case report

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Abstract

Background: BRAF mutation mostly was observed in lung adenocarcinoma, accounting for about 4.9%. It mainly includes V600E mutation and other rare mutations, among which non-V600E positive accounted for about 43.3%.

Case presentation: We report a case with postoperative recurrent NSCLC with brain metastasis and multiple lymph nodes metastasis, who had developed hemiplegia. The gene mutation was positive for BRAF non-V600E and a partial response was observed despite brain and multiple lymph nodes lesions after trametinib monotherapy.

Conclusion: Our case shows that trametinib could potentially be a promising therapeutic agent for chemotherapy-refractory BRAF non-V600E mutant NSCLC patients.

Background

The primary treatment for advanced non-small-cell lung cancer (NSCLC) has been updated from traditional chemotherapy and radiotherapy to targeted therapy and immunotherapy based on the pathological subtypes and gene sequencing results. We report a case of BRAF non-V600E mutation advanced NSCLC with retroperitoneal, hilar lymph nodes, and brain metastases in partial response after a short course of trametinib monotherapy.

Case Presentation

A 71-year-old never-smoker man presented to our hospital complaining of abdominal hidden pain for 1 week. There was no atony, fever, fleshless or other symptoms. A history of gastric ulcers was noted. He had undergone left upper lobectomy and thymectomy 18 months ago. Pathology reported a (left lung) adenocarcinoma. The tumor invaded the pleura and thymic lymph nodes; thus 6 cycles of pemetrexed 800 mg (d1) and carboplatin 400 mg (d1) were subsequently delivered until January 2019. Then he agreed to undergo the accurate Gamma Knife (GK) radiosurgery to the lesions in the upper left side of the mediastinum (DT 38.4 GY/12F). Then the patient took a Chinese medicine to recuperate, the specific details were unknown.

A computed tomography (CT) scan performed immediately detected multiple lung and lymph nodes lesions (Fig. 1), and CEA level increased to 14.8 ng/ml (normal range, 0-4.7 ng/ml), and CA153 level increased to 28.6 U/ml (normal range, 0-26.4 U/ml) and CA125 level increased to 47.8 U/ml (normal range, 0-35.0 U/ml). Ultrasound-guided needle biopsy of the intraperitoneal lymph node was performed. Pathology reported metastatic adenocarcinoma originated from the lung. Immunohistochemically, the tumor cells tested positive for cytokeratin 7 (CK7), NapsinA, Ki-67 (labeling index = 30%), P40, and CKAE1/AE3 and the tumor cells were negative for cytokeratin 20 (CK20) and CK5/6. The next generation sequencing (NGS) was performed and the molecular results from intraperitoneal lymph node tissue biopsy did not show any abnormality (EGFR, KRAS, NRAS, ALK, ROS1, MET, HER-2, FGFR2, NTRK1,

NTRK2, RET, PIK3CA) except BRAF exons 15 (p.D594N pathogenic mutation). The patient developed symptoms of right progressive hypotonia to grade 1 and distortion of right commissure. MRI brain showed that there was a mass (about 1.3 cm in diameter) in the left frontal lobe with brain edema, which was deemed metastatic (Fig. 1). Furosemide and 20% mannitol were used to treat cerebral edema and the muscle tone recovered to grade 2. The patient refused the treatment of whole brain radiotherapy and systemic chemotherapy.

The patient started to take trametinib (2 mg orally, once daily) based on the molecular results. There have been systemic pruritus and hand-foot syndrome during the treatment, which was evaluated as grade 2 adverse reaction according to Common Terminology Criteria for Adverse Events (CTCAE) 5.0. and no other adverse reactions were observed. He got relieved after taking positive measures. A CT scan performed 8 months after medication showed a partial response of brain metastasis, pulmonary nodule, portal lymph node metastasis and peritoneal lymph node metastasis (Fig. 1). CEA, CA125, and CA153 all returned to normal level. The improvement of quality of life of the patient was dependent on the recovery of muscle tone. In November 2020, the patient developed melena without an obvious cause, and gastroscopy showed compound ulcer, so he stopped taking trametinib. The patient eventually died of gastrointestinal bleeding. He had an 8 months progression-free survival on trametinib.

Discussion And Conclusions

Non-small-cell lung cancer (NSCLC) including squamous cell carcinoma, adenocarcinoma and large cell carcinoma accounts for 80–85% of lung cancer [1]. The incidence of brain metastasis (BMs) has started to climb up sharply in recent years and 5–10% of NSCLC patients may develop BMs [2]. Early BMs are usually asymptomatic and the most common symptoms of BMs include headache, vomiting, dizziness, diplopia, ataxia, hemiplegia and epileptic seizures [3]. Such patients have short survival period, poor quality of life and adverse prognosis. Surgical resection and radiotherapy are the main treatment options. In recent years, the strategies for the diagnosis and treatment of NSCLC have been gradually transforming into a precise target treatment era with the development of tumor molecular biology and genomics. There are a number of emerging therapeutic biomarkers and therapeutic concepts that show promise. BRAF mutation mostly was observed in lung adenocarcinoma, accounting for about 4.9%. It mainly including V600E mutation and other rare mutations such as L956V and G468A, among which non-V600E positive accounted for about 43.3% [4]. In June 2017, Dabrafenib in combination with trametinib were approved for the treatment of advanced NSCLC with BRAF V600E positive [5]. Gautschi O et al [6] believed that BRAF non-V600E positive were only found in smokers and the BRAF inhibitor dabrafenib was ineffective. No cases of BRAF non-V600E positive NSCLC with BMs have been reported. The genetic sequencing of this never-smoker patient is the BRAF exon D594N mutation, which is a rare mutation. We tried to treat with trametinib monotherapy instead of combining with dabrafenib or whole brain radiotherapy based on the patient's performance status, previous treatment and compliance. Trametinib is a MEK1/2 inhibitor which blocks MEK1/2 kinase activity and prevents RAF-dependent MEK phosphorylation [7]. It was approved initially as a monotherapy in treatment of advanced BRAF V600-

mutant melanoma [8]. This patient has a postoperative recurrence NSCLC with brain metastasis and multiple lymph nodes metastasis, who had developed hemiplegia and other nervous system symptoms. Multiple brain and lymph nodes lesions were gradually regressing during the treatment of trametinib. The patient had survived for 8 months on treatment and his quality of life was good. It is suggested that trametinib can effectively control intracranial lesions by crossing the blood-brain barrier, and the anti-tumor effect on systemic and intracranial lesions deserve further study. Common adverse reactions of trametinib include rash, diarrhea, hypertension, nausea, fatigue, pneumonia and fever, while rare adverse reactions include hemorrhage, venous thrombosis and cardiomyopathy [9]. In this case, grade 2 skin adverse reactions occurred in a short period of time, and no specific adverse events during the treatment. All toxicities were managed by positive measures. However, the patient later developed complex ulcerative gastrointestinal bleeding, leading to discontinuation of medication. It cannot be ruled out whether it was an adverse drug reaction considering the patient's previous history of gastric ulcer.

In conclusion, in the present non-smoking patient whose tumor showed a BRAF non-V600E positive mutation, A partial response after trametinib was observed despite brain and multiple lymph nodes lesions after trimetinib monotherapy. Trametinib could potentially be a promising therapeutic agent for chemotherapy-refractory BRAF non-V600E mutant NSCLC patients. This case may help physicians develop a strategy for optimizing their approach to NSCLC. Nevertheless, in order to obtain more scientific experimental results, a large sample and high-quality randomized controlled trial is still needed to confirm the conclusions of this study.

Abbreviations

NSCLC: non-small-cell lung cancer; CT: computed tomography; MRI: Magnetic resonance imaging; PFS: progression-free survival; BMs: brain metastasis.

Declarations

Ethics approval and consent to participate: This study was approved by the Medical Ethics Committee of Jiangyin People's Hospital.

Consent for publication: Written informed consent was obtained from the patient and his son for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request. T. P. and X. H. will make the data available to readers.

Competing interests: The authors declare that they have no competing interests.

Authors' contributions: X. Z. designed the study. T. P. collected data. T. P., X. Z. analyzed data and wrote the case report. T. P., X. Z. contributed to the discussion of results and to the review of the manuscript. All authors read and approved the final manuscript.

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Figures

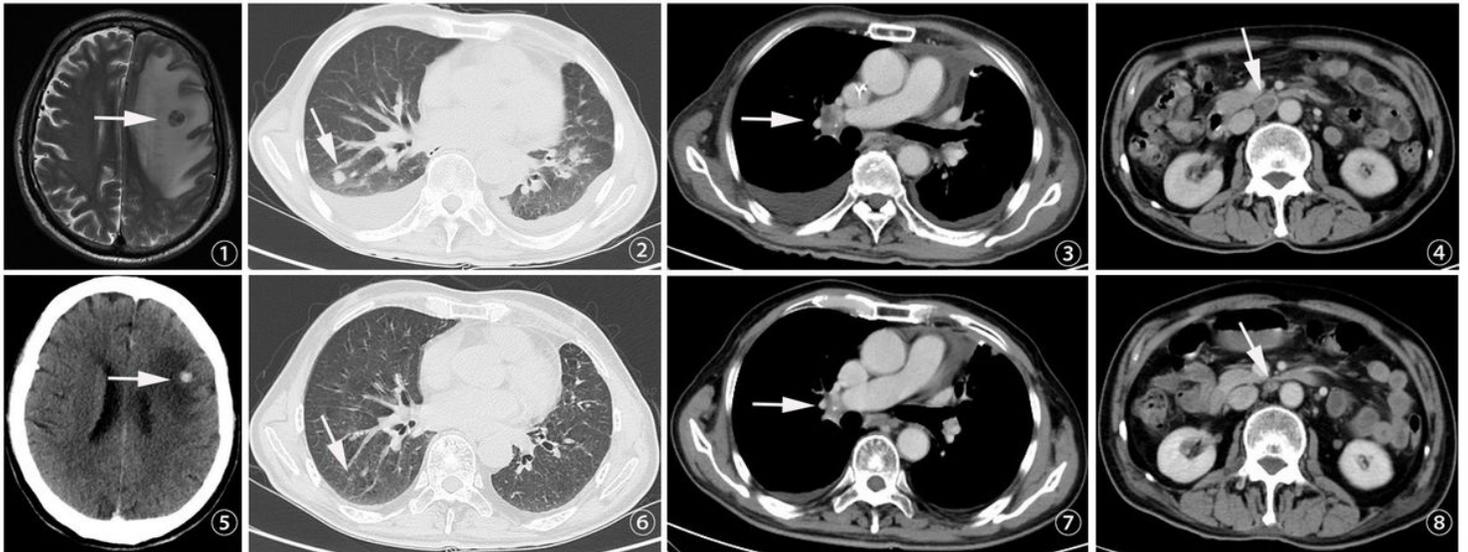


Figure 1

MR and CT imaging of a 71-year-old male with NSCLC before and after the therapy. ☒-☒ The scan showed brain metastasis, pulmonary nodule, portal lymph node metastasis and peritoneal lymph node metastasis (arrowhead). ☒-☒ The scan performed 8 months later showed shrinkage with associated lesions (arrowhead).

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