中文題目：帶有ROS-1罕見的融合重組之非小細胞癌以Crizotinib治療後從有效治療反應至快速進展並產生抗藥性：個案報告

英文題目：A ROS-1 mutated NSCLC with uncommon fusion partner treated with crizotinib -from initial good response to acquired resistance with rapid progression

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Introduction:

ROS-1 rearranged non-small cell lung cancer (NSCLC) accounted for around 1% of the NSCLC. Several tyrosine kinase inhibitors (TKIs) had been developed and proved to provide survival benefits for these patients. Crizotinib is a TKI targets anaplastic lymphoma kinase (ALK), which was also proved by FDA for ROS-1 rearranged NSCLC in March 2016. G2032R mutation is the most frequently identified in crizotinib-resistant NSCLC and cabozantinib was reported as one of the potentially agents targeted the G2032R mutated NSCLC. We here reported a case of advanced uncommon ROS-1 fusion gene rearrangement lung adenocarcinoma showing an initial response to crizotinib but developing recurrence within 3 months. The DNA Next-Generation Sequencing (NGS) for liquid biopsy showed G2032R and L2026M mutation, but patient experienced progressive disease instead of respond to cabozantinib.

Case report:

A forty-seven-year-old woman visited our outpatient department with complaints of general weakness and dyspnea for 1 month. Chest radiography showed massive right pleural effusion. Chest computed tomography was arranged and revealed right upper lung tumor with pleural seeding, superior vena cava thombi, mediastinal and neck lymphadenopathy. Diagnostic thoracentesis was done, and cytology showed malignant cell. Neck lymph node biopsy showed poor-differentiated adenocarcinoma with positive TTF-1, which was compatible with pulmonary-origin. EGFR mutation RT-PCR test was negative. Further immunohistochemistry test showed positive result for ROS-1. Brain MRI did not show brain metastasis at the time of first diagnosis.

Bone scan showed multiple bone metastasis and the clinical staging was stage IVB (T4N3M1c). She was then treated with Crizotinib(500mg/day) for ROS-1 rearranged NSCLC and apixaban for SVC thrombi. Her dyspnea improved after crizotinib use since her pleural effusion decreased as follow-up.

However, three months later, brain MRI was arranged because patient complained of headache. The MRI image showed nodules in left parietal lobe and left cerebellar hemisphere compatible with new brain metastasis lesion. Chest CT also showed interval progression of RUL lung cancer with bilateral lung metastasis, lymphangitic carcinomatosis, metastatic lymphadenopathy in the mediastinum, bilateral neck, and upper abdomen, and progressive SVC thrombi. We sent the peripheral blood sample for DNA NGS study, and the result showed G2032R , L2026M mutation and uncommon ROS1 fusion with intron (ROS1-LOC100505984 rearrangement).

We then shifted treatment to cabozantinib 60mg daily. Grade 2 adverse effect such as headache and paronychia were noted after cabozantinib use. One months later, she suffered from worsening headache, unsteady gait, nausea, vomiting and progressive dyspnea, and was sent to our emergency department. The brain MRI image revealed progression of metastases in bilateral cerebral hemispheres and left cerebellar hemisphere with edema change, and newly found leptomeningeal metastases. Lumbar puncture was performed and increased intracranial pressure was noted. CSF cytology showed malignant cell. She then received 1 cycle of pemetrexed but experienced progressive disease complicated with pneumonia and respiratory failure. The survival duration is less than 7 months.

Discussion:

1. In the PROFILE 1001 study of 52 patients with ROS-1 rearranged NSCLC, crizotinib treatment contributed to a median progression-free survival of 19.3 months. Previous case reports and *in vitro* studies showed the promising efficiency of cabozantinib in treating patients with acquired resistance to crizotinib.
2. In our patient, in addition to G2032R and L2026M mutation ROS1 mutation identified on blood NGS study, ROS1 fusion with intron (ROS1-LOC100505984) which was not yet reported before was also

identified. Unlike previous clinical trial or case report, our patient showed an short-term response but rapid progression of primary cancer and metastatic brain lesions after crizotinib 250 mg twice per day within 3 months. Furthermore, cabozantinib was prescribed according to new detected G2032R and L2026M from DNA NGS for liquid biopsy, but patient did not respond to the treatment.

3. Recent study emphasized that intergenic-breakpoint fusions, in which one or both genomic breakpoints localize to intergenic regions may confound kinase fusion detection. DNA-based NGS is sufficient to identify actionable mutations and fusions in the majority of cases. In which a rearrangement with an intergenic-breakpoint is identified, RNA- based NGS assay may add value about the functional fusion transcript being generated or not. However, the clinical significance of these intergenic breakpoint remained unclarified.

Conclusion

We reported a case with ROS-1 rearranged advanced NSCLC, responding to crizotinib initially but with shorter progression-free survival for around 3 months. The DNA NGS for liquid biopsy identified a G2032R, L2026M mutation and an uncommon ROS1 fusion with intron (ROS1-LOC100505984 rearrangement) which was not reported before. Although cabozantinib was prescribed according to previous preclinical data, patient did not benefit from cabozantinib treatment and developed rapid progression of lung cancer as follow. The impact of the rare ROS1 fusion gene of the intron (ROS1-LOC100505984 rearrangement) in this case may be a novel topic of interest in further research.