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ROS1 Positive Non-Small Cell Lung Cancer Patient with Brain Metastases Who Overcame Crizotinib Resistance with Lorlatinib: Case Report

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Abstract **Case Report**

Background: ROS1-positive patients account for 1-2% of non small cell lung cancer (NSCLC) cases. Crizotinib is the first tyrosine kinase inhibitor (TKI) indicated in first line treatment of ROS1-rearranged NSCLC. However, crizotinib resistance is frequent within the first 12 months of treatment. Lorlatinib is a novel tyrosine kinase inhibitor of ROS-1 recently indicated for metastatic or locally advanced crizotinib-resistant NSCLC. ***Case report***: We report a case of a 43-year-old female patient with no medical history, diagnosted with stage IVB NSCLC including asymptomatic brain metastasis, and harboring ROS1 rearrangement. Within the first three months of starting crizotinib, the patient showed on CT scan evaluation new bone and brain metastases. Lorlatinib in the second line revealed a noteworthy improvement in metastasis and primary lesion. ***Conclusion***: Brain metastases frequently occur in ROS1-rearranged NSCLC at the time of diagnosis and treatment course. However the efficacy of crizotinib might not translate to intracranial control of the disease, one of the cause of resistance to this drug.

Keywords: Non-small cell lung cancer, ROS1, crizotinib, lorlatinib.

BACKGROUND

Lung cancer is the leading cause of cancer death worldwide, with approximately 2.2 million new cancer cases and 1.8 million deaths, according to GLOBOCCAN 2020 [1].

Non-small cell lung cancer (NSCLC) accounts for approximately 85% with more than 50% of patients having metastatic disease at the time of initial diagnosis [2].

However, major advances in the diagnosis and treatment of advanced NSCLC, including the identification of genetic alterations, have changed the history of lung cancer in carriers of these oncogenic drivers [3].

Among these drivers, ROS 1 rearrangements are rare and represent approximately 1 to 2% of NSCLC. They correspond to chromosomal rearrangements leading to fusion genes that encode a chimeric protein with abnormally high ROS1 kinase activity, as described in other tumors, including NSCLC [4].

Crizotinib, a ROS-1 and ALK inhibitor, is currently the standard treatment for these tumor subtypes. However, resistance to crizotinib is frequent, which makes the treatment of ROS1-positive lung cancers more difficult.

New-generation tyrosine kinase inhibitors have been specifically designed to overcome this resistance, including lorlatinib.

CASE REPORT

A 43-year-old female patient, a non-smoker with no medical history, was admitted for the exploration of cervical adenopathy, which gradually increases in size over time.

The patient underwent a biopsy of her cervical mass, and the pathological report revealed poorly differentiated adenocarcinoma, and immunohistochemistry stained positively for CK7 (+), TTF-1 (+), and CK20 (-), considered to originate from the lung.

Chest computed tomography (CT) detected a primary malignant neoplasm of the right upper lobe associated with multiple diffuse pulmonary nodules and enlarged mediastinal lymph nodes (LN).

Additionally, brain magnetic resonance imaging (MRI) showed multiple brain metastases.

Hence, a PET/CT (Fig 1) examination was carried out and found right pulmonary tumor hypermetabolism with multiple focal uptakes corresponding to metastasis, including brain, pulmonary nodules, lymph nodes, and bones. The patient was diagnosed with stage IVB, non-small lung cancer (NSCLC).

Molecular analysis using next-generation sequencing revealed ROS 1 rearrangement, with no EGFR mutation or anaplastic lymphoma kinase (ALK) rearrangement. PDL 1 was 0%.

A whole brain irradiation was performed, and the patient received a frontline treatment with crizotinib 250 mg twice daily. After three months of treatment, the patient follow-up showed enlargement of brain and bone lesions, which were consistent with progressive disease.

The patient was subsequently started on lorlatinib 100 mg daily. After 6 months of lorlatinib treatment, 18F-FDG PET/CT (Fig 2) showed a rapid and complete regression of recurrent metastatic lesions and an attenuation of the size and intensity of the right upper lobe tumor.

Fig 1: Fluorodeoxyglucose-positron emission tomography-CT (FDG-PETCT) scan demonstrated strong FDG uptake in : the primary lung lesion (SUVmax =10,2), multiple nodules of the right and left pulmonary parenchyma creating the cannonball pulmonary appearance, the right basicervical (SUVmax=3,9) , right (SUVmax = 4,1)and left (SUVmax =6,6) paratracheal, subcarinal (SUVmax =10,6) and hilar (SUVmax=4) lymph nodes, parietal posterior regions (SUXmax =22,8)

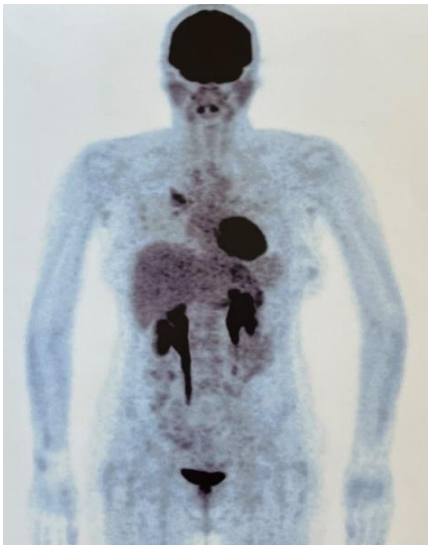

Fig 2: (FDG-PETCT): disappearance of secondary cerebral, pulmonary nodular, lymph node and bone hypermetabolisms. Attenuation of the intensity and size of the right lung tumor process. Absence of appearance of new metabolic lesions

DISUSSION

The ROS1 proto-oncogene (ROS1), encoded by the ROS1 gene, is a rare driver oncogene initially identified in NSCLC in 2007. This fusion is typically associated with a younger age, a light smoking history, or no smoking history at all, and a histological subtype of adenocarcinoma [5].

Structurally resembling anaplastic lymphoma kinase (ALK), ROS1 and ALK share approximately 49% homology within the kinase domain. Due to these similarities, tyrosine kinase inhibitors (TKIs) targeting ALK, such as crizotinib and lorlatinib, have demonstrated significant clinical efficacy and are presently recommended as first- or second-line therapy for ROS1-positive NSCLC [6].

Similar to testing for other targeted mutations, assessing for ROS1 rearrangement should be conducted for all advanced-stage non-small-cell lung cancer patients, regardless of clinical features. Crizotinib was the first TKI approved by the U.S. Food and Drug Administration (FDA) for treating advanced ROS1-rearranged NSCLC in 2016 [7]. Subsequently, entrectinib and lorlatinib have emerged as alternative treatment options.

Crizotinib has been evaluated in one phase I trial and four phase II trials, demonstrating efficacy with objective response rates (ORR) ranging from 67% to 72% and median progression-free survival (mPFS) ranging from 15.9 to 19.2 months [8-12]. The PROFILE trial, the first prospective evaluation of crizotinib in ROS1 fusion-positive NSCLC, revealed a median final PFS of 19.3 months and OS of 51.4 months [13].

In our case, crizotinib resulted in rapid progression, with the disease advancing after 3 months of treatment. Progression under crizotinib often stems from the acquisition of resistance mechanisms and/or progression at the brain level [14].

Despite initial positive responses to crizotinib, a significant number of ROS1-rearranged patients experience disease progression due to the development of resistance mechanisms, such as pathway bypass or the emergence of new mutations affecting ROS1's kinase domains. Regarding the ROS1 mutation, both clinical and preclinical investigations have identified point mutations in the ROS1 kinase domain, present in approximately 50–60% of crizotinib-resistant malignancies [15].

The ROS1 G2032R mutation is the most frequently reported secondary mutation, observed in 41% of patients treated with crizotinib. It was the first documented mechanism of crizotinib resistance found in a patient with altered ROS1 in non-small-cell lung cancer [16].

Identifying the type of secondary mutation is crucial for selecting an effective targeted therapy in the second line capable of inhibiting the mutant target, offering a potential method to overcome crizotinib resistance.

Additionally, in ROS1-rearranged NSCLC, activation of bypass signaling has been linked to crizotinib resistance. The targeted TKI can induce tumor cells' resistance by upregulating parallel or downstream cell signaling pathways such as EGFR, MET, HER2, KRAS, KIT, BRAF, and MEK [17].

Another consideration is that crizotinib, being a substrate of human ATP-binding cassette subfamily efflux transporters and P-glycoprotein, has limited blood-brain barrier (BBB) penetration. Consequently, the majority of crizotinib-treated patients often experience relapses due to either the development of new brain lesions or the progression of pre-existing intracranial disease [18, 19]. The objective response rate of crizotinib for ROS1-rearranged NSCLC patients is reported to be 69.3–72%; approximately 30% of them did not respond adequately to crizotinib, as observed in our case.

Lorlatinib, a potent and highly selective third-generation ALK and ROS1 TKI with robust central nervous system (CNS) penetration, is currently FDA-approved as a second-line treatment for patients with ALK-rearranged NSCLC. It is at least 10 times more potent against ROS1 compared to other TKIs. Lorlatinib's higher cerebrospinal fluid-to-plasma ratios result in improved CNS penetration [20].

In addition to its activity against several ROS1 mutations (G2032R, D2033N, and S1986Y), which confer resistance to crizotinib, promising results were recently reported by a phase II study including 47 patients with ROS1-positive NSCLC, both TKI-naive and pretreated. The study observed a median PFS of 21.0 months and an objective response rate of 61.5% among the 13 crizotinib-naive patients. Among the 34 crizotinib-pretreated patients, a median PFS of 8.5 months and an objective response rate of 26.5% were reported [21, 22].

Given crizotinib's limited ability to penetrate the BBB, and the unavailability of entrectinib in our country, lorlatinib was considered as an option in our case.

CONCLUSION

It is important to identify its ROS-1 rearrangement in patients with non-small cell lung cancer (NSCLC) in order to treat them appropriately.

Post-progression biopsies are needed to identify potential resistance mechanisms and are important in choosing second-line therapies, whether with another

TKI, or transitioning to a chemotherapy and immunotherapy-based approach.

For patients with CNS metastases, lorlatinib is a more appropriate option in this setting, as these drugs are specifically designed to penetrate the BBB.

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