Clinical Case Report

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RET fusion in advanced non-small-cell lung cancer and response to cabozantinib

A case report

Yucong Wang, MB[a], Yinghui Xu, MD[a], Xu Wang, MD[a], Chao Sun, MM[a], Ye Guo, MM[a], Guoguang Shao, MD[b], Zhiguang Yang, MD[b], Shi Qiu, MM[a], Kewei Ma, MD[a,*]

Abstract

Rationale: Lung cancer is a series of gene-driven disease. *EGFR*, *ALK*, and *ROS1* are 3 major driver genes that play an important role in lung cancer development and precision management. Additionally, rare genetic alterations continue to be discovered and may become novel targets for therapy. The *RET* gene is one of such rare genetic alteration of non-small cell lung cancer (NSCLC). In this report, we present a RET-positive case that benefited from cabozantinib treatment.

Patient concern: A 50-year-old male patient was diagnosed with lung adenocarcinoma 2 years ago, at that time he received palliative surgery of pulmonary carcinoma and completed 4 cycles of chemotherapy with gemcitabine and cisplatin. Six months later, he was hospitalized in our cancer center due to the disease recurrence, presenting with pleural metastasis.

Diagnosis: Gene alteration was examined using the intraoperative specimen by PCR method, and *KIF5B/RET* gene fusion was detected. Therefore, the patient was diagnosed with late-stage lung adenocarcinoma with *RET* gene mutation.

Interventions: The patient received treatment with cabozantinib from June 2017.

Outcomes: Cabozantinib was administered (140 mg orally, once daily) for approximate 9 months, and his disease achieved stable disease (SD). During that period, there were no severe adverse events (AE), except for a grade II rash (CTCAE 4.0).

Lessons: We found that the *RET* fusion gene is a novel driver molecular of lung adenocarcinoma in patients without common mutations in such genes as *EGFR*, *ALK*, and *ROS1*. This case report supports a rationale for the treatment of lung adenocarcinoma patients with a RET fusion and provides alternative treatment options for these types of NSCLC patients.

Abbreviations: AEs = adverse events, GDNF = glial cell line–derived neurotrophic factor, NCCN = National Comprehensive Cancer Network, NSCLC = non-small-cell lung cancer, ORR = overall response rate, OS = overall survival, PD = progressed disease, PFS = progression-free survival, RTKs = receptor tyrosine kinases, SD = stable disease.

Keywords: cabozantinib, non-small-cell lung cancer, *RET* gene, targeted therapy

1. Introduction

Lung cancer is a series of gene-driven disease. *EGFR*, *ALK*, and *ROS1* are 3 major driver genes that play an important role in lung cancer development and precision management.[1] Additionally, a rare genetic alteration, which is called RET rearrangement, is detected in 1% to 2% of non-small cell lung cancer (NSCLC).[2] On the other hand, Gene rearrangements involving *RET*, have been characterized most extensively in papillary thyroid carcinomas, and later have been observed in other cancers, especially lung cancer.[3] Cabozantinib (XL184) is a small-molecule kinase inhibitor with activity toward MET and *VEGFR2*, as well as *RET*, KIT and *FLT3*.[4,5] It could inhibit tumor angiogenesis, invasiveness, metastasis, and tumor progression.[5] A phase II study had reported the response to cabozantinib in patients with *RET* fusion-positive lung adenocarcinoma, and the partial response with a 66% decrease was observed after 4 to 12 weeks of treatment.[3] The final outcomes of this study reported the overall response to cabozantinib in patients with *RET* fusion-positive lung adenocarcinoma could achieve 28%.[6] Basing on this rationale, cabozantinib has been suggested as a novel targeted therapy according to the guideline of National Comprehensive Cancer Network (NCCN). However, there is still no data about progression-free survival (PFS) or overall survival (OS) of cabozantinib used in RET fusion-positive lung cancer. Furthermore, related clinical trials and reports about the duration of effectiveness with cabozantinib in NSCLC are

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Informed written consent was obtained from the patient for publication of this case report and accompanying images.

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[a] Cancer Center, [b] Thoracic surgery department, The First Hospital of Jilin University, Changchun, Jilin, China.

[*] Correspondence: Kewei Ma, Cancer Center, The First Hospital of Jilin University, 71 Xinmin Street, Changchun, Jilin 130021, China (e-mail: makw@jlu.edu.cn).

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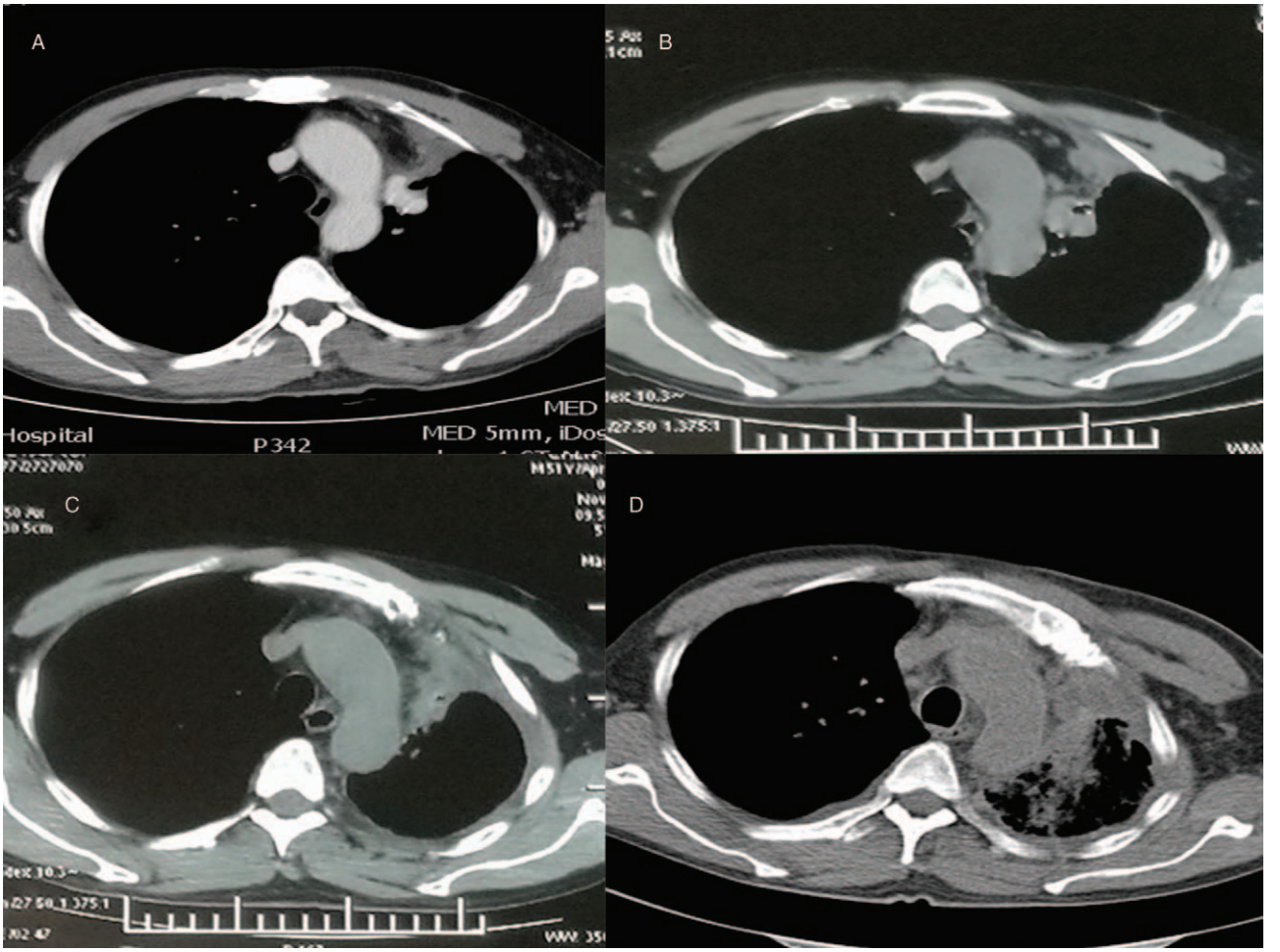

Figure 1. Chest CT. (A) shows SD after 4 cycles of chemotherapy on December 15, 2016. (B) shows multiple pleural metastases on May 31, 2017. (C) shows SD after 5 months cabozantinib on November 9, 2017. (D) shows disease progression after 9 months cabozantinib in March 2017.

limited. In this report, we present a RET-positive case that benefited from cabozantinib treatment in the real world, from the response to PFS, and still from the effectiveness to adverse events (AEs).

2. Case report

The patient was a 50-year-old male presenting with a cough, sputum, and left chest pain that persisted for 20 days; he sought medical attention from a doctor on July 20, 2016. A chest CT scan (performed July 12, 2016) showed a lesion measuring approximately 2.5×2.0 cm in the left lung and the absence of enlarged lymph nodes in the mediastinum. No metastases were found in other areas of the body, which supported an initial clinical diagnosis of left lung upper lobe cancer (cT1bN0M0 Stage IA) before surgery. The patient underwent resection and lymphadenectomy for the left lung upper lobe cancer on July 25, 2016. Postoperative pathology showed a left lung upper lobe middle differentiated adenocarcinoma measuring $2.5 \times 2 \times 1.8$ cm. Para-aortic lymph nodes in the mediastinum and multiple visceral pleural metastases were found. Immunohistochemistry analyses of the tumor showed TTF-1+, Syn-, Ki-67 (20%), CD31 +, CK+, *EGFR*- and *ALK*-. Following postoperative pathology, a new diagnosis was made of left lung upper lobe adenocarcinoma (pT1N2M1, Stage IV, *EGFR*-, *ALK*-). Subsequently, the patient received 4 cycles of chemotherapy with gemcitabine and cisplatin from August 2016 to December 2016; stable disease (SD) was observed during this period by chest CT (Fig. 1A). Chemotherapy could not continue due to the poor tolerance of this patient. Six months later, he felt pain in his left chest. Multiple pleural metastases were revealed by chest CT (May 31, 2017) (Fig. 1B), indicating progressed disease (PD). He did not accept second-line chemotherapy due to the obvious adverse effects. Furthermore, we performed genetic testing of the patient's resected tumor tissue and identified the presence of the *KIF5B/RET* fusion gene; other mutations in *EGFR*, *KRAS*, *ALK* and MET were all negative. According to NCCN guidelines, the patient began treatment with cabozantinib (140 mg orally, once daily), which is a receptor tyrosine kinase inhibitor of *RET*. Subsequently, the patient's left chest pain was alleviated and disappeared after 1 month of targeted therapy. Chest CTs were performed every 2 months, and SD continued (Fig. 1C) until March 2018 (Fig. 1D). At this point, *RET* inhibitor (cabozantinib) therapy was stopped. The complete PFS was more than 9 months. No severe AEs were observed in this process, except rash (grade II).

3. Discussion

The *RET* gene is a novel driver of lung cancer differing from other major driver genes, such as *EGFR*, *ALK*, and *ROS1*. *RET* is an

oncogene located on chromosome 10q11.2 initially identified from the NIH3T3 cells of transformed cultured mice by Takahashi et al in 1985.[7,8] The *RET* gene encodes the *RET* receptor protein, one of the first receptor tyrosine kinases (RTKs) found to play a role in neoplasia.[9] RTKs consist of 3 domains:

1. an extracellular domain (containing 4 cadherin-like repeats, a calcium binding site and a cysteine-rich region),
2. a transmembrane domain, and
3. an intracellular tyrosine kinase.[8,9]

The ligands of the RET receptor belong to the glial cell line-derived neurotrophic factor (GDNF) family of proteins, which includes GDNF, neurturin (NRTN), artemin (ARTN), and persephin (PSPN). The RET receptor and its ligand form a multimeric complex that can activate the kinase domain, resulting in autophosphorylation of the intracellular domain. Activation of RET protein can activate several signaling pathways, including those of mitogen activated protein kinase (MAPK), phosphoinositide 3-kinase (PI3K)/AKT, Rac/c-jun NH, kinase (JNK), phospholipase C-γ, and Ras/mitogen-activated protein (MAP) kinase (also known as ERK).[9,10] Normally, RET is essential for the development of the enteric nervous system, kidney and embryogenesis of mammals, and its expression level in normal lung tissue is notably low.[11,12] The mechanisms of the relationship between RET and distinct neoplastic diseases remain largely unknown. The first association of RET with tumorigenesis was its discovery in papillary thyroid carcinoma (PTC) in 1987.[13]*RET* gene rearrangements are frequently found in papillary thyroid carcinomas.[14] Furthermore, increased *RET* gene expression was identified in different diseases, including multiple endocrine neoplasia type 2 (MEN2)[14,15] and Hirschsprung disease.[16] Recently, the *RET* gene has been reported in lung cancer development.

The *RET* gene was first identified in lung adenocarcinoma patients in 2012 by Kohno et al[2] Several studies reported that the *RET* gene, accounting for approximately 1% to 2% of non-small-cell lung carcinomas (NSCLCs) worldwide,[2,17–19] is almost observed in lung adenocarcinoma patients, especially in younger individuals, females, and/or never/light-smokers.[20] Meanwhile, *RET* is often regarded as an independent factor that does not co-occur with such mutations as *KRAS*, *EGFR*, *BRAF*, *MEK1*, *HER2*, and *ALK* fusions.[2,6,20,21]

The *RET* gene combines with a partner gene to form a fusion gene, activating the *RET* tyrosine kinase, subsequently evading regulation by ligands and activating tyrosine kinase by autophosphorylation.[2,12,22,23] Multiple *RET* fusion genes were identified in lung adenocarcinoma patients. To date, at least 7 *RET* fusion partner genes involving KIF5B, CCDC6, CUX1, TRIM33, NCOA4, KIAA1468 and KIAA1217 have been identified in lung adenocarcinoma.[24,25]*KIF5B*, presented in the case report, is the most common fusion partner gene accounting for approximately 70% to 80% of the rearrangements followed by CCDC6-RET and NCOA4-RET.[3,18,19,22]*KIF5B-RET* is a fusion gene between *KIF5B* and the *RET* proto-oncogene caused by a pericentric inversion of 10p11.22–q11.21. This fusion was first revealed by whole-genome and transcriptome sequencing by Ju et al[12] The fusion occurred between the 16th exon of KIF5B and the 12th exon of *RET*.[12] The fusion kinase consists of 638 N-terminal residues of *KIF5B* and 402 C-terminal residues of *RET* kinase. The fusion protein contains a coiled-coil domain of *KIF5B* and a tyrosine kinase unit from *RET*; the coiled-coil domain induces dimerization of the fusion kinase, which activates the fusion oncogene.[12]

As emerging targeted agents, cabozantinib and vandetanib have been recommended by NCCN guidelines (which are based on a series of clinical trials) for non-small-cell lung cancer with *RET* fusion. As a receptor tyrosine kinase inhibitor with activity against *MET*, *VEGFR2*, *FLT3*, *c-KIT*, and *RET*, cabozantinib could decrease metastasis potential and tumor invasiveness.[4] Cabozantinib was first approved by the Food and Drug Administration (FDA) for medullary thyroid carcinoma in 2012. In 2015, based on a prospective phase II trial (NCT01639508), cabozantinib was recommended by the NCCN guidelines for RET rearrangements in patients with non-small-cell lung cancer. This trial (NCT01639508)[6] in patients with advanced RET-rearranged lung adenocarcinoma reported an overall cabozantinib response rate of 28%. Treatment-related adverse events were predominantly grade 1 or grade 2, and the most common treatment-related adverse events of any grade were increased alanine aminotransferase, increased aspartate aminotransferase, hypothyroidism, diarrhea, palmar plantar erythrodysesthesia, and skin hypopigmentation. The most common grade 3 treatment-related adverse events were lipase elevation (15%), increased alanine aminotransferase (8%), increased aspartate aminotransferase (8%), decreased platelet count (8%) and hypophosphataemia (8%).[6] In addition, a recent global multicenter prospective trial[19] collected and analyzed 165 NSCLC patients with a RET-rearranged gene from 29 centers across Europe, Asia and the United States from April 2016. Of those patients, the rate of any complete or partial response to cabozantinib (21 patients), vandetanib (11 patients), and sunitinib (10 patients) were 37%, 18%, and 22%, respectively.

In this case report, we found that the NSCLC patient with the *KIF5B-RET* fusion gene benefited from cabozantinib with a PFS of greater than 9 months and no apparent severe AEs. Given these results, we have identified the RET gene as a new alternative target for lung adenocarcinoma patients without common mutations, such as *EGFR*, *ALK*, and *ROS1*. This case report also provided a useful reference for the treatment of lung adenocarcinoma patients with RET fusions and may provide support for an alternative therapy for this category of NSCLC patient. However, the mechanisms involved in RET-rearranged lung cancers should be further investigated, and larger population samples are needed to verify the effects of therapy targeting RET.

Author contributions

Data curation: Yinghui Xu, Kewei Ma.
Formal analysis: Yucong Wang, Yinghui Xu.
Funding acquisition: Yinghui Xu.
Investigation: Yucong Wang, Yinghui Xu.
Methodology: Yucong Wang, Yinghui Xu.
Project administration: Xu Wang.
Resources: Xu Wang, Chao Sun, Ye Guo, Shi Qiu, Kewei Ma.
Supervision: Chao Sun, Ye Guo, Shi Qiu, Kewei Ma.
Validation: Chao Sun, Ye Guo, Shi Qiu.
Writing – original draft: Yucong Wang.
Writing – review & editing: Yucong Wang, Yinghui Xu, Xu Wang, Guoguang Shao, Zhiguang Yang, Kewei Ma.
Yucong Wang orcid: 0000-0002-9878-9833.

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