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ORIGINAL ARTICLE

Trametinib in the Treatment of Advanced Lung Adenocarcinoma with KRAS G12D Mutation: A Case Report and Literature Review

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ABSTRACT

The lung cancer poses a great threat to the patients' health and social activities. Luckily, epithelial growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) have greatly improved the response of patients getting EGFR-mutated non-small cell lung cancer (NSCLC), but the targeted therapy of KRAS mutations in lung cancer is still being explored; Currently, the effectiveness of drugs for KRAS mutations NSCLC is unsatisfactory. In this case, we present a advanced NSCLC with KRAS G12D mutation successfully treated with single-agent trametinib therapy. A 65-year-old non-smoking woman was diagnosed with stage IV lung adenocarcinoma after a lung CT for coughing revealed a lung lesion. She underwent next-generation sequencing (NGS) and revealed the KRAS G12D mutation. The single-agent target therapy of trametinib showed clinical benefit without obvious toxicity. This successful case of trametinib in advanced lung adenocarcinoma patients with KRAS G12D mutation suggests that trametinib may provide longer survival time for such patients. At the same time, we briefly reviewed the research progress of KRAS in NSCLC, and proposed possible challenges in the future.

INTRODUCTION

Lung cancer is one of the most frequently diagnosed cancers and the leading cause of cancer-related deaths worldwide with an estimated 2 million new cases and 1·76 million deaths per year. Thai et al. (2021) This results a huge burden on society, and also poses a great threat to the health of individuals. The traditional treatment for non-small cell lung cancer (NSCLC) mainly includes surgery, chemotherapy, and radiotherapy; however, these provide limited benefit to patients. Duma et al. (2019) The advent of precision medicine has brought light to the treatment of NSCLC, expanding the options for patients with advanced NSCLC by targeting therapy through genetic and epigenetic cues. Wu et al. (2022) Statistically, Rat sarcoma virus oncogene homolog (RAS) is the most frequently mutated oncogene in human cancer, with Kirsten mouse sarcoma virus oncogene homolog (KRAS) being the most commonly mutated RAS isoform. Overall, KRAS accounts for 85% of RAS mutations observed in human cancers and is present in 35% of lung adenocarcinomas. However, historical attempts to directly target KRAS have had little success, and so far, only covalent inhibitors of the mutant subgroup KRAS G12C have been approved. Blair et al. (2021) In addition, there is hope for the development of targeted therapies targeting downstream effector molecules.

MEK1 and MEK2 are also downstream effectors of KRAS. They activate ERK effectors which translocate to the nucleus to catalyze the phosphorylation of transcription factors and other regulatory proteins and are gatekeepers of the MAPK pathway. Preclinical data suggested that MEK inhibition could be an appealing strategy for the treatment of NSCLC driven by upstream effector mutations such as KRAS mutations and several MEK inhibitors have been developed to inhibit KRAS mutant NSCLC. Jeanson et al. (2019) Trametinib is an oral, reversible, potent, selective inhibitor of MEK1 and MEK2 with an IC50 of 0.7-0.9 nmol/L46. Trametinib in combination with dabrafenib represents the only MEK inhibitor containing regimen that is approved for advanced NSCLC patients with BRAFV600E mutation. Kim et al. (2018) In this report, we share cases of advanced lung adenocarcinoma patients with KRAS G12D mutations who have received trimethoprim treatment and achieved good results, and briefly review the research progress of KRAS mutations in NSCLC.

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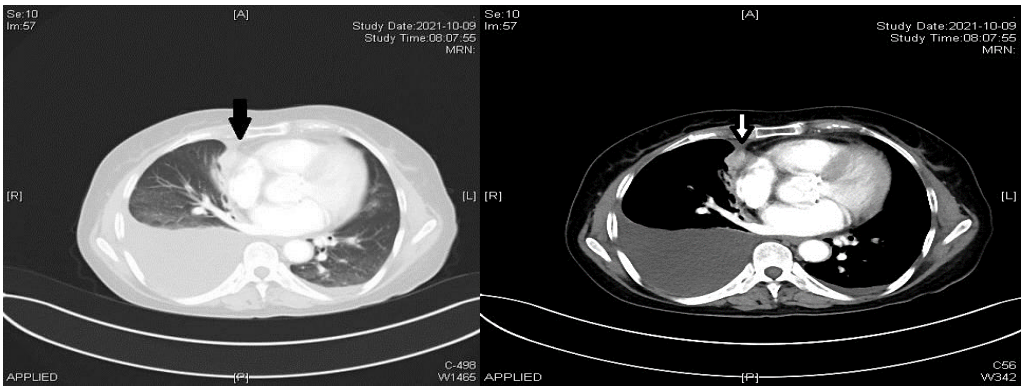
CASE REPORT :

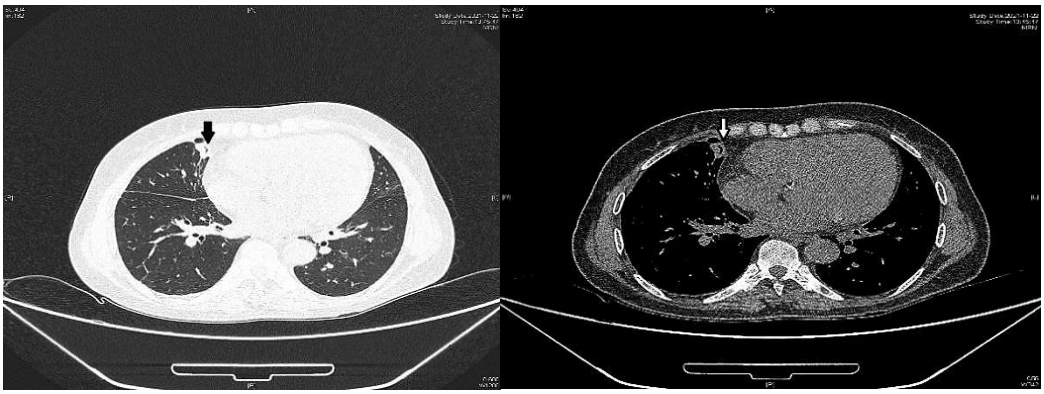
The patient was a 65-year-old female with no smoking history. She underwent radical resection of rectal cancer and fistulation ten years ago. In October 2021, she went to our hospital because of cough for 1 week. The patient had no fever, chest pain and hemoptysis. Chest enhanced CT showed a 2.1cmx2.8cm tumor in the middle region of the right lobe of the lung, thickening of the right pleura and massive pleural effusion in the right chest. （Figure 1A）

Figure 1: CT scans of the patient before trametinib and follow-up after Trametinib treatment. The meaning of arrows is the location of the lesion.

A:



B:



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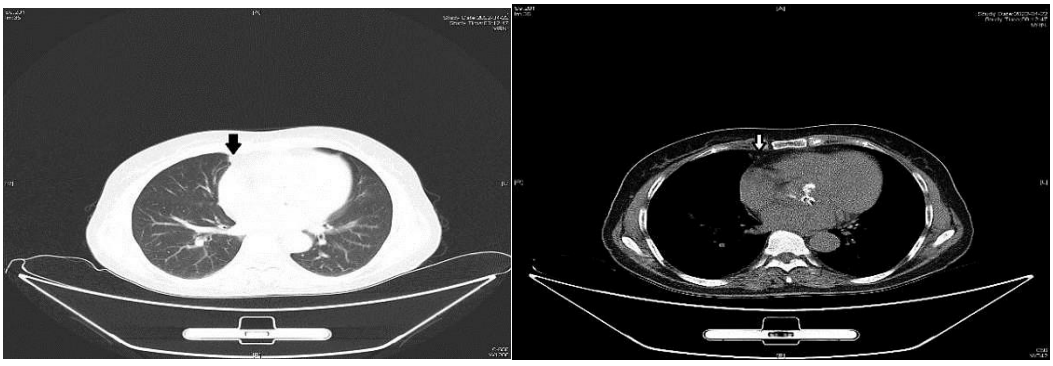
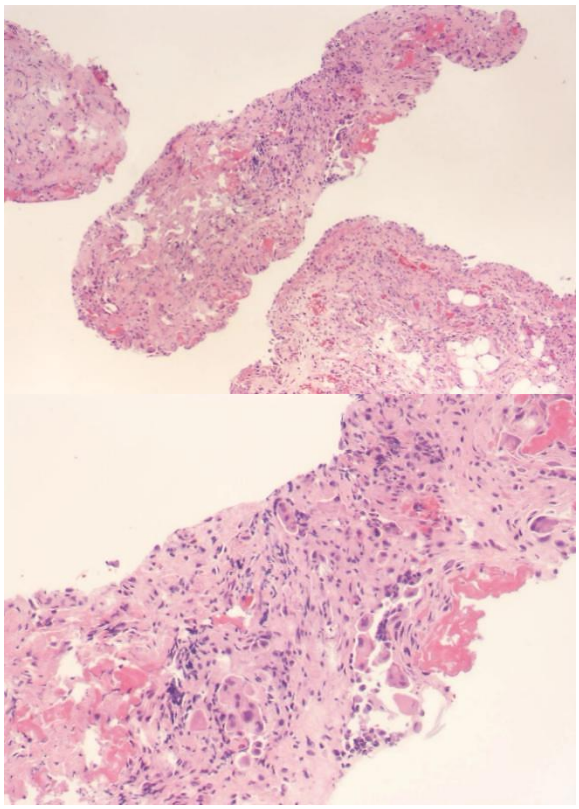


(A) October 9, 2021: physical examination of chest CT, tumor size is 2.1cm × 2.8 cm; (B) November 22, 2021: CT images after trametinib treatment;(C): April 22, 2022 : CT images during trametinib treatment.

Abdominal CT showed peritoneal and omental metastasis. Brain magnetic resonance imaging revealed no additional abnormalities. The pathological diagnosis of the biopsy was adenocarcinoma (Figure 2), stage IVA (T3N3M1).

Figure 2: The pathological diagnosis of the biopsy was adenocarcinoma.



Because the patient had no operational condition, she underwent right thoracic puncture drainage and intrathoracic perfusion of cisplatin 40mg once. To explore possibility of targeted therapy, the tumor samples were subjected to genomic sequencing by using next-generation sequencing (NGS), and the results showed that This patient has a KRAS G12D mutation, and has a co mutation of TP53 and FGFR1, while EGFR, ALK, ROS1, and other sensitive genes are all negative (Figure 3). On October 29th 2021, the patient subsequently received trametinib (2 mg, qd po) treatment.

After one month of trametinib, her cough was alleviated a lot. CT re-examination showed the size of tumor was reduced and the assessment was partial response (PR) according to RECIST 1.1 (Figure 1B). The patient continued to take trametinib, and after 5 months, the tumor is still not enlarged, and no new lesions were found (Figure 1C). The patient maintained trametinib therapy until disease progression was confirmed by a CT scan of the chest in July 2022, with a progression-free survival of 8.3 months.

The main treatment-related side effect observed were skin itching and paronychia, but it was manageable. The patient underwent a second NGS after progression, which showed MET amplification with a mutation frequency of 1.5%. The patient is now stable and is taking Crizotinib for treatment.

Figure 3: Patient next-generation sequencing (NGS) test results.

Mutated genes	Transcription sequence	Modified base	Modified amino acids	Function area	Mutation frequency
FGFR1	NM_023110.2	c.304G>A	p.V102I	EX3	49.3%
KRAS	NM_033360.2	c.35G>A	p.G12D	EX2	4.7%
TP53	NM_000546.5	c.451C>T	p.P151S	EX5	1.9%

DISCUSSION

Kirsten mouse sarcoma virus oncogene homolog (KRAS) is a mutant subtype of Rat sarcoma virus oncogene homolog (RAS), and is one of the most common mutant genes in NSCLC. Prior et al. (2012), Singh et al. (2015) KRAS encodes a membrane-bound guanosine triphosphatase (GTPase) and as a switches between the active guanosine triphosphate (GTP) binding state and the inactive guanosine diphosphate (GDP) binding state. Kranenburg et al. (2005) The active form of KRAS acts like a cellular switch that, when activated by extracellular upstream signal stimulation (such as EGFR), activates downstream signaling pathways responsible for basic cellular processes. Malumbres et al. (2003) Point mutations are a common disorder in the KRAS gene, leading to a structurally active GTP binding state that triggers downstream carcinogenic pathways. Bourne et al. (1990), Bourne et al. (1991), Scheffzek et al. (1997) In the case of NSCLC, KRAS mutations occur predominantly (95%) at codons 12 (> 80%) and 13. A large study found that the most common codon variants in the protein were G12C, which accounted for 39% of KRAS mutations, followed by G12V (21%) and G12D (17%). Compared with other KRAS mutations, G12C is more common in women and smokers. In addition, among never-smokers, the most common KRAS mutation was KRAS G12D (56%). Dogan et al. (2012) The type of KRAS mutation can also affect downstream signal transmission. For example, cell lines containing KrasG12D activate the PI3K-AKT pathway better than other KRAS mutant subtypes. Ihle et al. (2012), Xu et al. (2017), Cruz-Migoni et al. (2019), Zeng et al. (2017) KRAS mutations are often associated with co mutations in other genes. A clinical study involving 330 patients with advanced KRAS mutant lung cancer found that TP53 (42%), STK11 (29%), and Keap1/NFE2L2 (27%) were significantly associated with KRAS co mutations. Different co mutations may exhibit different biological characteristics, modes of

immune system involvement, and treatment vulnerabilities. Arbour et al. (2018) For example, a study on the impact of KRAS mutations on immune biomarkers showed that the expression of PD-L1 protein and the infiltration of immune cells (activated CD4 memory T cells, helper T cells, M1 macrophages, and NK cells) in the KRAS G12D/TP53 mutant group were significantly reduced. Gao et al. (2020) Our patient is an elderly nonsmoking woman with a KRAS G12D mutation and a TP53 co mutation in advanced lung adenocarcinoma.

Some prospective studies have shown that KRAS mutations predict poor survival and efficacy of EGFR TKI. Ying et al. (2015) Because as a downstream gene of EGFR, KRAS mutations can lead to sustained activation of the downstream Raf-ERK-MEK pathway, resulting in reduced efficacy of EGFR-TKIs. Mao et al. (2010) In contrast, patients with KRAS mutations may respond better to immune checkpoint inhibitors (ICIs), Cinosero et al. found that patients with KRAS mutations responded better to PD-1 inhibitors than patients with KRAS wild-type mutations. Cinausero et al. (2019) In a 2017 meta-analysis involving 3025 patients, immunosuppressants prolonged OS in the KRAS mutant subgroup (HR=0.65, P=0.03). Lee et al. (2018) The study by Liu et al. suggests that this result may be related to an increase in immunogenicity caused by an increase in the proportion of PDL1/CD8 tumor infiltrating lymphocytes (TILs) in patients with KRAS mutations. Liu et al. (2020) Unlike the predicted efficacy results of EGFR TKI and ICIs, there is considerable controversy as to whether KRAS mutations can predict the efficacy of chemotherapy in patients. For example, early preclinical data suggest that the presence of KRAS mutations in the NSCLC model induces higher sensitivity to pemetrexed. Moran et al. (2014) In the TRIBUTE trial, when paclitaxel/carboplatin combined with erlotinib or placebo were compared in patients with advanced NSCLC, there was no difference in the objective response rate (ORR) and overall survival (OS) for KRAS mutation status. Eberhard et al. (2005) And in a retrospective clinical study receiving KRAS mutations in advanced nonsquamous NSCLC patients treated with first-line platinum-based chemotherapy have no predictive value. Mellema et al. (2013) However, different KRAS mutant subtypes may have different responses to chemotherapy. For example, in a retrospective analysis of 1190 NSCLCs with KRAS mutations, models carrying KRAS G12C were associated with increased responses to taxanes and pemetrexed, and showed resistance to cisplatin. Models containing KRAS G12D were resistant to taxanes. Finally, KRAS G12V models were sensitive to cisplatin and resistant to pemetrexed. Renaud et al. (2018)

As the most common genetic mutation in NSCLC, KRAS has historically been considered a target that cannot be administered. Most of the past efforts, including targeting the KRAS protein itself and its post translational modifications, membrane localization, and protein protein interaction, have not been proven successful in clinical studies. Christensen et al. (2020) This has recently begun to change with novel targeted therapies that have been developed to target KRAS G12C. Previous studies have shown that the lack of pockets for RAS proteins to bind to small molecules with high affinity, as well as the high intracellular concentration of GTP and its high affinity for KRAS have led to the failure of direct targeting of KARS proteins. Papke et al. (2017), Ostrem et al. (2016), Cox et al. (2014) However, other studies have found that the cysteine of mutant KRAS G12C is adjacent to the pocket (P2) of inactivated KRAS. Ostrem et al. (2013) Therefore, the development of many covalent inhibitors has become the focus of attention, especially sotorasib (AMG 510) and adagrasib (MRTX849), which have received high attention. Sotorasib (AMG 510) is an irreversible KRAS G12C inhibitor that provides encouraging results in ORR and response duration (DOR). Hong et al. (2020) It received accelerated approval from the US FDA in May 2021 for the treatment of locally advanced or metastatic NSCLC with KRAS G12C mutations.4 Adarasib (MRTX 849), another KARS G12C inhibitor, was found in the Phase I/II study (Krystore 1: NCT03785249) to exhibit good safety and significant clinical activity in patients undergoing extensive pre-treatment. However, there is acquired resistance to the KRASG12C inhibitor. Reactivation of upstream and downstream pathways has been proven to be the cause of drug resistance. Xue et al. (2020) Other resistance mechanisms have also been described. Awad et al. (2021) A number of selective inhibitors of KRAS G12D are also currently being investigated, MRTX1133 was identified as a noncovalent, potent, and selective inhibitor of KRASG12D. MRTX1133 suppresses KRASG12D signaling in cells and in vivo, and its antitumor benefit was demonstrated in a murine animal model. Wang et al. (2022) Currently, another strategy with high attention is to inhibit its downstream signal transduction, involving the mechanism targets of PI3K, MEK, Ral, rapamycin kinase, and p70S6 kinase. Cully et al. (2008) Studies on the PI3K/AKT/mTOR pathway suggest that using a single therapeutic inhibitor may not be sufficient. In the phase II trial, 79 patients received an oral mTOR inhibitor, ridaforolimus, with an ORR of 1% for complete and partial remission at 8 weeks. There was no significant improvement in the OS group. Vansteenkiste et al. (2015) In a randomized phase II study, the encouraging activity observed with the addition of the MEK inhibitor selumetinib to docetaxel was subsequently not confirmed in a phase III SELECT-1 trial involving more than 500 pre-treatment patients with

KRAS mutant NSCLC. Jänne et al. (2017), Jänne et al. (2013)

Trametinib is an allosteric inhibitor of MEK1/2 capable of inhibiting tumor cells with KRAS mutations by blocking the downstream pathway. Similar to selumetinib, in a previous phase II study, the drug showed similar PFS and response rates to docetaxel in NSCLC patients who had previously treated for KRAS mutations. Blumenschein et al. (2015) More clinical outcomes with trametinib were not as promising enough, the reported overall ORR were just from 12–30%. Haura et al. (2010) We believe that these clinical studies should be further stratified and analyzed, and underestimate the biological heterogeneity resulting from the presence of different KRAS mutant subtypes, coexisting mutations of KRAS mutations, which may significantly affect treatment responses. Previous studies have shown that different amino acid substitutions of KRAS can lead to different downstream effects. Different KRAS mutant subtypes can have different clinical behaviors, and cancers with the same activation gene mutations have significantly different responses to the same targeted treatment. Ihle et al. (2012), Garassino et al. (2011), Ferrer et al. (2018) In another study showed that unique KRAS mutations and concurrent mutations in tumor-suppressor genes are important factors for lung tumor responses to MEK inhibitor. Li et al. (2018) In a previous study, RAS G12C and G12D mutant lung adenocarcinoma cells were effectively inhibited by treating with a combinatorial approach of trametinib and FGFR1 inhibitor. Manchado et al. (2016) With the emergence of immunotherapy as a form of cancer treatment, KRAS mutations are also closely associated with proven immunotherapy biomarkers in NSCLC, including tumor mutation load, programmed death ligand 1 (PD-L1), and tumor infiltrating lymphocytes, indicating that patients with NSCLC with KRAS mutations may benefit from immunotherapy. Liu et al. (2020) However, as mentioned earlier, KRAS symbiotic mutations determine heterogeneity in KRAS mutant cancers. For example, KRAS G12D combined with TP53 co mutation may lead to immunosuppression and reduce the efficacy of immunotherapy. Gao et al. (2020) Based on the characteristics of these preclinical studies, we chose trametinib to treat this patient and ultimately achieved good expectations. Moreover, the side effects of trametinib were manageable in this case. For our Patients, the drug side effects including pruritus and onychomycosis, and no grade III or IV adverse reactions appeared. This is consistent with previous studies, AEs in the trametinib group were rash (59%), diarrhea (47%), hypertension (34%), and nausea (34%), which were mostly grade 1 or 2. We will continue focus on the patient' s treatment.

In summary, our case suggests that patients with advanced NSCLC with KRAS G12D mutations may benefit from trametinib monotherapy, which is inconsistent with previous clinical studies. Therefore, we can boldly speculate that trametinib may play a role by inhibiting KRAS activity, or it may directly inhibit KRAS G12D. On the other hand, we speculate that KrasG12D cell lines are better at activating the MAPK pathway or have higher sensitivity to MAPK than other KRAS mutant subtypes. Therefore, the relationship between trametinib and KRAS G12D needs further in-depth study. Our case herein provides encouraging supporting data to support this type of research.

In recent years, many efforts have been made to achieve the possibility of treatment for patients with NSCLC with KRAS mutations. Certain drugs have been introduced into preclinical and current clinical practice. However, there are still many challenges in the treatment strategy for KRAS mutations. Although small molecule covalent inhibitors of KRAS G12C like sotorasib (AMG 510) and adagrasib (MRTX849) have been developed, drug resistance inevitably occurs in clinical settings and can only be applied to specific mutant subtypes. Therefore, it is necessary to fully study the mechanism of resistance generation and accelerate the development of inhibitors for other mutant subtypes. In addition, due to different mutation subtypes and tumor heterogeneity caused by different symbiotic mutations, treatment and immunotherapy of the KRAS downstream signaling pathway may also have different therapeutic effects. Therefore, the genetic characteristics, mutation mechanisms, and sensitivity to treatment of various KRAS mutant subtypes and different co mutations should be studied more extensively. In addition, considering the limited benefits of the above single therapy for patients, combined treatment is needed to enhance the anti-cancer effect. Currently, a large number of clinical trials of combined therapy are also ongoing. For example, a preclinical experiment showed that the combination of sotorasib and EGFR, MEK, PI3K, or AKT inhibitors can produce stronger synergistic effects. In vivo, sotorasib combined with MEK inhibitors also showed more significant antitumor effects. Canon et al. (2019) In a preclinical study, it was demonstrated that the combination of MEK inhibitors and anti PD-1 inhibitors can increase the number of CD8+tumor infiltrating lymphocytes. Liu et al. (2015) In other preclinical studies, it has been shown that dual inhibition of the RAF/MEK/ERK and PI3K/AKT/mTOR pathways will eliminate compensatory effects and produce better antitumor efficacy. Haagensen et al. (2012), Roberts et al. (2012) However, in a phase Ib open label, dose-increasing, multicenter study, many patients discontinued combined therapy due to the intolerant toxicity of the PI3K inhibitor BKM120 and the MEK1/2 inhibitor MEK162. Bardia et al. (2020)

Therefore, although combination therapy strategies for KRAS mutant subtypes and co mutations have yielded encouraging results in preclinical studies, these combination therapy strategies should be further studied.

All in all, more personalized precise treatment and comprehensive treatment are the inevitable trend in the future treatment of KRAS mutant NSCLC.

DECLARATIONS

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Shandong Provincial Hospital.

Consent for publication

Written informed consent for publication was obtained from this patient.

Competing interests

The authors declare that they have no competing interests.

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