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

A case report

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Abstract

Rationale: Lung cancer is a series of gene-driven disease. \textit{EGFR}, ALK, and \textit{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 \textit{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 \textit{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 \textit{RET} fusion gene is a novel driver molecular of lung adenocarcinoma in patients without common mutations in such genes as \textit{EGFR}, ALK, and \textit{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: AE = 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, \textit{RET} gene, targeted therapy

1. Introduction

Lung cancer is a series of gene-driven disease. \textit{EGFR}, ALK, and \textit{ROS1} are 3 major driver genes that play an important role in lung cancer development and precision management.\textsuperscript{[1]} Additionally, a rare genetic alteration, which is called RET rearrangement, is detected in 1% to 2% of non-small cell lung cancer (NSCLC).\textsuperscript{[2]} On the other hand, Gene rearrangements involving \textit{RET}, have been characterized most extensively in papillary thyroid carcinomas, and later have been observed in other cancers, especially lung cancer.\textsuperscript{[3]} Cabozantinib (XL184) is a small-molecule kinase inhibitor with activity toward MET and VEGFR2, as well as \textit{RET}, \textit{KIT} and \textit{FLT3}.\textsuperscript{[4,5]} It could inhibit tumor angiogenesis, invasiveness, metastasis, and tumor progression.\textsuperscript{[3]} A phase II study had reported the response to cabozantinib in patients with \textit{RET} fusion-positive lung adenocarcinoma, and the partial response with a 66% decrease was observed after 4 to 12 weeks of treatment.\textsuperscript{[1]} The final outcomes of this study reported the overall response to cabozantinib in patients with \textit{RET} fusion-positive lung adenocarcinoma could achieve 28%.\textsuperscript{[4]} 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 \textit{RET} fusion-positive lung cancer. Furthermore, related clinical trials and reports about the duration of effectiveness with cabozantinib in NSCLC are
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 × 2 × 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 2017 (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. The RET gene encodes the RET receptor protein, one of the first receptor tyrosine kinases (RTKs) found to play a role in neoplasia. 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.

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).

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.

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