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Case Report

Case Report of Non-small Cell Lung Cancer Patient with EGFR T790M Mutation Treated with Third Generation Inhibitor

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ABSTRACT

Lung cancer treatment based on the molecular classification of the tumor has paved the way for multiple lines of targeted treatment, even though the development of resistance remains a major cause of concern. Epidermal growth factor receptor (EGFR) remains the poster boy for the use of targeted therapy, and the presence/absence of mutations in this gene has led to the development of inhibitors targeting specific mutations. We present the case of an advanced non-small cell lung cancer patient with EGFR T790M mutation treated with Osimertinib, a third-generation inhibitor.

Keywords: Non-small cell lung cancer, T790M, Osimertinib

BACKGROUND

Adenocarcinoma is the most commonly occurring form of non-small cell lung cancer (NSCLC) as per the recent literature from India and usually presents at an advanced stage with limited treatment options (e.g., taxane, platinum, gemcitabine, vinorelbine, pemetrexed) with poor response to the standard chemotherapy regimens.[1] Targeted therapies, including afatinib, bevacizumab, ceritinib, crizotinib, and so on, are being investigated as therapeutic strategy for patients with advanced disease.[2] Oncogenic targets presently well defined are epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) for which targeted therapies are being routinely used. However, there are different mechanisms of resistance, and the challenge lies in developing therapeutic strategies, which will overcome these resistance mechanisms. A common resistance mechanism in EGFR-driven adenocarcinoma is T790M mutation. Better agents are being investigated to manage this heterogenous group of cancers based on their molecular profiling.

CASE REPORT

A pleasant 51-year-old lady with no co-morbidities presented with complaints of dyspnea and dry cough of short duration. Preliminary investigations including ultrasound of chest revealed gross left pleural effusion. CT scan chest was suggestive of left lung collapse with subtle hypodensity

seen in collapsed lung and gross left pleural effusion. She presented to the hospital with these investigations in December 2013. Pleural fluid cytology was positive for malignant cells. PET-CT showed metabolically active left lung mass with contralateral lung nodule, lymph nodal and pleural involvements, and pleural effusion. Biopsy from left lung mass was suggestive of NSCLC favoring adenocarcinoma. Her hematological and biochemical parameters were within normal limits. She was planned and started on Pemetrexed- and Carboplatin-based chemotherapy. Post three cycles of chemotherapy, PET-CT was suggestive of partial response to treatment. Her EGFR mutational status was reported as deletion in exon 19 and was hence offered oral tyrosine kinase inhibitor (TKI)-based targeted treatment and put on Tab Tarceva (Erlotinib) 150 mg daily from February to October 2014.

PET-CT in May 2014 showed regression in left lung lesion with near complete metabolic response. Left hilar lymph node and pleural thickening also showed complete metabolic response. Residual left pleural effusion and right lung nodule were persistent. Eight months post erlotinib treatment, PET-CT in October 2014 showed progressive disease. In view of occurrence of skin toxicity with 150 mg Erlotinib (multiple furuncles in anterior abdominal wall), she was given Tab Iressa (Gefitinib) 250 mg OD. She continued on Gefitinib for 6 months till April 2015 when PET-CT scan was suggestive of progressive disease. Left lung lesion and left hilar lymph node showed increase in size and metabolic activity. Left pleural thickening showed increase in extent with focal nodular deposits. Transbronchial biopsy was suggestive of NSCLC adenocarcinoma with similar molecular profiling.

In May 2015, she was started on second generation TKI Tab Afatinib 30 mg but showed poor tolerance to treatment in the form of dryness of skin, abdominal cramps, and diarrhea. She developed grade 3 skin toxicity (large furunculosis on anterior abdominal wall). The dose of Afatinib was reduced to 20 mg per day, which was also taken irregularly till January 2016 for about 9 months. PET-CT in January 2016 showed metabolically active progressive disease with increase in size and metabolic activity of left lung lesion, pleural, subpleural lesion, and lymph node. Development of new sites of metastatic disease in left 7th, 9th, and 10th rib-lytic lesions with soft-tissue component was noted. Biopsy from left lung mass was suggestive of NSCLC – morphologically adenocarcinoma. She also received Inj Xgeva 120 mg for bony disease progression. She further complained of headache and vomiting. MRI brain was suggestive of multiple supra and infra tentorial enhancing lesions in brain suggestive of metastasis for which she received WBRT. EGFR mutational status was reported as T790M mutation in exon 20 and deletion in exon 19. While exploring the options for third generation TKI-like Osimertinib (Tagrisso), she was put on Tab Iressa (Gefitinib).

She was referred for an Expanded Access Programme to Singapore and was started on treatment with Tagrisso in March 2016 and tolerated the treatment fairly well except that she had anorexia and weight loss (grade 2). Interim evaluation post 2 months of treatment with Tab Osimertinib in May 2016 revealed partial response to treatment with significant persistent residual left lung lesion with lymph nodal and left pleural involvement with left pleural effusion [Figure 1]. The metabolically active rib lesion and soft tissue deposits also showed decrease in extent and metabolic activity. Accompanying MRI showed post-treatment status as residual metabolically inactive bilateral cerebral and cerebellar parenchymal lesions and as compared to earlier MRI, showed significant decrease in size and number.

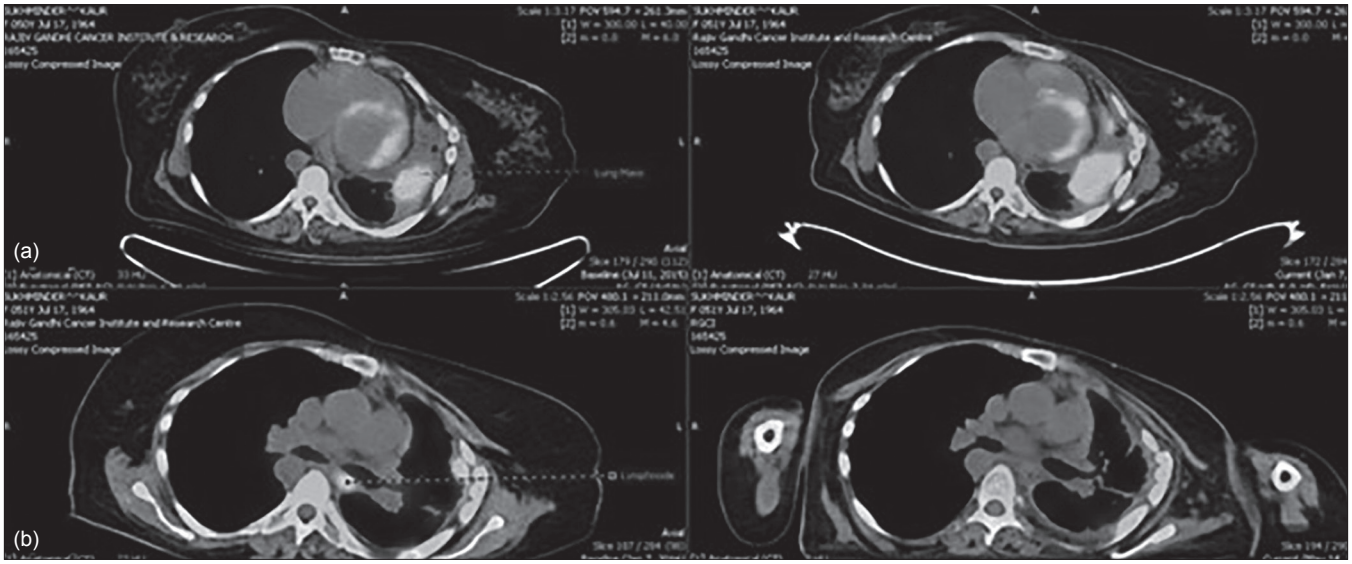

Figure 1. PET-CT images showing (a) progressive lung mass in January 2016 and (b) response to therapy in May 2016.

DISCUSSION

NSCLC is a heterogeneous aggregate of histological subtypes, and among these patients with adenocarcinomas, mutations have been observed in around 80% tumors. Also, the disease biology and mutation frequencies are different between the west and east populations.[3-5] Numerous driver mutations including mutations in the genes for epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), ROS1, RET, HER2, and so on play a vital role in the development and maintenance of the malignant phenotype and further, the intra- and inter-tumor heterogeneity tend to guide the targeted therapy of cancer.[6]

The recognition and identification of EGFR mutations in NSCLC adenocarcinoma have been game changing in the management of EGFR-mutated adenocarcinomas. EGFR is a transmembrane receptor protein kinase and is a member of the avian erythroblastic leukemia viral oncogene homolog (ErbB) family of receptors, which includes EGFR (ErbB-1), HER2/neu (ErbB-2), Her 3 (ErbB-3), and Her 4 (ErbB-4).[7] Somatic mutation in the tyrosine kinase (TK) domain of EGFR has been commonly observed in lung adenocarcinoma. Different ethnic populations have reported variations in the incidence of EGFR mutation in NSCLC at the rate of 10%–15% in North Americans and Europeans, 10% in African Americans, 24% in Koreans, 50.5% in Taiwanese, 26.3% in Japanese, 38.1% in Chinese, and 23.2% in Indian populations.[8] Exons 18–21 are the most commonly studied exons, which generally serve as mutation hotspots. In-frame deletions and point mutations are the most frequently found mutations.

Furthermore, a single amino acid substitution from threonine to methionine at position 790 in EGFR wild-type kinase domain confers resistance to EGFR-targeted TKI therapy to NSCLC subclonal population.[9] The C-to-T base-pair change at position 790 (T790M) occurs in the catalytic pocket of the EGFR tyrosine kinase domain. T790M may be critical for the binding of TKIs to EGFR, and the mutation leads to steric hindrance of TKIs binding. This may be due to the presence of the bulkier methionine side chain. Treatment of metastatic disease with EGFR mutation will not render any benefit with oral TKIs. A new-targeted agent, Osimertinib (Tagrisso) has been approved by the US Food and Drug Administration under its accelerated approval program for treating metastatic NSCLC patients bearing EGFR T790M mutation, especially for patients with progressive disease upon treatment with EGFR TKI. Complete or partial objective tumor responses were observed in these patients in the AURA extension and AURA2 phase 2 clinical trials. *In vitro* studies have shown that HER2, HER3, HER4, ACK1, and BLK activities can be blocked with the use of Osimertinib.[10] The development of these targeted therapies has considerably improved the future of patients with NSCLC.

CONCLUSION

Osimertinib may be a potential option in advanced NSCLC patient harboring T790M mutation.

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Conflicts of interest

There are no conflicts of interest.

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