ScientificScholar®
Knowledge is power
Publisher of Scientific Journals

www.ijmio.com

International Journal of Molecular and Immuno Oncology

Case Series

Dual driver in non-small cell lung carcinoma – therapeutic dilemma

Gangothri Selvarajan[1], Perumal Kalaiyarasi Jayachandran[1]

[1]Department of Medical Oncology, Cancer Institute (WIA), Chennai, Tamil Nadu, India.

***Corresponding author:**
Dr. Perumal Kalaiyarasi Jayachandran,
M.D., M.R.C.P (UK)., D.M.,
Associate Professor,
Department of Medical Oncology, Cancer Institute (WIA), Chennai, Tamil Nadu, India.

dr.pkjayachandran@gmail.com

Received: 13 September 2021
Accepted: 20 September 2021
EPub Ahead of Print: 27 November 2021
Published: 20 January 2022

DOI
10.25259/IJMIO_22_2021

Quick Response Code:

ABSTRACT

The presence of a targetable driver mutation in advanced non-small cell carcinoma is seen in about 40–50% of patients. The most common targetable driver identified is the mutation of the epidermal growth factor receptor gene. Conventionally, it was thought that these driver mutations of mutually exclusive. But due to the availability of a wider panel of molecular testing and highly sensitive methods of testing, there have been multiple case reports of more than one driver being identified in a single patient. Here in this series, we have described five such cases and have discussed the possible hypothesis and strategies in treatment.

Keywords: Double driver, Epidermal growth factor receptor and anaplastic lymphoma kinase, Dual targets, Non-small cell lung carcinoma, Driver mutation in lung cancer

INTRODUCTION

The 5-year overall survival (OS) rate in stage IV non-small cell lung carcinoma (NSCLC) is <10%.[1] Median progression-free survival (PFS) was 6–8 months and median OS was 10–12 months with chemotherapy alone irrespective of epidermal growth factor receptor (EGFR)/anaplastic lymphoma kinase (ALK)/C-Ros Oncogene 1 (ROS1) aberrations.[2]

Activating EGFR mutations in lung adenocarcinoma constitute around 10–15% among Caucasians and around 50% among Asians.[3] Most mutations in the EGFR gene are located within exons 19–21 of the tyrosine kinase domain. The rearrangement of ALK with echinoderm microtubule-associated protein-like 4 (EML4) oncogene on the chromosome 2p activates a specific tyrosine kinase, involved in the processes of survival and cell proliferation and is found in about 3–7% of lung adenocarcinomas. The ROS1 gene, that is present in the chromosome 6p encodes for a receptor tyrosine kinase can undergo rearrangement with multiple partner genes like CD74, EZG, FIG1, etc. renders the kinase constitutionally active. The ROS1 rearrangement can be seen in about 2% of the NSCLC population.[4]

EGFR gene testing is done using hot spot mutation testing by polymerase chain reaction (PCR) and Sanger sequencing or by next-generation sequencing (NGS). The ALK and ROS1 gene screen testing is done by immunohistochemistry (IHC). The rearrangement of ALK and ROS1 genes are confirmed by fluorescence *in-situ* hybridization (FISH). The other genes which are commonly being tested for mutations are the BRAF, MET, and RET. These mutations can be targeted using various available drugs for specific genetic aberrations.

Generally among these driver mutations, only one of the mutations occurs in the tumor cells. On most occasions, these mutations are mutually exclusive. On very rare occasions, more than one driver mutation may coexist in the tumor. The most common reason for this co-existence is tumor heterogeneity. We describe five such cases of coexistence of two driver mutations (EGFR and ALK/ROS1 mutations).

CASE REPORT

Case 1

A 50-year-old male non-smoker presented to us with dyspnea and cough. He was diagnosed with stage IV NSCLC with bone and brain metastasis. He was initially given palliative whole-brain RT and then was started on Zoledronic acid for bone metastasis. His EGFR mutation was done by Amplification Refractory Mutation System (ARMS) Real-Time PCR. It was positive for Exon 21 L858R mutation. ALK by IHC was also positive. The patient was initially started on Gefitinib. After 2 months, the patient had progressive disease. Hence, he was started on chemotherapy with Pemetrexed and Carboplatin. After four cycles of chemotherapy, he had a partial response and hence was given two more cycles of the same chemotherapy and then was started on Pemetrexed maintenance. After ten cycles of maintenance, the patient presented with progressive dyspnoea and was diagnosed with progressive disease. His performance status deteriorated rapidly and he was given a trial of Crizotinib for 4 days. However, he did not respond to it and deteriorated and succumbed to the illness.

Case 2

A 50-year-old male non-smoker presented to us with dyspnoea and cough. He was diagnosed with Stage IV Adenocarcinoma of the Lung (Pleural effusion positive). His EGFR mutation analysis was done by ARMS real-time PCR. It was both exon 19 deletion and ALK-positive. For confirmation, The ALK FISH was sent. He was started on Gefitinib 250 mg once daily. His ALK FISH could not be performed due to the inadequacy of the tumor tissue in the paraffin block. After 3 months of Gefitinib, he came with a history of increasing dyspnoea and was found to have progressive disease. He was planned to be started on an ALK inhibitor. However, he was not willing for further treatment and was lost to follow-up.

Case 3

A 44-year-old female presented to us with cough, shortness of breath, loss of weight, and appetite for 3 months duration. There were mediastinal nodes that were encasing the main bronchus and the superior vena cava (SVC) with SVC thrombus. She was diagnosed with Stage IV Adenocarcinoma of the Lung (Liver metastasis). The molecular investigations were sent and the patient was started on supportive measures and pemetrexed-carboplatin based chemotherapy. Her EGFR analysis showed Exon 20 insertion mutation. Her ALK test by IHC was also positive. Gefitinib was added to the chemotherapy. After four cycles of chemotherapy, reassessment showed stable disease. Hence maintenance with Gefitinib with Pemetrexed was started. She presented to us after three cycles of Pemetrexed maintenance with symptoms of headache and vomiting. She was evaluated and was found to have multiple brain metastases. She received palliative whole-brain radiotherapy and was planned to be started on Crizotinib.

Case 4

A 53-year-old female presented to us. Almost 6 years before coming to our hospital, she was diagnosed with Stage IV NSCLC of the Lung in another hospital. It was a routine to send only an EGFR test then. She was started on Pemetrexed and Cisplatin. The EGFR report turned out to be positive with the presence of Exon 21 L858R mutation. In the meantime, as the patient showed a symptomatic improvement, she was continued on the chemotherapy. On the completion of six cycles, there was a partial response and hence she was put on Pemetrexed maintenance with routine follow-up positron emission tomography (PET) scans. After 4 years of Pemetrexed maintenance, she had signs of progression on the PET scan and so Bevacizumab was added to the Pemetrexed maintenance. After 8 months, she had further progression; hence she was put on Pemetrexed, Cisplatin, and Bevacizumab. After three cycles of the chemotherapy, there was no response on PET scan and hence she came to our hospital. Here at our hospital, a repeat biopsy confirmed the histology as adenocarcinoma of the lung, and the tissue was sent for NGS of a panel of genetic mutations which included EGFR, ALK, BRAF, KRAS, MET, RET, etc. The tissue was also sent for ALK, ROS, and PDL1 IHC. The EGFR report turned out to be positive with the presence of the same mutation as above (p.Leu858Arg (L858R)/Exon 21–4678×, 20.1%). ROS1 IHC was also positive (H score–280/300). Hence ROS1 FISH test was sent on the tissue to confirm the report. The ROS1 FISH was also positive (76% tumor cells positive). She was started on Gefitinib and reassessment after 6 months showed a stable disease on PET-CT and hence was continued on Gefitinib.

Case 5

A 50-year-old female evaluated for low backache elsewhere was found to have a pathological fracture of L2 and L4 vertebra when she presented to us. On further evaluation was diagnosed to have Metastatic adenocarcinoma of

the Lung with liver and bone metastasis. She received palliative radiotherapy for L2 and L4 vertebral lesions. Her EGFR analysis by NGS showed Exon 19 deletion mutation (p.Leu747_Pro753del insSer–4.6%). Her ALK testing by IHC (D5F3 antibody) was also positive. IHC for PDL1 was 0% (TPS). She was started on Pemetrexed, Carboplatin with Gefitinib with Q3 monthly Zoledronic acid. She is planned for reassessment after 3 months.

DISCUSSION

Two different hypotheses exist to explain the presence of dual-driver mutations. The first hypothesis is that the genetic instabilities can cause genetic and phenotypic heterogeneity in the tumor, leading to different genetic alterations in different tumor cells rather than in a single clone of cells. The second hypothesis is that there can be activation of multiple oncogenic pathways due to alteration in a single clone of tumor cells.[5] Such cases require molecular tumor board discussion for optimal management of patients.

The incidence of dual EGFR and ALK aberrations is about 1–5% in literature but conventional testing like the Sanger sequencing method has lower sensitivity to detect mutant cells.[6-8] The targeted NGS has a sensitivity to detect <1% of mutants.[9] More sensitive detection methods like NGS of the whole EGFR gene and mutant-enriched NGS have increased the rate of co-existence of EGFR mutation and ALK–translocations up to 15%.[6]

Although EGFR mutations and ALK translocations are generally considered mutually exclusive, their concomitant prevalence differed due to direct sequencing for EGFR mutations. Their responses to EGFR and/or inhibitors were conflicting. Despite a response rate of 60–70% in EGFR-mutated lung cancer patients treated with EGFR-TKIs, 10–20% of individuals developed primary resistance. Possible contributing factors are KRAS mutation, MET amplification, and PIK3CA mutation. The co-existence of a low burden EGFR mutation in the dual-positive patients might lead to the unfavorable response to EGFR-TKIs.[10] The median PFS with the use of EGFR-TKIs in patients with EGFR mutations alone or with concomitant ALK/ROS1 aberrations were 10.7 and 6.6 months respectively.[7] But there was no OS difference (23 months in both groups). Minor clone of EGFR mutant may have little influence on the responsiveness to ALK inhibitors in dual-positive patients. The presence of concomitant EGFR mutations has been regarded as a resistance mechanism of ALK inhibitors suggesting that there may be a need to use a combination therapy.[6]

In a literature review of 100cases by Lo Russo *et al*., the disease control rates using EGFR (n = 53) and ALK (n = 39) TKIs were 69.8% versus 79.5% respectively and overall response rates (ORR) were 43.4 % and 51.3%, respectively. About 22 patients in this review series received EGFR TKIs followed by ALK TKIs. The ORR in this subgroup of 22 patients using EGFR TKI was 23.1% and ORR using ALK TKIs were 42.3%. Statistical comparisons and analysis of PFS and OS were not done in the above series.[11] The responses to ALK TKIs were better than EGFR TKIs and this observation was similar to other series also.[6,7]

Here in our series, the first three patients and case 5 were EGFR with ALK mutation and Case 4 was EGFR with ROS mutant. Regarding cases 1-3, the progression on EFGR TKIs happened in less than 6 months. The responses of the first 4 patients were either progressive disease or stable disease. We could also see that the responses were poor with EGFR TKIs which is similar to other series.[6,7,11] In our series, we could not start any of our patients on ALK TKIs due to logistic issues.

Variant allele frequency (VAF) is the percentage of a specific sequence reads (DNA variant) observed divided by the overall coverage at that locus. VAF acts as a surrogate to measure the proportion of variant DNA molecules carried in the tumor biopsy/specimen.[12] In a study by Friedlaender *et al*., high allelic frequency was significantly associated with PFS but not OS.[13] When combined analysis of VAF and co-occurring mutations were performed those without co-mutations and with high VAF for EGFR mutation were classified as tumor sensitive to EGFR TKIs. They did significantly better in both PFS and OS. In a retrospective study by Gieszer *et al*., they calculated adjusted VAF (aVAF) for each patient. In this VAF was normalized to the proportion of neoplastic cells in each specimen. High EGFR-aVAF showed significant PFS and OS benefits compared to low EGFR-aVAF.[14] These studies imply that therapy can be individualized based on VAF, especially when dual-driver mutations/heterogeneity exist depending on the mutation with high VAF. These hypotheses need to be validated in randomized control trials.

Over time, we shall come across more and more cases due to multiple reasons like the use of more sensitive methods for detection of mutations, the use of higher sensitive methods such as whole-genome sequencing,[6] the use of expanded genetic panel testing. Identification of dual drivers per se may be identified as a factor for primary resistance soon. The optimal strategies for treatment in such cases either to sequence or to combine TKIs is not known yet. It requires more insight into molecular pathways or cross-talks between two driver pathways and more experience in treating such cases to identify appropriate treatment protocol.

CONCLUSION

Usage of highly sensitive wider molecular panels for testing in NSCLC will lead to a surge in the number of patients

with dual drivers. These patients will require molecular tumour board discussion and a specialized approach for management. Further research is required in performing VAF analysis as a guide in the selection of drugs in such patients with dual drivers.

Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Amin MB, Edge S, Greene F, Byrd DR, Brookland RK, Washington MK, *et al*., editors. AJCC Cancer Staging Manual. 8th ed. Berlin, Germany: Springer International Publishing; 2017. Available from: https://www.springer.com/gp/book/9783319406176 [Last accessed on 2021 May 03].
2. Reck M, Popat S, Reinmuth N, Ruysscher DD, Kerr KM, Peters S. Metastatic non-small-cell lung cancer (NSCLC): ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2014;25:iii27-39.
3. Shi Y, Au JS, Thongprasert S, Srinivasan S, Tsai CM, Khoa MT, *et al*. A prospective, molecular epidemiology study of EGFR mutations in Asian patients with advanced non-small-cell lung cancer of adenocarcinoma histology (PIONEER). J Thorac Oncol 2014;9:154-62.
4. Riely GL. What, when, and how of biomarker testing in non-small cell lung cancer. J Natl Compr Canc Netw 2017;15:686-8.
5. Doebele RC, Pilling AB, Aisner DL, Kutateladze TG, Le AT, Weickhardt AJ, *et al*. Mechanisms of resistance to crizotinib in patients with ALK gene rearranged non-small cell lung cancer. Clin Cancer Res 2012;18:1472-82.
6. Won JK, Keam B, Koh J, Cho HJ, Jeon YK, Kim TM, *et al*. Concomitant ALK translocation and EGFR mutation in lung cancer: A comparison of direct sequencing and sensitive assays and the impact on responsiveness to tyrosine kinase inhibitor. Ann Oncol 2015;26:348-54.
7. Mao Y, Wu S. ALK and ROS1 concurrent with EGFR mutation in patients with lung adenocarcinoma. Onco Targets Ther 2017;10:3399-404.
8. Yang JJ, Zhang XC, Su J, Xu CR, Zhou Q, Tian HX, *et al*. Lung cancers with concomitant EGFR mutations and ALK rearrangements: Diverse responses to EGFR-TKI and crizotinib in relation to diverse receptors phosphorylation. Clin Cancer Res 2014;20:1383-92.
9. de Biase D, Visani M, Malapelle U, Simonato F, Cesari V, Bellevicine C, *et al*. Next-generation sequencing of lung cancer EGFR exons 18-21 allows effective molecular diagnosis of small routine samples (cytology and biopsy). PLoS One 2013;8:e83607.
10. Zhou Q, Zhang XC, Chen ZH, Yin XL, Yang JJ, Xu CR, *et al*. Relative abundance of EGFR mutations predicts benefit from gefitinib treatment for advanced non-small-cell lung cancer. J Clin Oncol 2011;29:3316-21.
11. Lo Russo G, Imbimbo M, Corrao G, Proto C, Signorelli D, Vitali M, *et al*. Concomitant EML4-ALK rearrangement and EGFR mutation in non-small cell lung cancer patients: A literature review of 100 cases. Oncotarget 2017;8:59889-900.
12. Strom SP. Current practices and guidelines for clinical next-generation sequencing oncology testing. Cancer Biol Med 2016;13:3-11.
13. Friedlaender A, Tsantoulis P, Chevallier M, de Vito C, Addeo A. The impact of variant allele frequency in EGFR mutated NSCLC patients on targeted therapy. Front Oncol 2021;11:644472.
14. Gieszer B, Megyesfalvi Z, Dulai V, Papay J, Kovalszky I, Timar J, *et al*. EGFR variant allele frequency predicts EGFR-TKI efficacy in lung adenocarcinoma: A multicenter study. Transl Lung Cancer Res 2021;10:662-74.

How to cite this article: Selvarajan G, Jayachandran PK. Dual driver in non-small cell lung carcinoma – therapeutic dilemma. Int J Mol Immuno Oncol 2022;1:16-9.