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Case Report

Durable Disease Control with Local Therapy following the Identification of an Acquired Resistance Mechanism in Oligo-Progressive KRAS G12C-mutated Non-small Cell Lung Cancer: A Case Report

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Abstract

KRAS G12C-mutated non-small cell lung cancer (NSCLC) is relatively uncommon in East Asian populations, and mechanisms of acquired resistance remain incompletely defined. We report a patient with metastatic KRAS G12C–mutated NSCLC who received frontline treatment with sotorasib, a KRAS G12C inhibitor. After 7 months of therapy, oligo-progression occurred at the primary tumor site. Repeat next-generation sequencing identified *KRAS* amplification as the putative resistance mechanism. The lesion was treated with stereotactic body radiation therapy, after which sotorasib was continued. The patient has remained free of progression for an additional 12 months to date. This case report highlights *KRAS* amplification as a possible on-target resistance mechanism and underscores the utility of local therapy in selected patients with oligo-progressive disease. Integrating molecular profiling and site-directed therapy may extend the clinical benefit beyond progression on tyrosine kinase inhibitors.

Keywords: Acquired resistance, case report, KRAS G12C, non-small cell lung cancer, sotorasib

Introduction

KRAS has been considered undruggable for the past decades. However, following the landmark study by Shokat *et al*. on the *KRAS* G12C mutation,[1] two approved medications, sotorasib and adagrasib, are now available for the treatment of KRAS G12C–mutated non-small cell lung cancer (NSCLC). The median progression-free survival of KRAS G12C–mutated NSCLC is approximately 5–7 months; however, the mechanism of acquired resistance is still under investigation.

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An analysis of 209 patients from 10 publications worldwide across various cancer types demonstrated that a mechanism of resistance could be identified in only about 60% of these patients.[2] Second-generation KRAS G12C inhibitors are still unavailable. Once progression on a KRAS G12C inhibitor occurs, conventional chemotherapy is widely accepted as the subsequent treatment, often accompanied by related toxicity. In this report, we present a patient with stage IV KRAS G12C–mutated NSCLC treated with frontline sotorasib, a KRAS G12C inhibitor. A putative mechanism of acquired resistance, *KRAS* amplification, was identified after repeat next-generation sequencing (NGS) of the oligo-progressive lesion. Following stereotactic body radiation therapy (SBRT) to the lesion, the patient continued sotorasib and has remained progression-free for an additional 12 months at the most recent follow-up.

Case Report

A 69-year-old man presented to the emergency department with a 3-week history of fever and productive cough. He also reported unintentional weight loss from 56 to 51 kg over the prior year. He was a heavy smoker (1.5 packs per day for 35 years). Chest radiography showed right upper lobe (RUL) atelectasis, and laboratory tests revealed leukocytosis and elevated C-reactive protein. Chest computed tomography demonstrated a 12.3-cm RUL lung mass with mediastinal and right supraclavicular lymphadenopathies and a hypodense component containing an air pocket. Lung cancer with obstructive pneumonia complicated by a lung abscess was suspected.

Ultrasound-guided biopsies of the RUL mass and right supraclavicular lymph node were performed, and the pathology from both sites showed thyroid transcription factor 1-positive adenocarcinoma. Brain magnetic resonance image revealed a solitary brain metastasis, and whole-body positron emission tomography demonstrated multiple bone metastases in addition to the primary lung lesion. Overall, the diagnosis was RUL lung adenocarcinoma, clinical stage T4N3M1c, stage IVB (American Joint Committee on Cancer 8th edition) with brain and bone metastases.

Initial molecular testing (Epidermal growth factor receptor [EGFR] with a cobas® EGFR Mutation Test v2 and anaplastic lymphoma kinase [ALK] with a VENTANA® ALK (D5F3) CDx Assay) identified no actionable alterations, whereas the programmed death-ligand 1 (PD-L1) expression was high (100% of the tumor cells; VENTANA® PD-L1 (SP263) Assay). While waiting for NGS results from FoundationOne® CDx, the patient received one cycle of pembrolizumab (200 mg). After appropriate antibiotic therapy and pigtail drainage, the pulmonary infection was controlled. NGS subsequently detected a *KRAS* G12C mutation, and sotorasib (the only available KRAS G12C inhibitor) was initiated. Laboratory tests, including liver function, were monitored twice during the 1st week, weekly for the remainder of the 1st month, and monthly thereafter. To date, the patient has not experienced specific adverse events during sotorasib therapy.

The first image assessment demonstrated a partial response, including regression of the intracranial lesion [Figure 1]. After 7 months, oligo-progression confined to the primary RUL lesion was observed, whereas all other disease sites remained in partial response. Because of solitary progression, the patient underwent SBRT for the lung lesion after a repeat biopsy, and sotorasib was continued. Pathology of the oligo-progressive lesion showed adenocarcinoma with morphology similar to the original specimen. Repeat NGS using FoundationOne® CDx demonstrated *KRAS* G12C with amplification, interpreted as a mechanism of acquired resistance.

At the time of this report, the patient has remained on sotorasib for an additional 12 months, with no evidence of progression at any site following local therapy to the oligo-progressive lung lesion.

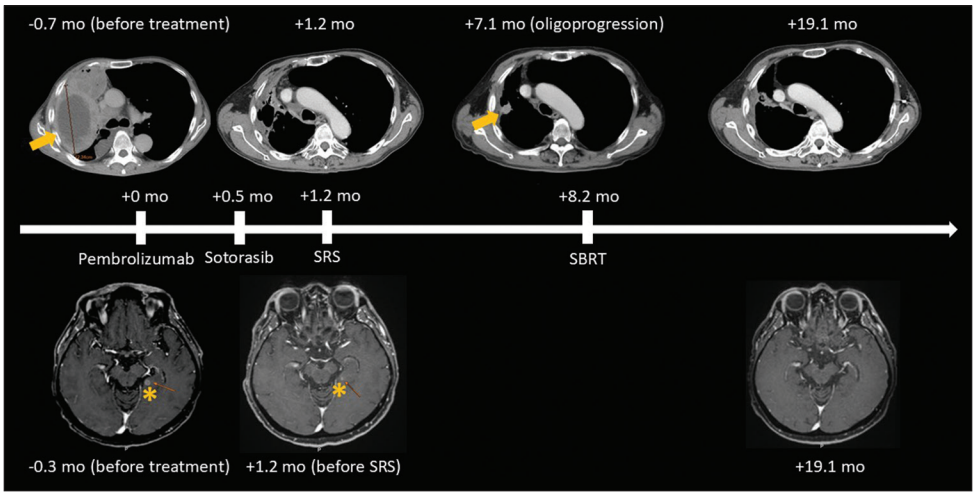

Figure 1: Treatment course: Contrast-enhanced computed tomography and magnetic resonance image demonstrating initial tumor response, oligo-progression, and post-SBRT stability. mo: Month, SRS: Stereotactic radiosurgery, SBRT: Stereotactic body radiation therapy. Arrows indicate the target thoracic tumor lesion. Asterisks (*) denote intracranial metastatic lesion

Discussion

RAS mutations are known oncogenic drivers across multiple cancer types, including pancreatic ductal adenocarcinoma (86%), colorectal cancer (CRC, 41%), NSCLC (32%), and melanoma (29%). RAS mutations are also less commonly found in head and neck squamous cell carcinoma (5%) and urothelial carcinoma (4%).[3] In NSCLC, *KRAS* G12C is the most common hotspot mutation, and it is strongly associated with smoking. The prevalence of *KRAS* mutations differs markedly between Western and East Asian populations, accounting for roughly 25%–30% of tumors in Western patients but only 5%–7% in East Asian patients.[4] This difference is likely multifactorial, reflecting genetic background and patterns of cigarette exposure. East Asian patients also have a higher prevalence of EGFR mutations and are predominantly nonsmokers.[5]

RAS proteins comprise a catalytic guanine-binding domain (G domain) and a hypervariable region (HVR). Based on HVR sequence variability, the RAS family includes four isoforms: HRAS, NRAS, KRAS4A, and KRAS4B. The HVR mediates membrane localization, whereas the G domain (containing the P loop, switch I, and switch II regions) binds guanine nucleotides, activates downstream signaling pathways, chiefly mitogen-activated protein kinase and PI3K/AKT/mTOR pathways, and results in cell proliferation and survival.[6] RAS proteins are switched between the GDP-bound "OFF" state and the GTP-bound "ON" state. For decades, KRAS was considered "undruggable." Its affinity for GTP is approximately six orders of magnitude higher than the affinity of BRAF for ATP, making it difficult for small molecule inhibitors to compete at the nucleotide binding site. A breakthrough in treatment occurred when Shokat's team noticed that the *KRAS* G12C mutation adds a "sticky" cysteine. They used this new handle to build drugs that covalently bind the mutant protein, hold it in its inactive GDP-bound form, and prevent downstream signaling.[1] The KRAS G12C (OFF) inhibitors sotorasib and adagrasib have since been approved by the United States Food and Drug Administration as subsequent-line therapy for KRAS G12C–mutated NSCLC and CRC [summarized in Table 1].

Immunotherapy with anti-PD-1 checkpoint inhibitors alone or combined with chemotherapy is now considered first-line therapy for KRAS G12C–mutated NSCLC. In subgroup analyses of the KEYNOTE-042 and KEYNOTE-189 trials, patients with *KRAS* G12C mutations appeared to benefit from pembrolizumab administered either as monotherapy or in combination with chemotherapy.[12] Sotorasib in combination with pembrolizumab was evaluated in the phase 1 CodeBreaK 100 and 101 trials, and pooled analysis showed that up to 50% of the patients experienced Grade 3–4 hepatotoxicity.[13] Several phase 3 trials investigating other KRAS G12C inhibitors in combination with checkpoint inhibitors, including KRYSTAL-7 (NCT04613596) and SUNRAY-01 (NCT06119581), are currently ongoing. Our patient initially received pembrolizumab monotherapy. However, because he declined further intravenous therapy, we prioritized maintaining both quality of life and treatment efficacy. He started sotorasib 2 weeks after receiving pembrolizumab and experienced no treatment-related hepatotoxicity.

Resistant mechanism of KRAS G12C inhibitors

As with other targeted therapies, resistance to KRAS G12C inhibitors is inevitable. Current post-progression options

Table 1: Summary of efficacy and safety of currently approved KRAS G12C inhibitors

Trials	Patients	Agents	PFS (months)	OS (months)	ORR (%)	≥ Grade 3 TRAEs	FDA approval
CodeBreaK 200 (phase 3)[7]	Advanced NSCLC, previously treated with platinum-based chemotherapy and anti-PD-(L)1 therapy	Sotorasib (vs. docetaxel)	5.6 versus 4.5, HR 0.66 (95% CI, 0.51–0.86) (Primary endpoint)	10.6* versus 11.3, HR 1.01 (95% CI, 0.77–1.33)	28.1 versus 13.2	Diarrhea (12%), ALT increase (8%)	2021 accelerated approval
KRYSTAL-12 (phase 3)[8]	Advanced NSCLC, previously treated with platinum-based chemotherapy and anti-PD-(L)1 therapy	Adagrasib (vs. docetaxel)	5.5 versus 3.8, HR 0.58 (95% CI, 0.45–0.76) (primary endpoint)	Immature	31.9 versus 9.2	ALT increase (8%), Diarrhea (5%)	2022 accelerated approval
CodeBreaK 300 (phase 3)[9,10]	Metastatic CRC, received prior fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy	Sotorasib† + panitumumab (vs. trifluridine–tipiracil or regorafenib)	5.6 versus 2.0, HR 0.48 (95% CI, 0.30–0.78) (Primary endpoint)	NR versus 10.3, HR 0.70 (95% CI, 0.41–1.18)	26.4 versus 0	Dermatitis acneiform (11.3%), hypomagnesemia (5.7%), rash (5.7%)	2025 approval
KRYSTAL-1 (phase 1/2)[11]	Advanced CRC, no available standard-of-care treatment	Adagrasib‡ + cetuximab	6.9	13.4	46 (primary endpoint)	Dermatitis acneiform (3%), diarrhea (3%), stomatitis (3%)	2024 accelerated approval

*34% of patients in the docetaxel group subsequently received a KRAS G12C inhibitor, †Only showing the 960-mg sotorasib group, ‡Not showing adagrasib monotherapy group. TRAEs: Treatment-related adverse events, NSCLC: Non-small cell lung cancer, CRC: Colorectal cancer, NR: Not reached, CI: Confidence interval, HR: Hazard ratio, PFS: Progression-free survival, OS: Overall survival, ORR: Objective response rate, FDA: Food and Drug Administration

Table 2: Mechanism of acquired resistance to KRAS G12C inhibitors

Mechanism[2,16]	Examples	Frequency (%)
Genetic		
On-target: Switch II pocket mutation	*KRAS* Y96 C/D, H95D, R68S	0–30
On-target: Another *KRAS* activating mutation	*KRAS* G12X, G13X, Q61X	15–60
On-target: *KRAS* G12C amplification	*KRAS* G12C amplification	10–60
Off-target: Upstream RTK bypass	Amplifications or mutations of EGFR, FGFR	25–75
Off-target: Downstream MAPK, PI3K bypass	*PIK3CA* mutation, PTEN loss	11–58
	Mutations of *BRAF*, *MEK*	11–31
Off-target: *HRAS*/*NRAS* activating mutation	*NRAS* Q61L, G13V	6–30
Adaptive		
Upregulation of RTKs and activating wild-type RAS	KRAS G12C inhibition leads to loss of negative feedback and then upregulation of upstream of RTKs	25–50

RTK: Receptor tyrosine kinase, MAPK: Mitogen-activated protein kinase, EGFR: Epidermal growth factor receptor, FGFR: Fibroblast growth factor receptor

include chemotherapy or immune checkpoint inhibitors, if they have not been previously administered. There are no specific recommendations for the management of oligo-progression in patients with KRAS G12C-mutant NSCLC. Based on clinical evidence of EGFR and ALK tyrosine kinase inhibitors,[14] we performed local therapy to the oligo-progressive lesion. Because the other lesions remained stable, we continued sotorasib with close monitoring. No further progression has been observed subsequently, suggesting resistance arose only within that lesion. To our knowledge, this is the first report to support the use of local ablative therapy for oligo-progressive disease in KRAS G12C-mutant NSCLC. A limitation of the report is that we were unable to perform biopsies and NGS on both progressive and non-progressive lesions.

Multiple mechanisms of acquired resistance to KRAS G12C inhibitors have been described [Table 2].[15,16] In NSCLC, approximately half involve genetic alterations, while the remainder reflect adaptive mechanisms. KRAS G12C (ON) inhibition via a tri-complex mechanism may overcome switch II pocket mutations. In a phase 1 study, elironrasib (RMC-6291) achieved an objective response rate (ORR) of 50% in CRC patients who had previously been treated with KRAS G12C inhibitors.[17] Because acquired genetic alterations are diverse, pan-KRAS/RAS inhibitors could potentially overcome this obstacle. Daraxonrasib (RMC-6236), a pan-RAS inhibitor (ON) that acts through a tri-complex mechanism, produced an ORR of 38% in patients with previously treated NSCLC.[18] The phase 3 RASolve-301 study (NCT06881784) is underway. Beyond mutant alleles, adaptive resistance mechanisms often emerge. Following KRAS inhibition, loss of negative feedback leads to upregulation of wild-type RAS proteins. Pan-RAS/KRAS inhibitors can address this issue by simultaneously inhibiting wild-type RAS. Preliminary data on the combination of elironrasib and daraxonrasib have shown greater efficacy but also increased toxicity.[19] KRAS amplification accounts for approximately 15% of on-target resistance mechanisms.[2] Dose escalation of a KRAS G12C inhibitor to overcome this mechanism may be reasonable; however, there are currently no published safety data on higher doses of sotorasib. Enrollment in a clinical trial of next-generation KRAS inhibitors could be considered if multiple progressive lesions are identified.

In conclusion, we describe a patient with KRAS G12C-mutated NSCLC whose disease was well controlled with frontline sotorasib. Repeat NGS indicated a potential mechanism of acquired resistance; nevertheless, oligo-progression was successfully managed with local therapy. The patient remains on sotorasib without evidence of progression, thereby preserving the option of enrollment in clinical trials of novel KRAS inhibitors in the future.

Declaration of patient consent

This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and its amendments. The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

Author contributions

Yi-Ting Tsai collected clinical data and drafted the manuscript. Wei-Hsun Hsu and Chien-Huai Chuang supervised data interpretation, and revised the manuscript. All authors reviewed and approved the final version of the manuscript.

Data availability statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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