Durable response to low-dose pralsetinib in a renal insufficient patient with NSCLC harboring concurrent CCDC6-RET, LINCO1264-RET, and SEMA5A-RET fusions
A case report

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Abstract

Introduction: RET-rearranged fusions have been considered as oncogenic drivers in 1% to 2% of non-small cell lung cancers (NSCLC). ARROW study has demonstrated a new selective RET tyrosine kinase inhibitors (TKIs) shows remarkable and durable responses in RET-rearranged NSCLC. In this study mainly recruited patients with common fusion partners KIF5B and CCDC6. There is still a lack of definitive conclusions about effective of rare RET fusion variants to anti-RET therapies.

Case report: A Chinese 58-year-old female renal insufficient patient with no history of smoking was diagnosed as stage IIIA (T2N2M0) lung adenocarcinoma. Next-generation sequencing targeting 520 cancer-related genes was performed on the pleural effusion samples and revealed 2 novel RET fusions LINCO1264-RET and SEMA5A-RET, concomitant with a common CCDC6-RET.

Management and outcome: The patient was first treated with multiple lines of chemotherapy and switched to lenvatinib but failed to respond. Due to renal insufficiency, she subsequently received pralsetinib with gradually reduced dosages (400 mg-300 mg-200 mg-100mg qd) and achieved a partial response (PR) lasting for more than 10 months, accompanied by the declined allele frequencies of all 3 RET fusions.

Discussion/conclusions: We reported the first case of the pralsetinib efficacy in NSCLC with 3 concurrent RET fusions. Our case also indicates the sensitivity of the newly identified RET fusions to this RET selective inhibitor pralsetinib, and highlights the low-dose treatment option for patients with renal insufficient background.

Abbreviations: NSCLC = non-small cell lung cancer, PR = partial response, TKIs = tyrosine kinase inhibitors.

Keywords: NSCLC, pralsetinib, renal failure, RET fusion, RET tyrosine kinase inhibitors

1. Introduction

Mapping to chromosome 10q11.2, RET gene encodes a receptor tyrosine kinase comprised of an extracellular domain, a transmembrane region and an intracellular kinase domain. Genomic rearrangements of RET gene can form chimeric tyrosine kinase fusion proteins that often confer the constitutive oncogenic RET activation if the intact kinase domain is retained. RET fusions occur in 1% to 2% of non-small cell lung cancers (NSCLC) and have been established as oncogenic drivers in this disease. To date, a number of clinical studies have investigated a variety of multikinase inhibitors with anti-RET activity, such as vandetanib, cabozantinib and alectinib, in patients with RET-rearranged lung cancer. However, the objective response rate (ORR) (16%–47%) and median progressive-free survival (mPFS) (2.3–7.3 months) are inferior to that seen in other oncogene-addicted NSCLC with targeted therapies, such as EGFR, ALK and ROS1. Moreover, it has been reported that the responsiveness of different RET fusion partners varies to the multi-target inhibitors. More recently, a new generation of highly selective RET tyrosine kinase inhibitors.

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The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this manuscript and any accompanying images.

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progressive disease, PFS = progressive-free survival, PR = partial response.

Figure 1. Timeline of the patient’s treatment history. BOR = best overall response, DFS = disease-free survival, NGS = next-generation sequencing, PD = progressive disease, PFS = progressive-free survival, PR = partial response.
3. Discussion

In NSCLC, more than ten RET fusion partners have been described,[3,6] among which KIF5B-RET occurs the most frequently with the prevalence ranging from 40% to 72%,[1,7] followed by CCDC6 (10-25%). Other identified partner genes include TRIM33, ZNF477P, ERCCI, HTR4, CLIP1 etc.[8] In the ARROW study, 13 cases had other or unknown types of RET fusion, accounting for 10.7%, but no specific fusion partner and its efficacy were reported.[9] In this case, we identified 2 novel RET fusions LINCO1264-RET and SEMA5A-RET co-occurring with the common CCDC6-RET. LINCO1264-RET (intergenic: R12) results in the exon 12 of RET gene 3'-juxtaposed with an intergenic region, while SEMA5A-RET (S5:R12) is predicted to produce an in-frame fusion of SEMA4 exon 5 with RET exon 12. Both novel fusions retain the intact RET kinase domain thus might be potential oncogenic drivers.

After the detection of RET fusions, the patient first received the treatment with a multikinase inhibitor lenvatinib, but the efficacy was limited, it similar with outcome of clinic trials, but no specific fusion partner and its efficacy were reported.[9] In this case, we identified 2 novel RET fusions LINCO1264-RET and SEMA5A-RET co-occurring with the common CCDC6-RET. LINCO1264-RET (intergenic: R12) results in the exon 12 of RET gene 3'-juxtaposed with an intergenic region, while SEMA5A-RET (S5:R12) is predicted to produce an in-frame fusion of SEMA4 exon 5 with RET exon 12. Both novel fusions retain the intact RET kinase domain thus might be potential oncogenic drivers.

Luckily with the recent approval of the new generation of selective RET TKIs, the patient switched to pralsetinib and showed an immediate response. Moreover, allele frequencies of all 3 fusions declined in the pleural effusion as the PR achieved, suggesting the responsiveness of all 3 of them to pralsetinib including the 2 novel ones. In our database, only 1 patient with 3 RET fusions was found, and the abundance
decreased significantly after treatment. In the phase ARROW trial, pralsetinib demonstrated a promising ORR of 60% and DCR of 93% in RET-rearranged NSCLCs. Most patients had a duration of response ≥ 6 months. So far, we have not found report about LINCO1264-RET and SEMA5A-RET co-occurring with the common RET was sensitive to pralsetinib or LOXO 292 (selpercatinib) in the NSCLC. Our case also showed that pleural effusion supernatant is an alternative liquid biopsy specimen for detecting rare RET fusion genes.

Of note, this case had a history of chronic renal insufficiency. The pralsetinib was administrated with gradually reduced dosages (down to 200 mg qd) and eventually discontinued due to the persistent increase in creatinine. Reducing the pralsetinib dosage to 100 mg qd administered creatinine was maintained at grade 2. Pralsetinib is primarily metabolized by liver enzyme CYP3A4 and to a lesser extent by liver enzyme CYP2D6 and CYP1A2, in vitro. It was predominately excreted in feces (approximately 73%). In addition, mild and moderate renal impairment (CLcr 30–89 mL/min) are safe on the exposure of pralsetinib. It has revealed a tolerable toxicity with most treatment-related adverse events (TRAEs) being grade 1 to 2, consisting of increased aspartate aminotransferase (31%), anemia (22%), increased alanine aminotransferase (21%), constipation (21%) and hypertension (20%), elevated blood creatinine (13%), no at grade 3 to 4. In the ARROW trial, 15% and 60% of NSCLC patients required permanent discontinuation of pralsetinib and dosage interruptions, respectively, due to adverse reactions. Dosage reduction was required in 36% of patients. In the last follow-up of our case, reducing the pralsetinib dosage to 100 mg qd the creatinine no further deterioration, and still have clinical benefits.

For the first time, we described a renal insufficient patient with NSCLC harboring 3 concomitant RET fusions, including 2 novel partners LINCO1264 and SEMA5A. The patient failed to respond to lenvatinib but achieved a PR to the reduced dosage of pralsetinib accompanied with declined frequencies of all 3 RET fusions. Our case also indicates the responsiveness of the newly identified RET fusions to pralsetinib and highlights the necessity of dosage interruption especially in treating patients with background diseases.

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