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Case Report

Targeted Therapies in EGFR and ALK Wild Type Advanced NSCLC in an Elderly Patient

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Abstract

Adenocarcinoma variants of NSCLC often present without an activating EGFR mutation or ALK translocation. In unresectable stage III Guidelines recommend definitive concurrent chemoradiotherapy or induction chemotherapy with platinum-based doublet chemotherapy followed by Radiotherapy. Patient's performance status, age, issues of toxicity, convenience and acceptability should be seen while selecting the appropriate therapy for an individual patient. EGFR TKIs show promising results even in EGFR wild type cases.

Keywords: Adenocarcinoma (NSCLC); EGFR Wild Type; Afatinib

Abbreviations

NSCLC: Non-Small Cell Lung Carcinoma; EGFR: Epidermal Growth Factor Receptor; ALK: Anaplastic Lymphoma Kinase; WT: Wild Type; TKI: Tyrosine Kinase Inhibitor; PET: Posistron Emission Tomography; CT: Computed Tomography; SUV: Standardized Uptake Values

Introduction

Lung cancer is the most cause of cancer-related deaths and is a growing in incidence around the world. The adenocarcinoma histology is the most common type of lung cancer seen in around 40% patients. Patients with adenocarcinoma having actionable driver mutations/translocation (EGFR or ALK) tend to have better prognosis and survival compared to their non-mutant counterparts [1,2]. Majority of the patients presenting at stage IV Adenocarcinoma histology of non-small cell lung carcinoma (NSCLC) present without an activating EGFR mutation or ALK translocation. Based on the current evidence, guidelines recommend initiation of therapy with platinum-based doublet chemotherapy for these patients [3-5]. However, it is also important to consider patient's performance status, age, issues of toxicity, convenience and acceptability while selecting the appropriate therapy for an individual patient. We present a case of an 86 years old elderly male with a 4 years survival after being diagnosed with stage IV WT-NSCLC and managed on EGFR TKIs.

Case Presentation

Mr. SNS, an 86-year-old male, former smoker having Diabetes mellitus, Hypertension, Parkinsonism (on oral hypoglycemics and antihypertensives with Syndopa), presented in January 2014 with breathlessness and was found to have right pleural effusion at a peripheral hospital. This effusion was tapped, and it was negative for malignant cytology. He again presented with vomiting and productive cough in February 2014 to another tertiary hospital, and there he was diagnosed to have rhinosinusitis with polyps and lower respiratory tract infection with sepsis caused by Klebsiella pneumoniae. His CT scan of thorax showed well defined nodular lesion with irregular outline in right upper lobe apical segment with few sub-centrimetric mediastinal nodes in pretracheal, precarinal and aorto-pulmonary regions.

He presented to my outpatient department on 7/3/2014 and a PET CT scan whole body was done which was suggestive of FDG avid speculated mass in apical segment of right lung measuring 1.7 x 1.6 x 1.6 cms with perilesional ground glass opacities (SUV = 4.3) along with FDG avid mediastinal lymph nodes of size 1.3 x 1.4 cms (SUV = 4.5). CT guided core biopsy from the lung mass was suggestive of Adenocarcinoma. He was staged as T1a N2 M0 (stage IIIA) EGFR was wild type, KRAS was negative for mutation and ALK was also negative for translocation. His LVEF was 60%. He was in performance status 3 on ECOG scale so option of surgery and was ruled out and he was also not willing to undergo radiotherapy and chemotherapy using conventional chemotherapeutic agents.

Remaining option of using EGFR Tyrosine Kinase inhibitors (TKIs) was discussed with the patient and his attendants and they agreed for that despite the fact that molecular marker status was not indicative of its use. He was eventually started on Tab. Erlotinib 150 mg OD from 19/4/2014.

He was tolerating it well as his performance status on ECOG scale improved to 2 and a PET CT on 21/8/2014 showed lung lesion of 1.8 x 1.7 x 1.7 cms (SUV = 2.7) and mediastinal lymph nodes of size 1.4 x 1.2 cms (SUV = 3.0). As the FDG avidity of lesions had responded, he was continued on Tablet Erlotinib 150 mg OD only.

A repeat PET CT on 6/1/2015 showed that lung mass increased to 2.1 x 2.0 x 2.3 cm with perilesional fibrotic strands (SUV=5.8) along with FDG avid mediastinal lymph nodes of size 1.2 x 0.8 cm (SUV= 5.8). As the lung lesion increased in size and avidity and mediastinal lymph node also increased in avidity, it was considered to be disease progression. As there were limited options of treatment available and patient still not fit for surgery and not willing for radiotherapy, option of conventional chemotherapy was re discussed but patient and his attendants denied, and they opted for oral agents only.

He was started on Afatinib 30 mg OD from 8/1/2015. He tolerated it well as his hematologic parameters were maintained and ECOG Performance status remained at 2. PET CT on 21/4/2015 showed a partial response as that lung mass remained at 2.3 x 2.1 x 2.2 cms with perilesional fibrotic strands (SUV = 4.2) along with FDG avid mediastinal lymph nodes of size 1.2 x 0.8 cms (SUV = 4.0). He was continued on Tablet Afatinib 30 mg OD.

During this period his haematological parameters were monitored monthly and they were within acceptable limits. Subsequent PET CT on 1/10/2015 showed that lung mass increased to 2.3 x 2.3 x 2.8 cms with perilesional fibrotic strands (SUV = 5.2) along with FDG avid mediastinal lymph nodes of size 1.3 x 1.0 cms (SUV = 5.7). As this was suggestive of mild increase in size and avidity of the lesions, the dose of Tablet Afatinib was increased to 40 mg OD.

PET CT done on 30/3/2016 showed that lung mass increased to 2.6 x 2.1 x 2.5 cms (SUV = 4.4) along with FDG avid subcentimetric mediastinal lymph nodes (SUV = 4.6). In absence of any other available option Tablet Afatinib 40 mg OD was only continued.

PET CT done on on 10/11/2016 showed that lung mass increased to 2.4 x 2.7 x 2.8 cms (SUV = 7.8) along with FDG avid mediastinal lymphnodes of size 1.2 x 0.8 cms (SUV = 6.6).

As there was no treatment option available Tablet Afatinib 40mg OD was continued and the patient-maintained Performance status of ECOG 2 with no haematological toxicity. The only toxicity encountered was grade 1 skin and GI toxicity and stuffy nose which were managed by supportive medications and it never required any treatment break.

PET CT done on 25/10/2017 showed that lung mass increased to 3.1 x 3.4 x 3.8 cms (SUV = 10.7) along with FDG avid mediastinal lymphnodes of size 1.1 x 0.9 cms (SUV = 7.0). This showed slight progression, but the patient was asymptomatic and was able to carry out his activities of daily living with minimal help and has attained 90 years of age. The option of stereotactic radiosurgery and stereotactic radiotherapy were rediscussed with him and his family members, but they did not agree for it. On compassionate grounds he was continued on Tablet Afatinib 40 mg OD only.

He was maintaining good health till 10/1/2018 when he presented to another tertiary hospital with shortness of breath and fever, which subsided after nebulisation, antibiotics and moist oxygen inhalation and required inpatient department admission. 2 D echo showed Left Ventricular Ejection Fraction=50-55% with dilated Left atrium. Two days later he again developed breathlessness and the Electrocardiogram was suggestive of ST elevation myocardial infarction. Despite of management by cardiologist his condition deteriorated, and he developed cardiogenic shock due to which he expired on 13/1/2018.

Discussion

The first EGFR TKIs (Gefitinib and Erlotinib) have shown potent in-vitro activity against wild type EGFR in addition to EGFR mutant cells. Afatinib, a second generation irreversible TKI, has also shown potent activity against wild type EGFR including those resistant to Erlotinib isoforms [6,7].

The first-generation EGFR TKIs were initially investigated for the treatment of unselected NSCLC patients but the results of IPASS study demonstrated superior efficacy of Gefitinib compared to Chemotherapy in subgroup of patients who were positive for EGFR mutation [8]. Thereafter, all the clinical trials for EGFR TKIs in NSCLC in first line were conducted in EGFR mutation positive patients [9-13]. Therefore, there is limited knowledge and understanding of the role of EGFR TKIs in first line treatment of unselected or EGFR mutation negative NSCLC patients.

There are several trials which investigated role of EGFR TKIs in second line and beyond in EGFR wild type NSCLC patients but results from these trials have been contrasting [14-17]. A systematic review of Erlotinib in wild type EGFR NSCLC demonstrated significant benefit compared to other therapies [18-19]. EGFR TKIs are, therefore, still good option recommended for those patients who are either not fit or not willing to receive chemotherapy [3].

The patient in question was an elderly presenting to us with PS-3 and was unwilling to receive chemotherapy and radiotherapy. Therefore, best supportive care (BSC) or EGFR TKIs were the only options available in this case. A decision to start Erlotinib 150 mg once daily was taken following discussion with the patient. The patient responded well to the therapy and his performance status improved to 2. After 11 months of therapy with Erlotinib, the patients showed signs of progression and a decision to switch to Afatinib (30 mg OD), an irreversible and pan-ErBb family blocker, was taken.

In LUX-Lung 1, a phase IIb/III trial, Afatinib was compared to best supportive care (BSC) in unselected patients who had progressed on chemotherapy or a first-generation EGFR TKI (Gefitinib, or Erlotinib). There was significant improvement in progression-free survival with Afatinib compared to BSC, but overall survival did not show a significant improvement. In patients fulfilling Jackman and colleagues' criteria of acquired resistance median PFS was 4.53 months with Afatinib compared to 0.99 months in the placebo arm.19 LUX –Lung 4, a single arm phase II Japanese trial, evaluating Afatinib in pretreated Gefitinib or Erlotinib beyond progression also demonstrated good PFS and OS benefit [20]. Afatinib could not get approval in patients who developed an acquired resistance to EGFR TKIs in most of the countries with exception of Japan. A phase II study, evaluating Afatinib in third line in wild type EGFR NSCLC, demonstrated disease control rate of 24% with median disease control duration of 19 weeks [21].

The patient following progression on Erlotinib performed well on Afatinib 30 mg once daily and when showed slight progression was escalated to Afatinib 40 mg once daily. Afatinib was well tolerated and patient survived for 4 years from the time of diagnosis.

Conclusion

EGFR TKIs have not shown statistically significant benefit compared to chemotherapy in wild type EGFR patients in randomized controlled trials. Although, this does not imply that they have no efficacy in wild type EGFR NSCLC and could not be used in these patients. Safety and tolerability of these agents was also acceptable in these trials. Therefore, in patients who are ineligible or unwilling to receive chemotherapy, EGFR TKIs could be a good alternative.

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