Case Report

Favorable response in "locally advanced stage" of adenocarcinoma lung to erlotinib: Quality of life and clinical and radiological outcome are satisfactory after 24 weeks

Shital Patil, Umesh Kanade[1]

Department of Pulmonary Medicine, MIMSR Medical College, [1]Department of Pathology, Government Medical College, Latur, Maharashtra, India

ABSTRACT

Lung cancer is one of the most common types of cancer and the leading cause of human cancer deaths worldwide. Adenocarcinoma is the most common histological type of lung cancer. Tyrosine kinase inhibitors of the epidermal growth factor receptor (EGFR) have been reported to exert a significant impact in the treatment of nonsmall cell lung cancer, particularly in patients harboring mutations in the *EGFR* gene. In this case report, 41 years male with "locally advanced stage" of lung cancer presented with shortness of breath on routine work and compromised quality of life, diagnosed to have malignant pleural effusion after pleural fluid cytology evaluation. We performed bronchoscopy guided transbronchial lung biopsy and confirmed to have adenocarcinoma lung after histopathology evaluation. We further analyzed thyroid transcription factor-1 and EGFR mutation study in histopathology sample and started "targeted therapy" with erlotinib. We documented excellent clinical and radiological response with complete resolution of pleural fluid and lung parenchymal lesion, and significant improvement in quality of life after 6 weeks of erlotinib. We used erlotinib as a "maintenance therapy" in adenocarcinoma lung for 24 weeks.

Key words: Adenocarcinoma lung, epidermal growth factor receptor mutation, erlotinib, lung cancer

INTRODUCTION

Lung cancer is one of the most common types of cancer and the leading cause of human cancer deaths worldwide.[1] The majority of the cases (85%) are classified as nonsmall cell lung cancer (NSCLC), often diagnosed at an advanced stage with poor prognosis. Platinum-based doublet chemotherapy has become the standard of care for the treatment of advanced or metastatic NSCLC with wild-type or unknown epidermal growth factor receptor (EGFR) status.[2]

Address for correspondence: Dr. Shital Patil,
Department of Pulmonary Medicine, MIMSR Medical College, Latur, Maharashtra, India.
E-mail: drsvpatil1980@gmail.com

Access this article online

Quick Response Code:

Website: www.ccij-online.org

DOI: 10.4103/2278-0513.186103

In Asian countries, EGFR mutations can be found in approximately 40% of patients, explaining in part why Asian patients are more responsive to EGFR tyrosine kinase inhibitors (TKIs); in contrast, *K-ras* mutations predict the resistance to TKIs, likely due to the downstream location of *K-ras* signaling to EGFR activation.[3] It is known that a mutation in the *EGFR* gene, clinical characteristics such as female sex, nonsmoking status, and Asian ethnicity, adenocarcinoma histology and skin toxicity reported during the treatment, give an increased response to EGFR inhibitors.[4]

Until 2009, platinum-based doublets chemotherapy was the accepted standard of care for first-line treatment

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

Cite this article as: Patil S, Kanade U. Favorable response in "locally advanced stage" of adenocarcinoma lung to erlotinib: Quality of life and clinical and radiological outcome are satisfactory after 24 weeks. Clin Cancer Investig J 2016;5:315-9.

of advanced NSCLC. The response rate was 30% with a median progression-free survival (PFS) and overall survival (OS) of 6.4 and 10–12 months, respectively. Since 2004, several studies have shown that patients with EGFR mutations are the best predictor of response to EGFR-TKIs such as erlotinib and gefitinib, the fact that has changed dramatically the paradigm of advanced NSCLC treatment.[4]

CASE REPORT

A 42-year-old male, teacher by profession, without any addiction for tobacco or tobacco products present to outdoor unit of pulmonary medicine with complaints of shortness of breath, dull aching chest pain on the right side since 2 months. He was advised for chest X-ray posterior to anterior (PA) and routine hematological investigations.

Figure 1 showing right middle and lower zone haziness/opacification with obliteration of cardiophrenic and costophrenic angles suggestive of mass/collapse/consolidation with effusion on the right side.

Complete blood counts

- Hemoglobin - 12 g%
- Total white blood cell count - 7400/mm^3
- Platelets - 2.73 lakhs
- HIV 1 and HIV 2 - tridot negative
- Blood sugar level - 124 mg%
- Erythrocyte sedimentation rate - 24 mm at the end of 1 h
- Lactate dehydrogenase - 380 units/L
- C-reactive proteins - titer 9.4 units
- Liver function tests - normal
- Kidney function tests - normal
- Ultrasound abdomen - predominant findings were mild hepatomegaly. No lymphadenopathy or ascites
- Ultrasound thorax - moderate pleural fluid in the right pleural cavity without internal echoes with underlying lung collapse.

Pleural fluid aspiration

Pleural fluid aspiration was done ultrasound guided from the right pleural cavity in 6th intercostal space in posterior axillary line. With all possible aseptic precautions, 1400 ml of straw-(yellowish) colored pleural fluid was aspirated. Pleural fluid was sent in four different aliquots (20 ml each) for Biochemical, microbiological, cytology analysis, and one aliquot for *Mycobacterium tuberculosis* DNA polymerase chain reaction for tuberculosis. Remained pleural fluid was sent for centrifugation and cell block preparation for cytology analysis.

Pleural fluid analysis

- Pleural fluid proteins - 5.6 g%
- Pleural fluid glucose - 56 mg%
- Pleural fluid cells - 12,000/mm^3 (lymphocytes 90% and polymorphs 10%).
- Predominantly lymphocytes
- Groups and cell ball of malignant cells having round hyperchromatic nuclei and eosinophilic and vacuolated cytoplasm.

After pleural fluid aspiration, check X-ray PA was taken showing clearance of pleural fluid with parenchymal opacity in the right lower zone. This opacity was sharply demarcated with residual pleural effusion in the right lower zone. We planned fiber-optic bronchoscopy to look for any endobronchial growth.

Computed tomography (CT) thorax imaging was done after pleural fluid aspiration for exact assessment of underlying lung parenchyma, pleural nodules, mediastinal and hilar lymphadenopathy, and opposite lung status.

Figure 2 showing lung parenchymal mass lesion in the right middle lobe with pleural effusion with "classical split pleura sign." Mediastinal lymphadenopathy including subcarinal and right hilar lymph nodes was also documented.

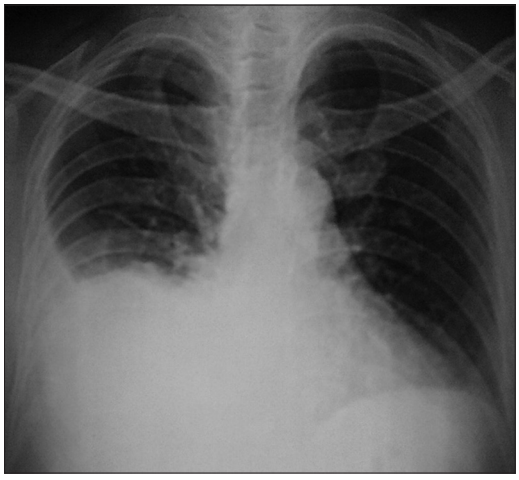

Figure 1: Chest X-ray posterior to anterior

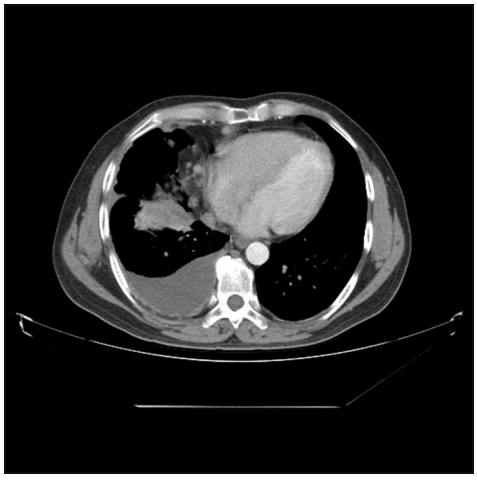

Figure 2: Computed tomography thorax contrast mediastinal window

Follow-up chest X-ray PA was done after 28 days of erlotinib treatment, and we documented resolving pleural effusion on the right side of thoracic cavity. After comparison with previous chest X-rays, there is a significant reduction in the size of the mass lesion in the right lower zone with cardiophrenic and costophrenic angles clear.

Figure 3 of right middle lobe bronchus showing ulcerated growth with whitish exophytic nodularity at the division of right middle and lateral lobe segmental opening. Six fiber-optic forcep biopsy samples were collected and sent for histopathology analysis and also for immunohistochemistry (IHC) analysis.

Pleural fluid cytology showing malignant cells having hyperchromatic nuclei with eosinophilic and vacuolated cytoplasm.

Figure 4 shows fragments of adenocarcinoma invading desmoplastic stroma with anthracotic pigment. A tiny piece of bronchial mucosa is noted aside.

Figure 5 shows tumor comprising disrupted tubules, acini, and solid nests; displaying moderate nuclear atypia, pleomorphism, and dense chromatin with abundant eosinophilic cytoplasm. Glandular mucin is however not seen; no squamous differentiation is identified. IHC with thyroid transcription factor-1 (TTF-1) and EGFR mutation study is necessary.

Immunohistochemistry study

Histopathology tissue sample block was analyzed for TTF-1 and EGFR marker studies. Results were TTF-1 positive with EGFR mutation analysis positive.

Chest X-ray PA [Figure 6] view after 48 weeks of erlotinib showing normal lung parenchyma without any obvious abnormality. There is no evidence of pleural effusion or hilar enlargement.

DISCUSSION

Lung cancer is one of the most common types of cancer and the leading cause of human cancer deaths worldwide; the majority of the cases (85%) are classified as NSCLC, often diagnosed at an advanced stage with poor prognosis.[1] It is recognized that the EGFR-dependent autocrine pathway plays an important role in the development and progression of human epithelial cancers including NSCLC. The EGFR is a member of the ErbB family of cell membrane receptors that are important mediators of cell growth, differentiation, and survival. However, the antitumor effects of EGFR inhibition in human cancer models are inhibition of cancer cell proliferation with G0/G1 cell cycle arrest and in some cases, induction of apoptosis; antiangiogenesis through inhibition of angiogenic growth factor production; inhibition of invasion and metastasis; and potentiation of antitumor activity of cytotoxic drugs and radiotherapy.[5]

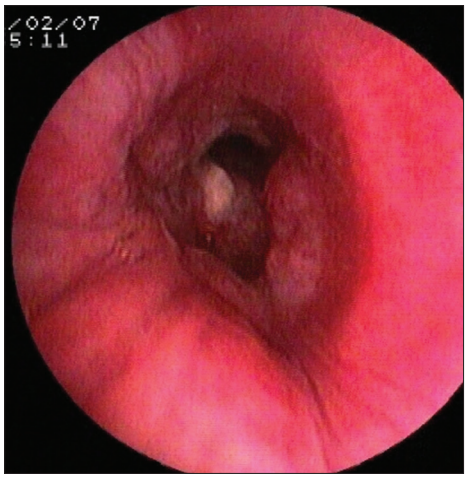

Figure 3: Bronchoscopy image

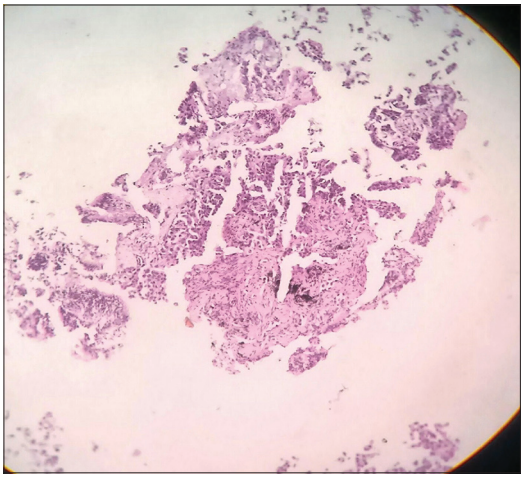

Figure 4: Bronchoscopy biopsy histopathology (×10)

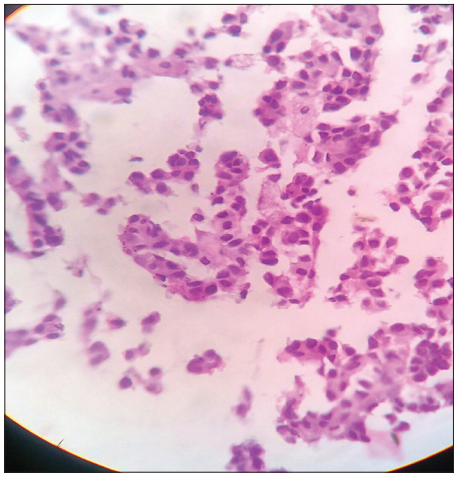

Figure 5: Bronchoscopy biopsy histopathology (×40)

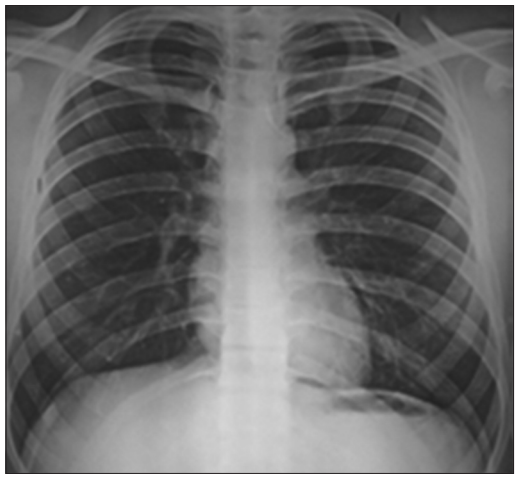

Figure 6: Chest X-ray posterior to anterior

Erlotinib has demonstrated efficacy in the first-line treatment of EGFR mutation-positive NSCLC. Several clinical trials have also demonstrated that erlotinib improves PFS and OS in the second- and third-line treatment of NSCLC as well as in the maintenance setting.[6,7] It is known that a mutation in the *EGFR* gene, clinical characteristics such as female sex, nonsmoking status, and Asian ethnicity, adenocarcinoma histology and skin toxicity reported during the treatment, give an increased response to EGFR inhibitors.[4]

A recent study showed that 50% of patients with EGFR mutation-positive primary lung tumors lose the mutation in metastasis, and that discordance rate of EGFR expression between primary tumor/metastases can reach 27%.[8] In view of current knowledge, the analysis of EGFR mutation status in the primary tumor may be inadequate for planning the use of TKIs for advanced NSCLC, reason why tissue sampling from distant metastases must be pursued to accurately determine EGFR mutations before treatment.[8] In addition, there is some evidence that EGFR exon 19 deletion is associated with better responses to erlotinib and longer survival compared to exon 21 mutation, which suggests that exon 19 deletion might still be present is our patient.[4]

In this case report, we documented the clear benefit of "targeted therapy" in "locally advanced stage of lung cancer" with erlotinib. Initially, before treatment, he was having Grade IV shortness of breath with decreased performance status clinically, and moderate malignant pleural effusion radiologically. After CT thorax, we confirmed as Stage IIIb with inoperable condition and not suitable for surgical treatment of lung cancer (adenocarcinoma). We performed IHC and found to be EGFR positive case, and offered best possible "targeted therapy" with erlotinib. We initially planned to give erlotinib 150 mg daily for 24 weeks, and if stable response is there to continue same for additional 24 weeks.

We observed significant reduction in pleural fluid; lung parenchymal mass size is reduced significantly and remarkable improvement in performance status with patient able to walk for 800 m without any respiratory discomfort after 4 weeks use of erlotinib. In addition, we observed complete radiological resolution in the form of absence of pleural effusion with cardiophrenic and costophrenic angles clear and normal lung parenchyma bilaterally after 24 weeks of the use of erlotinib. We consulted our medical oncologist regarding continuation of erlotinib as a maintenance therapy for additional 24 weeks as lung adenocarcinoma is EGFR positive and initial satisfactory clinical and radiological response. We continued it for 24 weeks to complete 48 weeks. After 48 weeks of follow-up with erlotinib treatment, we observed stable clinical and radiological response. We are performing follow-up evaluation as 3 monthly chest X-ray and assessment is done for relapse of tumor in the same or opposite lung. We also perform ultrasound abdomen for liver and visceral metastasis. We are also performing CT thorax at 6 months interval to look for occult intrathoracic metastasis. After 2 years of follow-up, no relapse has been documented.

Similar results were also documented in few published case reports.[9,10]

CONCLUSION

Adenocarcinoma lung is common histological type of lung cancer, rising trends in India as compared to previously known squamous cell as common histological type. Pleural fluid cytology analysis is very useful tool to diagnose metastatic lung cancer to pleura, with satisfactory yield in "fluid block preparation." We recommend to prepare pleural fluid block preparation in all the cases of malignant pleural effusion as it will help to identify exact histological type and will also enhance its diagnostic sensitivity by providing adequate cytological material for IHC analysis. Histopathology expertise in the field of oncology is must while managing these cases.

EGFR mutation analysis made dramatic change in lung cancer outcome, especially in adenocarcinoma because of excellent response to "targeted therapy for EGFR positive" cases to erlotinib. We documented satisfactory and stable response to erlotinib in "Locally advanced stage of Lung cancer" in our case of adenocarcinoma lung. We recommend the use of erlotinib for 24 weeks as "primary treatment" and additional 24 weeks as "maintenance therapy" in EGFR positive adenocarcinoma.

Financial support and sponsorship
Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin 2011;61:69-90.
2. Peters S, Adjei AA, Gridelli C, Reck M, Kerr K, Felip E; ESMO Guidelines Working Group. Metastatic non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2012;23 Suppl 7:vii56-64.
3. Linardou H, Dahabreh IJ, Kanaloupiti D, Siannis F, Bafaloukos D, Kosmidis P, *et al.* Assessment of somatic K-ras mutations as a mechanism associated with resistance to EGFR-targeted agents: A systematic review and meta-analysis of studies in advanced non-small-cell lung cancer and metastatic colorectal cancer. Lancet Oncol 2008;9:962-72.
4. Rosell R, Moran T, Queralt C, Porta R, Cardenal F, Camps C, *et al.* Screening for epidermal growth factor receptor mutations in lung cancer. N Engl J Med 2009;361:958-67.
5. Normanno N, Bianco C, De Luca A, Maiello MR, Salomon DS. Target-based agents against ErbB receptors and their ligands: A novel approach to cancer treatment. Endocr Relat Cancer 2003;10:1-21.
6. Zhou C, Wu YL, Chen G, Feng J, Liu XQ, Wang C, *et al.* Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): A multicentre, open-label, randomised, phase 3 study. Lancet Oncol 2011;12:735-42.
7. Rosell R, Carcereny E, Gervais R, Vergnenegre A, Massuti B, Felip E, *et al.* Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): A multicentre, open-label, randomised phase 3 trial. Lancet Oncol 2012;13:239-46.
8. Gow CH, Chang YL, Hsu YC, Tsai MF, Wu CT, Yu CJ, *et al.* Comparison of epidermal growth factor receptor mutations between primary and corresponding metastatic tumors in tyrosine kinase inhibitor-naive non-small-cell lung cancer. Ann Oncol 2009;20:696-702.
9. Vitale MG, Riccardi F, Mocerino C, Barbato C, Monaco R, Galloro P, *et al.* Erlotinib-induced complete response in a patient with epidermal growth factor receptor wild-type lung adenocarcinoma after chemotherapy failure: A case report. J Med Case Rep 2014;8:102.
10. Gonçalves I, Ladeira I, Castro A, Antunes A, Barroso A, Parente B. Advanced lung adenocarcinoma in an EGFR-positive patient treated with Erlotinib for 52 months. Respir Med Case Rep 2013;10:10-12.