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LONG TERM RESPONSE TO GEFITINIB IN AN EGFR MUTATED LUNG CANCER EVEN AFTER A SOLITARY RECURRENCE: A CASE REPORT AND LITERATURE REVIEW

Oncology

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ABSTRACT

Courtesy advancement in precision medicine in the past decade, oncotherapy has become more personalised. This has led tremendous improvement in treatment modalities in non-small cell lung cancer. Cardinal molecular changes like mutation in the epidermal growth factor receptor (EGFR) are known to participate in proliferation and survival of cells in the neoplasm. It is observed that patients harboring certain mutations in the EGFR exons 18, 19 or 21, have increased response rate and progression free survival with the use of EGFR tyrosine kinase inhibitors. This is more likely seen in females, patients of Asian origin, never-smokers and having adenocarcinoma. Despite the initial good response with gefitinib (an EGFR tyrosine kinase inhibitor), majority of the patients have progression with progression free survival of 10.8 months and an overall survival of 30.5 months only. Such patients require switching over to next generation EGFR tyrosine kinase inhibitors or chemotherapy. We report a unique case of a middle aged female deriving benefit from a first line EGFR inhibitor for a long period of 6 years and still continuing to have benefit.

KEYWORDS

EGFR mutation, EGFR-TKI, adenocarcinoma lung, durable response

INTRODUCTION

Lung cancer is responsible for most cancer-related deaths worldwide.[1,2] It is estimated that every year 43,500 patients are diagnosed with lung cancer in India and 37,500 tend to die of the disease.[2] With the development of targeted therapy, the treatment of locally advanced or metastatic non-small cell lung cancer patients is now personalised. All three generations of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are well established as standard of care in EGFR mutated carcinoma of the lung.[3]

Despite an initial favorable response to EGFR-TKIs, patients typically experience disease progression within 9 to 12 months.[3] We present an interesting case of a middle-aged non-smoker female deriving benefit from a single agent first generation EGFR-TKI even after 6 years of initiation of therapy.

Case Report

A 52-year-old non-smoker diabetic female reported to the us with lump in the left axilla and left sided neck swelling since 1 week in September, 2017. All routine laboratory investigations were done which were within the normal range.(Hemoglobin:11.9, White Blood Cell Counts: 7700, Platelet Counts:350000).

On physical examination, the patient had no pallor or organomegaly. Left sided level IV cervical and axillary lymph nodes were palpable. Bilateral mammography showed a tiny cyst in the right breast at 9'O clock position (BIRADS 2) and the left breast showed a small lobulated lesion in the upper outer quadrant (BIRADS 5). A USG guided core biopsy done from the left axillary tail showed metastatic mucin secreting adenocarcinoma (TTF 1 and Napsin positive) likely of lung origin. The limited panel next generation sequencing (NGS) study was done on the tumor tissue whose results would take 3 to 4 weeks.

Meanwhile, the PET-CT was performed which showed metabolically active large lobulated soft tissue mass lesion measuring 6 cm X 6.5 cm X 7.6 cm involving the upper lobe of left lung, multiple enlarged left axillary, sub pectoral, bilateral supraclavicular, mediastinal and left hilar lymph nodes, suggestive of primary lung neoplasm (Figure 1A). There was no demonstrable metabolically active lesion in both the breasts.

Thus, a final diagnosis of a locally advanced non-small cell lung cancer (adenocarcinoma) was made.

She was then referred to thoracic onco-surgeon who opined against surgery due to the extensive nature of the disease and advised systemic therapy.

On NGS study, she was found to harbor EGFR mutation in exon 19 was thus, started on tablet gefitinib 250 mg once a day in October, 2017. An interim scan done in January, 2018 showed reduction in the size of primary and the lymph nodes along with complete resolution of metabolic activity at the primary site and lymph nodes, highlighting good response to the therapy (Figure 1B).

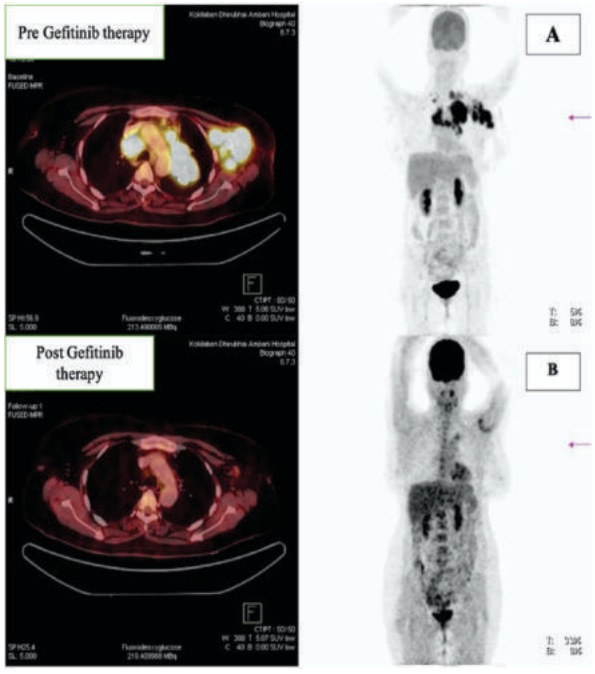

FIGURE 1: The post gefitinib therapy PET-CT after 3 months (Figure 1B) showed reduction in size of lesion at the primary site along with complete resolution of the metabolic activity at the primary site and lymph node in comparison to the pre therapy PET-CT(Figure 1A).

The patient continued gefitinib regularly with only grade 1 dermatological toxicity as a side effect and followed up every 3 months showing good control of the disease until November, 2021.

The routine follow up PET-CT done in November, 2021 showed increased FDG uptake in prevascular lymph node measuring 1.3 cm X 1.4 cm (Figure 2). She underwent video assisted thoracoscopic surgery for the excision of the prevascular lymph node.

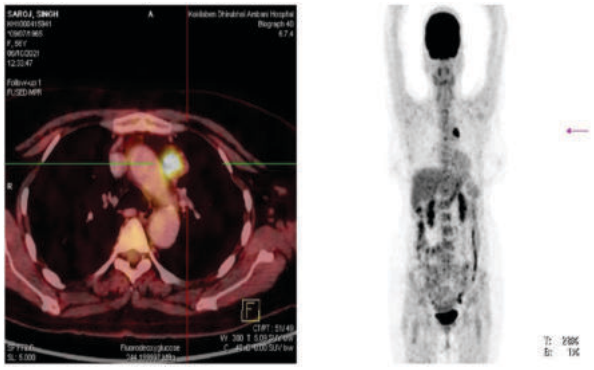

FIGURE 2: The follow up PET-CT showed increased FDG uptake in solitary prevascular lymph node only.

The histopathology report was consistent with the metastatic adenocarcinoma lung and the NGS showed absence of EGFR T790M mutation at exon 20. NGS still confirmed mutation in exon 19 and no other druggable mutations were found. Hence, she was continued on tablet gefitinib 250 mg once a day and was closely followed up every 3 months. The last scan done in April, 2023 showed good control of the disease even after 2 years post last surgery for oligometastatic disease, making it totally 6 years of single agent gefitinib therapy with little or no toxicity.

DISCUSSION

Around 85% of the lung cancer cases are non-small cell lung cancer (NSCLC). The discovery of targeted treatment against anaplastic lymphoma kinase (ALK) rearrangements, epidermal growth factor receptor (EGFR) mutations, and other receptor tyrosine kinases has revolutionised the standard treatment of patients with lung cancer.[3]

Several studies suggest that ethnicity may have a relationship with EGFR-mutant lung cancer, with mutations occurring in approximately 15% of patients with NSCLC in Western population and 35% in the Asian population.[4] Female patients of Asian origin who have never smoked and have adenocarcinoma have higher chances to harbor EGFR mutation.[5]In Indian population, the frequency of EGFR mutation is about 35%.[6]

According to literature, about 45 to 54% of EGFR mutations are seen as in-frame deletions in exon 19, while about 40% of EGFR mutations present with missense mutations in L858R in exon 21 and around 4 to 9% of the mutations are found in exon 20.[7] In our study the mutation was seen in exon 19.

Despite the reassuring survival results, evidence for long-term survival of non-small cell lung cancer patients treated with anti EGFR therapy is limited. The updated results from the IPASS study show, the median progression free survival was 9.5 months while the overall survival in mutation positive patients was 21.6 months.[8] In Indian patients enrolled in the ISEL study, median survival was 6.4 months with gefitinib.[9]

Similarly, with Osimertinib, the median overall survival was 38.6 months in the study conducted by Ramalingam et al.[10]

The majority of patients responding to epidermal growth factor receptor EGFR-TKIs initially, develop acquired resistance and disease progression occurs. The drug resistance mechanisms include, acquiring of the EGFR T790M exon 20 mutation, HER2 amplification, MET amplification, PIK3CA mutation and small cell histological transformation.[11] Subsequent management requires patient to be shifted to next generations EGFR TKIs or chemotherapy and treatment beyond progression rarely helps.

To the best of our knowledge, we report the first case from India where gefitinib has been used for 6 years and still continues to provide benefit to the patient with good disease control even after a solitary node recurrence in between which was managed surgically.

The toxicity analysis highlighted that patients who received gefitinib show reduced incidence of hematologic toxicity, neurotoxicity, alopecia, etc. However, with gefitinib, there are higher incidences of dry skin, rash, pruritus, abnormal hepatic function, and diarrhoea.[12]

Our patient had rash and dry skin (grade 1 dermatological toxicity) with prolonged use but the side effects were always manageable with daily gefitinib and is still on the therapy.

To conclude, in an era of third generation anti-EGFR therapy (Osimertinib), a first generation anti EGFR drug like gefitinib is still a reliable option for the patients in a resource limited country like India where majority cannot afford Osimertinib due to the cost factor.

CONCLUSION

Our case illustrates, gefitinib, a first generation anti-EGFR therapy alone can achieve a long term survival in EGFR mutation positive NSCLC in a country like India where the majority cannot afford the costly Osimertinib. It also proves its efficacy in treatment beyond progression especially in oligometastatic settings with durable response.

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