Article published online: 2023-12-28

Clinical Outcomes of Crizotinib Readministration in Patients with Nonsmall Cell Lung Cancer with Anaplastic Lymphoma Kinase Rearrangement: Case Report and Review of Literature

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Ind J Med Paediatr Oncol

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Abstract

Recent studies have demonstrated promising outcomes of the first-line anaplastic lymphoma kinase-tyrosine kinase inhibitor (ALK-TKI) "crizotinib" in patients with locally advanced and metastatic lung cancers with high expression of the fusion protein "EML4-ALK." High drug resistance, however, restricts the therapeutic advantages of ALK-TKIs in patients with nonsmall cell lung cancer (NSCLC). The contemporary literature documents limited treatment approaches for patients with NSCLC relapse or nonresponsiveness to second-/third-generation ALK-TKIs. We hereby provide a descriptive analysis of five NSCLC cases treated with crizotinib, ceritinib, and alectinib for a median duration of 54 months. The outcomes indicate a profound therapeutic response in patients receiving 4th and subsequent line of treatment with crizotinib. The crizotinib retreatment actively reduced patient resistance to the ALK-TKIs by reversing the mesenchymal epithelial transition amplification. The results from this case series also emphasize the possible role of next-generation sequencing in determining therapeutic resistance and transforming the treatment paradigm for NSCLC. Partial response was observed in the patients after 6 months of crizotinib readministration. This is possibly the first case series reporting crizotinib rechallenge in patients of ALK positive NSCLC who failed on subsequent ALK-TKIs and multiple lines of chemotherapies.

Keywords

- NSCLC
- lung cancer
- EML4-ALK
- ALKi

Introduction

Findings in medical literature reveal a 3 to 7% incidence rate of anaplastic lymphoma kinase (ALK) rearrangements in patients with nonsmall cell lung cancer (NSCLC).[1–3] However, high treatment resistance after 1 to 2 years of follow-up minimizes the therapeutic advantage of ALK-tyrosine kinase inhibitor (ALK-TKI) in patients with NSCLC.[4,5] The treatment resistance is possibly the outcome of several genetic alterations impacting the signaling mechanisms and inducing secondary mutations in the ALK-TK domain.[5–7] Repeat biopsy is the potential method to evaluate the resistance processes in NSCLC cases. The contemporary literature emphasizes the role of targeted next-generation sequencing (NGS) in determining the possible mechanisms governing patient responses and resistance patterns against individualized treatments. In addition, NGS assesses potential mutations against targeted therapies and helps improve medical decision-making and clinical outcomes in patients with NSCLC.[8]

DOI https://doi.org/10.1055/s-0043-1777040.
ISSN 0971-5851.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

Clinical Findings

Case 1

A female patient (age: 46 years) visited our hospital in April 2015 with dyspnea and a productive cough. The patient was a nonsmoker and her clinical history was unremarkable. A chest computed tomography (CT) was performed and indicated the presence of a large heterogeneous lesion invading the right lung, middle and upper lobes of the left lung, and mediastinal nodes. Stage IV metastatic adenocarcinoma of both lungs was subsequently confirmed by the CT-guided biopsy of this lesion. However, brain metastasis was ruled out by magnetic resonance imaging (MRI) of the brain. Subsequently, the ALK D5F3 immunohistochemistry essay indicated ALK rearrangements correlating with the patient's treatment resistance. The patient was administered 250 mg crizotinib twice a day as a first-line treatment that subsequently improved her symptoms. She responded well to crizotinib, while visual disturbance was the only adverse effect observed during the early phase of the treatment. Subsequently, the positron emission tomography-CT (PET-CT) scan indicated a complete metabolic response after 6 months of therapy (►**Fig. 1**). ►**Table 1** demonstrates various treatments the patient received for ALK-rearranged NSCLC and the duration of each treatment in months. In May 2016, PET-CT was recommended for diagnostic assessment since the patient did not adhere to crizotinib treatment for duration of 3 weeks. The findings revealed a questionable recurrent (early-stage) lesion in the parenchyma of both lungs. Eventually, crizotinib was readministered to delay the disease flare and the patient showed an appropriate response to retreatment. However, PET-CT findings indicated disease progression in January 2017 when the patient developed symptoms after the follow-up of 26 months (►**Fig. 2**). Subsequently, a combination therapy of pemetrexed and carboplatin (4 cycles) was initiated. Ceritinib was initiated in January 2018 since the patient denied continuing intravenous chemotherapy. The PET-CET after 21 months of follow-up indicated progressive disease and the patient developed symptoms of chest pain, dyspnea, and cough. The lung biopsy was repeated, which confirmed the development of NSCLC. Nab-paclitaxel with carboplatin was administered, resulting in the control of symptoms. The patient denied further intravenous treatment despite achieving a good response following the completion of 4 cycles of carboplatin with nab-paclitaxel. Crizotinib was subsequently

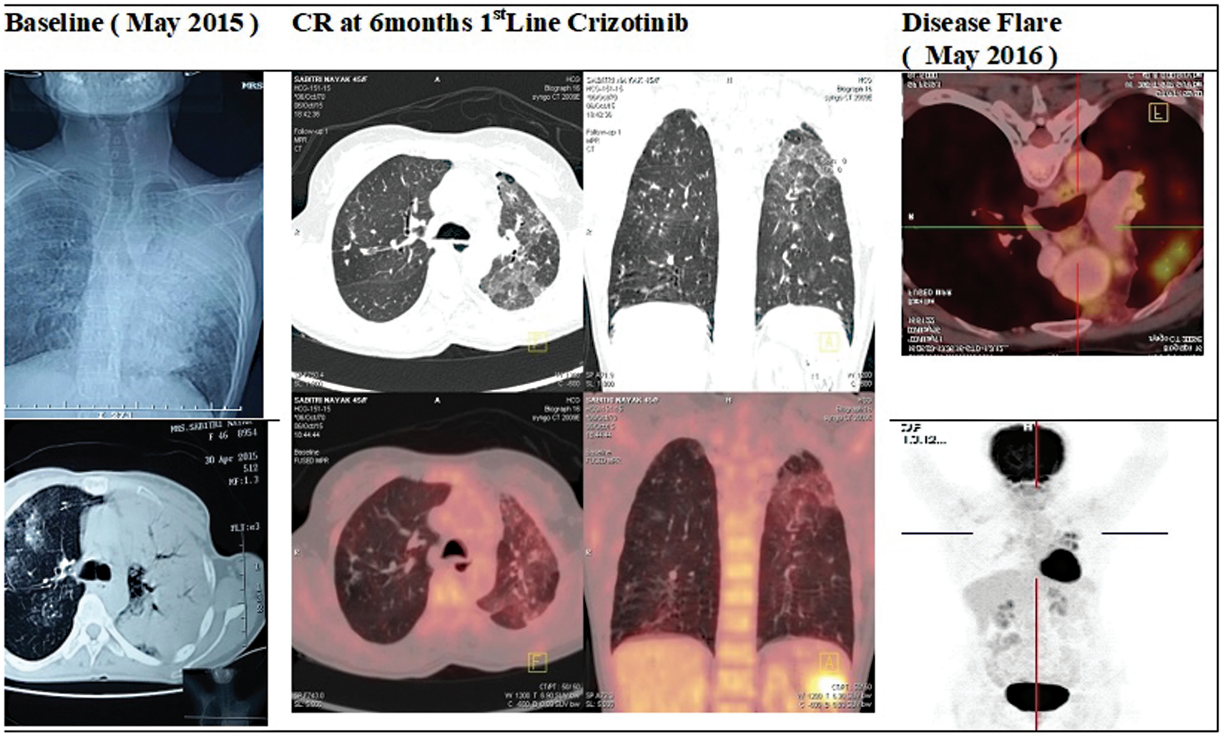

Fig. 1 Positron emission tomography-computed tomography (PET-CT) findings reflecting a complete metabolic response after 6 months of therapy.

Table 1 Treatment paradigm for anaplastic lymphoma kinase (ALK)-rearranged NSCLC

Biopsy					
	Crizotinib	Carboplatin + pemetrexed	Ceritinib	Carboplatin + nab-paclitaxel	Crizotinib
Months	26	37	59	63	71

Abbreviation: NSCLC, nonsmall cell lung cancer.

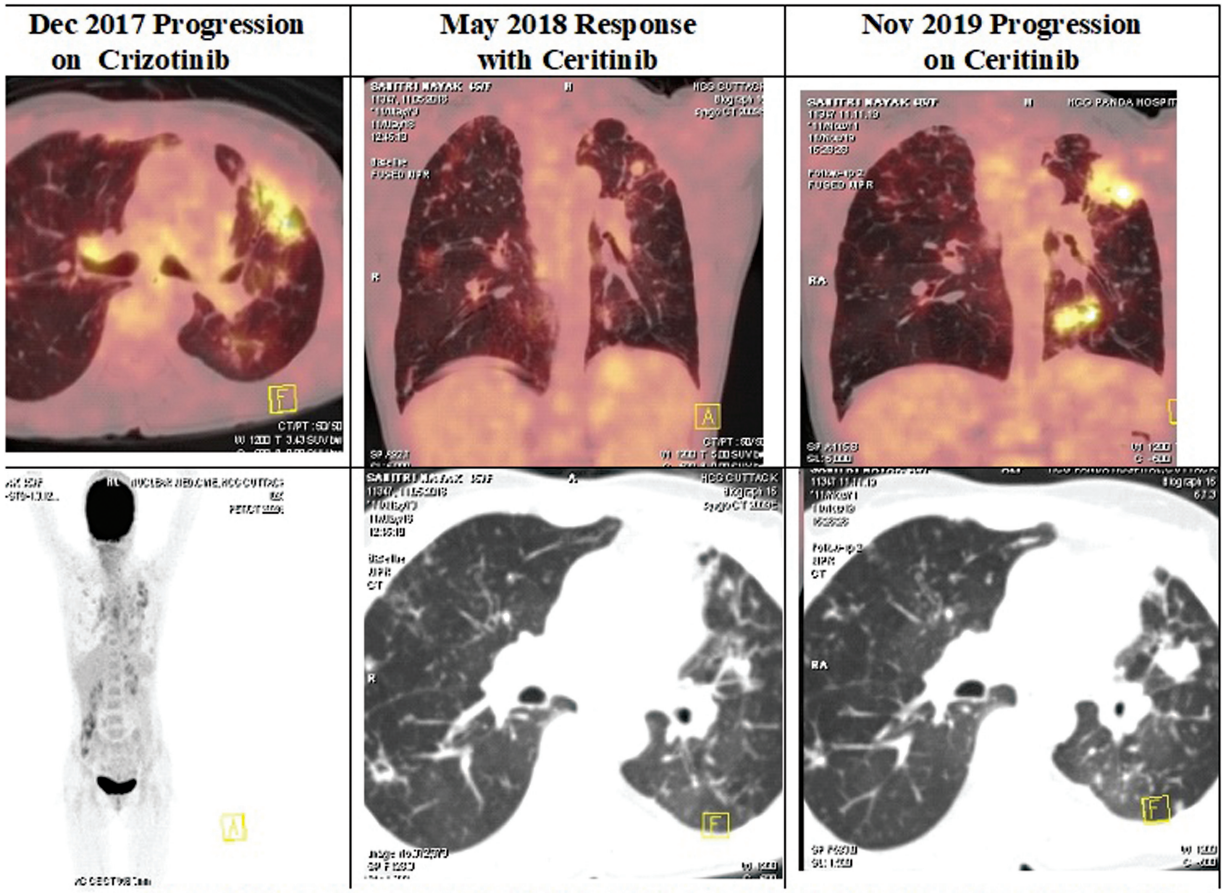

Fig. 2 Positron emission tomography-computed tomography (PET-CT) results indicating disease progression (follow-up duration: 26 months).

readministered in March 2020 due to the unavailability of lorlatinib and continued for duration of 35 weeks till her death in December 2020 due to progressive disease.

Case 2

An adult female (age: 40 years) visited our hospital in the month of May 2020. The presenting indications were dyspnea and productive cough. The patient had an insignificant medical history and was a nonsmoker. The PET-CT findings were consistent with a large heterogeneous lesion infiltrating the middle and upper lobe of the patient's right lung. The lung mass had metastasized to the supraclavicular and mediastinal nodes. In addition, metastasis was indicated at multiple locations in the liver. The results from immunohistochemistry and supraclavicular node biopsy were strongly positive for Napsin A and thyroid transcription factor-1 (TTF-1). The overall findings by biopsy, PET-CT, and brain MRI were consistent with primary pulmonary adenocarcinoma (stage IV) with liver and brain metastases. The immunohistochemistry analysis of the biopsy specimen indicated high activity of ALK D5F3. Subsequently, 250 mg of crizotinib was administered twice a day as first-line treatment at the start of May 2020. The patient's symptoms improved gradually, and PET-CT after 6 months showed a near-complete metabolic response (►**Fig. 3**). However, PET-CT (in February 2021) indicated disease progression with the appearance of lung and liver lesions following 10 months of crizotinib administration (►**Fig. 3**). Alectinib (600 mg) twice a day was administered since the patient denied biopsy. The whole brain radiotherapy was undertaken after 5 months of alectinib administration based on symptomatic brain metastasis and disease progression. Crizotinib was readministered since the patient did not give her consent for intravenous chemotherapy at that time. She continued crizotinib for 11 months till her disease progression and after that she received 4 cycles of carboplatin plus nab-paclitaxel. Currently she is on lorlatinib and responding it well.

Case 3

An adult male patient (age: 62 years) was seen at our hospital in the month of November 2017. The presenting indications were dyspnea and productive cough. A CT of the chest was planned and undertaken, which showed the appearance of a large heterogeneous lesion with progressive nodules in both lungs and the right supraclavicular node, in addition to invaginations in the lower lobe of the left lung. Subsequently, the lung mass was biopsied with CT guidance, and the findings were consistent with adenocarcinoma (stage IV) with metastatic nodules in both lungs. No metastasis was confirmed by the MRI of the brain. The patient's biopsy specimen was subsequently analyzed at the molecular level by immunohistochemistry and revealed the activity of ALK

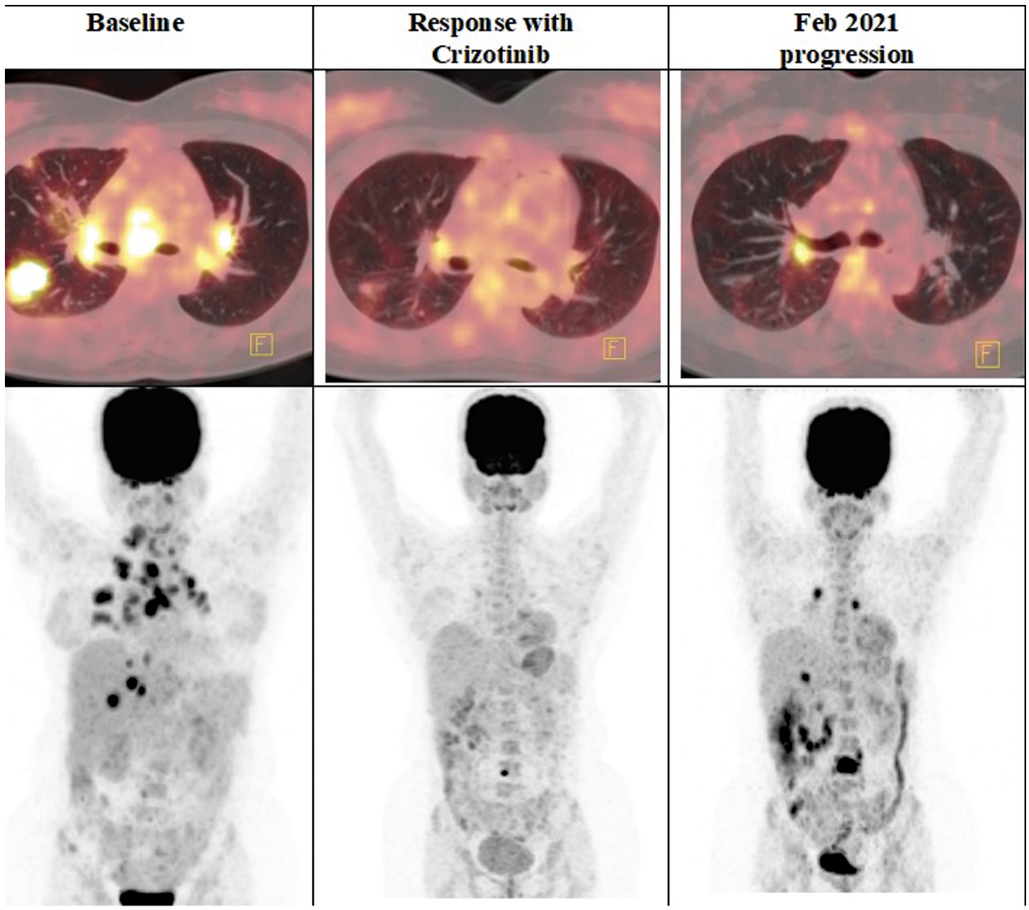

Fig. 3 Positron emission tomography-computed tomography (PET-CT) findings indicating disease progression with the appearance of lung and liver lesions following 10 months of crizotinib administration.

D5F3. A gradual improvement in the patient's symptoms was observed after administering crizotinib twice a day as first-line therapy at the beginning of November 2017. A favorable response to treatment was shown by PET-CET after 19 months of crizotinib therapy. However, carboplatin and pemetrexed were subsequently started due to symptomatic disease progression. Ceritinib was administered to the patient after 6 cycles of pemetrexed-based maintenance treatment and resulted in a good response. Crizotinib was readministered for disease progression after 11 months of ceritinib therapy. The crizotinib rechallenge resulted in a favorable response for 8 months; however, the patient did not survive due to disease progression and metastasis to bones and brain. ►**Table 2** depicts the treatment paradigm, including the duration of each therapy for NSCLC with ALK rearrangement.

Case 4

A male patient (age: 33 years) arrived at our hospital with dyspnea, cough, and chest pain (month/year of initial visit: August 2016). The patient's clinical history was insignificant, except for his past smoking status. A CT chest was performed and revealed a wide-range heterogeneous mass in the left lung (middle and upper lobes) with extensions to the mediastinal nodes. In addition, prominent nodules in the patient's right lung appeared to be the extensions of the heterogeneous lesion. The lung lesion was found to be consistent with adenocarcinoma (stage IV) based on the results from the CT-guided biopsy. In addition, metastases were observed in the bilateral lungs. However, the findings from the brain MRI ruled out metastasis in the brain structures. The immunohistochemistry findings of the biopsy specimen confirmed ALK D5F3 positive lung cancer. Subsequently, the patient was

Table 2 Illustration of the various treatments the patient received for anaplastic lymphoma kinase (ALK)-rearranged nonsmall cell lung cancer and the duration of each treatment in months

Biopsy					
	Crizotinib	Carboplatin + pemetrexed	Pemetrexed maintenance	Ceritinib	Crizotinib
Months	19	22	28	39	47

Table 3 Treatment paradigm, including the duration of each therapy for NSCLC with ALK rearrangement (Supplementary File)

Biopsy				
	Crizotinib	Cisplatin + pemetrexed	Lost to follow-up	Crizotinib
Months	17	22	29	37

Abbreviations: ALK, anaplastic lymphoma kinase; NSCLC, nonsmall cell lung cancer.

started with 250 mg crizotinib twice a day (first-line therapy) at the beginning of September 2016, resulting in symptom improvement. In addition to the appearance of symptoms following 17 months of crizotinib therapy, the findings from the CT scan in January 2018 indicated disease progression. Eventually, the patient was started with pemetrexed with cisplatin (6 cycles), resulting in favorable responses. After chemotherapy, the patient did not receive any treatment and was lost to follow-up for 7 months. The patient developed symptoms with disease progression in January 2019, which was followed by crizotinib retreatment since he did not agree to a repeat biopsy. Finally, a noticeable reduction in symptoms and disease control was established after 8 months of crizotinib treatment. However, the patient could not survive further and died due to disease progression. ►**Table 3** illustrates the treatment paradigm, including the duration of each therapy for NSCLC with ALK rearrangement (►**Table 3**).

Case 5

An adult male patient (age: 46 years) was seen in our hospital for dyspnea and productive cough (month/year of initial visit: April 2015). The patient's clinical history was insignificant and he was a nonsmoker. A CT chest was planned and undertaken; a widespread heterogeneous lesion was reported in the middle and upper lobes of the left lung, with extensions to the right lung and mediastinal lymph nodes. An adenocarcinoma (stage IV) with metastatic invaginations to the bilateral lungs was indicated by the CT-guided biopsy of the heterogeneous lung lesion. However, no metastasis was revealed in the brain structures by the MRI brain. The immunohistochemistry indicated ALK D5F3 positivity in the biopsy specimen. The patient was started on crizotinib (250 mg) in the first week of May 2015. The early phase of the treatment reported visual disturbances; however, the patient tolerated the therapy and the symptoms subsided gradually. The findings from the PET-CT indicated a complete metabolic response following 6 months of crizotinib treatment. Crizotinib was discontinued for 21 days in April 2016, and a repeat PET-CT in May 2016 raised suspicion of recurrence of the disease in the parenchyma of both lungs. The patient, however, remained asymptomatic and was retreated with crizotinib to minimize disease flare. Crizotinib retreatment resulted in a favorable response; however, the patient developed symptoms with disease progression (after a follow-up of 26 months) in January 2017. Subsequently, he received 4 cycles of cisplatin and pemetrexed with partial response to therapy. Finally, he died in October 2017 due to progressive disease.

Discussion

In recent years, the prognosis for patients with ALK positive NSCLC has significantly improved, and the median survival of these patients has exceeded 5 years. Several ALK-TKIs, including crizotinib, ceritinib, brigatinib, and alectinib, have been approved for ALK-rearranged NSCLC. Unfortunately, as is the case for other kinase inhibitors in clinical use, sensitive tumors inevitably relapse due to acquired resistance. Commonly, resistance to crizotinib develops within 1 to 1.5 years after treatment is initiated.[6] Our patients had clinical benefit from crizotinib ranging from 17 to 26 months, which was significantly longer than the median progression-free survival of patients receiving first-line crizotinib therapy.[4] A range of mechanisms governs the clonal and dynamic processes driving the resistance of patients with lung adenocarcinoma against ALK TKIs. These mechanisms include the alternative signaling pathway activation and ALK-TK secondary mutation.[5,6,9] The sensitivity of ALK-dependent crizotinib-resistant tumors is recorded for lorlatinib, brigatinib, ceritinib, and similar second- and third-generation ALK-TKIs.[5,10–13] Wide range of mechanisms related to ALK-TKI have been published which include ALK-resistant mutations, triggering of bypass signaling, and phenotypic alteration including small cell lung cancer transformation and epithelial-to-mesenchymal transition.[14] In a case report published by Shaw et al[15] crizotinib rechallenge on patients showed good response after relapse on lorlatinib with ALK C1156Y-L1198F mutation. In another case report published by Sakakibara-Konishi et al[16] in ALK-rearranged NSCLC patients crizotinib readministration showed good response after progression on lorlatinib. NGS in Oncomine comprehensive assay ver. 3 showed no sensitive mutations to crizotinib, but G1269A, which was predicted to be sensitive to lorlatinib and resistant to crizotinib based on IC50 values.[7] Our patients have been treated with ceritinib, alectinib, and multiple lines of chemotherapy after crizotinib failure. However, we could not investigate the underlying treatment resistance mechanisms since our patients denied a repeat biopsy after developing resistance to ceritinib, alectinib, and crizotinib. Alternatively, the patients responded to multiple lines of ALK TKIs, which confirmed their treatment benefit. Chemotherapy was finally administered because of the absence of the next-generation ALK TKI-based therapy with the potential to undo the patient's resistance to lorlatinib, the third-generation inhibitor. The patient, however, had no additional benefit from the chemotherapy treatment. Previous publications regarding the retreatment of patients with secondary resistance to epidermal growth factor receptor (EGFR)-TKIs suggest that a drug holiday and treatment with a conventional chemotherapeutic may reestablish sensitivity to TKIs.[17] Although this strategy is well described for EGFR-TKIs, there is to date only little case report indicating that crizotinib retreatment of ALK-positive patients after a

drug holiday and chemotherapy improves crizotinib sensitivity. In a case report published by Schrödl et al[18] crizotinib retreatment of ALK-positive patients with secondary resistance to crizotinib after a drug holiday and conventional chemotherapy improves crizotinib sensitivity and improves the quality of life. This case report illustrates that patients with secondary resistance to crizotinib can benefit from a range of therapeutic strategies, including drug holiday, chemotherapy, and retreatment with crizotinib.

After resistance develops to one targeted inhibitor, targeted NGS analysis could provide clinically relevant insights into the underlying mechanisms of resistance to targeted therapies and guide optimal therapeutic strategies that could improve the treatment outcome of the patient. The contemporary literature emphasizes the role of NGS of the biopsy specimens to investigate the etiopathology of ALK-positive NSCLC.[18] The biopsied primary lung lesion in the current study showed ≥ 5 gene copy number (mean value) or mesenchymal epithelial transition (MET) amplification other than EML4-ALK mutation. Of note, in patients with NSCLC with EFGR mutation, MET amplification predominantly reduces their responses to ALK-TKIs.[5,9] However, MET amplification was not determined in our study because we could not get the opportunity for a repeat biopsy of the patient's lung lesion. The sensitivity of the tumor to the fifth-line crizotinib retreatment in our study was evidenced by a profound short-term objective response. In addition, the ALK G1269A mutation substantially increased the patient's resistance to the crizotinib therapy. It is important to note that the findings in the NSCLC management guidelines in medical literature do not advocate biomarker assessment and repeat biopsy of the lesion in patients with low responsiveness to ALK TKIs.[19] This shortcoming eventually restricts the subsequent line treatments in NSCLC cases. The NGS assessment following the development of resistance to an ALK TKI is a robust approach to gain insights into its potential causes and drive optimal treatments for improving clinical outcomes.[20,21]

Finally, this study provides clinical evidence concerning the role of crizotinib rechallenge in countering the ALK-TKI resistance based on MET amplification. The outcomes substantiate the need for next-genome sequencing-directed analysis to improve the treatment paradigm in patients with advanced NSCLC with ALK positivity.

Conclusion

The outcomes from this case series indicate the role of crizotinib rechallenge in improving the treatment responses and delaying the disease progression in patients with NSCLC and ALK rearrangement. However, the challenge in performing the repeat biopsy of the metastatic lung lesion restricted the assessment of mechanism of action of crizotinib retreatment in NSCLC cases. Future studies should investigate the safety and efficacy of crizotinib rechallenge in NSCLC to discover alternative treatment approaches for improving the treatment outcomes.

Patient Consent

The author certifies that he has obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/ her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial Support and Sponsorship

None.

Funding

This study was supported by Department of Medical Oncology, Acharya Harihar Post Graduate Institute of Cancer, Cuttack, Odisha, India.

Conflict of Interest

None declared.

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