

# Response to afatinib, after gefitinib and erlotinib, in a patient with advanced adenocarcinoma of lung with brain metastasis: A case report

Prashant Mehta<sup>1</sup>, Pranjit Santonu Bhajoni<sup>2</sup>, Swati Pabbi Mehta<sup>3</sup>

<sup>1</sup>Department of Medical Oncology/Hematology/BMT, Asian Institute of Medical Sciences, Faridabad, Haryana, <sup>2</sup>Department of Pharmacology, PGIMER, Dr. Ram Manohar Lohia Hospital, New Delhi, <sup>3</sup>Department of Pathology, Sardar Patel Medical College, Bikaner, Rajasthan, India

**Correspondence to:** Prashant Mehta, Asian Institute of Medical Sciences, Faridabad, Haryana, India. E-mail: prashant.mehta@aimsindia.co.in

## ABSTRACT

Non-small-cell lung cancer (NSCLC) accounts for 80–85% of all lung cancer cases. The majority of patients present with advanced disease. Adenocarcinoma of the lung forms one of the major histopathological subtypes of metastatic NSCLC. A 70-year-old male was diagnosed with adenocarcinoma right lung with clinical staging of cT<sub>2</sub>N<sub>0</sub>M<sub>0</sub> in 2012. Patient was treated with adjuvant chemotherapy with 4 cycles of vinorelbine and cisplatin followed by image guided radiation therapy that was completed in November 2012. The patient was started on gefitinib in Jan 2014 till January 2015 due to recurrence and progression and was subsequently switched to erlotinib as the gefitinib was becoming ineffective. However, the patient developed toxicity leading to diarrhea, and the patient had to discontinue erlotinib. In view of poor general condition of the patient (ECOG performance status 4), and progression post gefitinib and erlotinib he was deemed unfit for chemotherapy and it was decided to start the patient on afatinib 40 mg once a day in July 2015, to which the patient responded. The patient showed significant improvement on afatinib. The response though partial and incomplete was substantial and further improvement was very much expected unfortunately the patient succumbed to a lower respiratory tract infection in November 2015.

**Key words:** Adenocarcinoma lung, Afatinib, Afatinib after gefitinib and erlotinib, Brain metastasis, Erlotinib, Gefitinib

## Introduction

Non-small-cell lung cancer (NSCLC) accounts for 80–85% of all lung cancer cases. The majority of patients present with advanced disease. Adenocarcinoma of the lung forms one of the major histopathological subtypes of metastatic NSCLC.<sup>[1]</sup> Adenocarcinoma cases have been increasingly reported these days possibly due to the shift to low-tar filter cigarettes, which are inhaled more deeply into the periphery of the lung. The pathogenesis of adenocarcinoma, like many other cancers, involves genetic mutations which drive the cells to become cancerous.<sup>[2]</sup>

Driver mutations in the epidermal growth factor receptor (EGFR) gene are found in a subset of lung adenocarcinomas.<sup>[3]</sup> In these cancers tumor, cell survival is exquisitely dependent on EGFR pathway signaling.<sup>[4]</sup> This leaves the cancers uniquely susceptible to selective oral EGFR tyrosine kinase inhibitors (TKIs).<sup>[4]</sup> Randomized phase III clinical trials have demonstrated that these drugs have already shown surprisingly high response rates, significantly longer progression-free survival (PFS) as well as dramatic tumor shrinkage as compared to chemotherapy.<sup>[5-9]</sup> The second-generation EGFR-TKI, Afatinib has also shown significantly improved overall survival in patients with advanced adenocarcinoma of the lung as compared to chemotherapy, which the first generation EGFR-TKIs have consistently failed to demonstrate.<sup>[3,7-9]</sup>

As the survival in these patients increases, the scope for metastasis to another organ also increases.<sup>[10]</sup> Most ominous metastasis among these is to the brain, which occur in more than 25% of patients at some point during their disease course.<sup>[11]</sup> These patients have a poor prognosis with a median survival of only 1 month from diagnosis if untreated, 2 months with glucocorticoid therapy, and 2–5 months with whole-brain radiation therapy.<sup>[11-17]</sup> Afatinib appears to penetrate into the central nervous system (CNS) with concentrations high enough to have a clinical effect on CNS metastases. Afatinib may, therefore, be an effective treatment for heavily pretreated patients with EGFR-mutated or EGFR-TKI-sensitive NSCLC and CNS metastasis.<sup>[14]</sup>

## Case Report

A 70-year-old male was diagnosed with adenocarcinoma right lung with clinical staging of cT<sub>2</sub>N<sub>0</sub>M<sub>0</sub> in 2012. Lower lobectomy was performed on 25/04/2012 with Hilar and mediastinal lymph nodal dissection. Patient's pathological staging was pT<sub>2</sub>N<sub>1</sub>M<sub>0</sub>. Thereafter, the patient received adjuvant chemotherapy with 4 cycles of vinorelbine and cisplatin followed by image-guided radiation therapy that was completed in November 2012. In January 2014, the patient had back pain for which imaging was done which revealed L3 vertebral metastasis with a soft tissue component. Biopsy of soft tissue

was performed, and molecular analysis was positive for EGFR-L858R mutation. Hence, the patient was started on an EGFR TKIs, gefitinib 250 mg once a day. The patient also received radiation therapy to spine as a palliative measure. The patient was continued on gefitinib till January 2015, when he eventually progressed. The patient was switched to erlotinib 150 mg once a day for 2 months. However, the patient developed toxicity leading to diarrhea, and the patient had to discontinue erlotinib. Thereafter, the patient did not take any further therapy for 2 months. The patient lost his appetite for almost 2 months and developed hypoalbuminemia. He presented with poor general condition, severe bone pains, and ECOG performance status score of 4 in June 2015. The patient had also developed a left sided pleural effusion followed by right side pleural effusion. Pleural tapping was done and 1.5 L fluid was drained.

On 01/07/2015, positron emission tomography-computed tomography (PET-CT) scan was performed which showed an ill-defined FDG avid peribronchial soft tissue thickening and consolidative opacities in the posterior segment of right upper lobe and in the right lower lobe, FDG avid subpleural nodule measuring  $1.7 \times 1.6$  cm posteriorly in the apical segment of right upper lobe, FDG avid pleural deposits, contralateral lung nodules and mediastinal lymphadenopathy, FDG avid metastases to the liver, bilateral adrenal glands, mesentery, omentum and multiple bones. On comparison with the report of previous PET-CT scan performed on 17/04/2015, the lesions in the left lung, liver, adrenals, and skeleton were new. These findings were suggestive of disease progression.

Contrast enhanced magnetic resonance imaging (MRI) was performed on 02/07/2015 which showed multiple nodular and ring enhancing lesions in bilateral cerebral and cerebellar hemisphere suggestive of intracranial metastases. Patient's complete blood counts were normal. However, liver function tests were deranged with SGOT 104 U/L and SGPT 98 U/L.

In view of the poor general condition of the patient (ECOG performance status 4), and progression post-gefitinib and erlotinib he was deemed unfit for chemotherapy and it was decided to start the patient on Afatinib 40 mg once a day from 7/7/2015.

As compared to the report of previous PET-CT scan done on 01/07/2015, the PET-CT scan done on 15/10/2016 showed partial response. The right lung consolidation had increased; however, it showed a decrease in metabolism with decrease in the size, number and FDG avidity in liver, adrenals, abdominal and skeletal lesions.

After 3 months of treatment with afatinib, patient's liver function tests normalized and the ECOG performance status improved from 4 to 2. Patient's nutritional status improved with improvement in the weight of about 4%. There were no reported adverse events with afatinib.

A follow-up PET-CT showed partial response. Brain MRI performed showed reduction in size of the supratentorial lesions.

In view of partial response, the patient was continued on afatinib. However, 1 month later the patient succumbed to a lower respiratory tract infection.

## Discussion

In this case study, a patient who had progressed after undergoing surgical resection of lung, radiation therapy, adjuvant chemotherapy, followed by receiving gefitinib and also erlotinib for metastatic disease, showed a partial response to Afatinib. Therapeutic options were limited in this case in view of his poor general condition and ECOG performance status. This case study emphasizes that even in such patients targeted therapy with a second generation TKI can be a treatment option. Analysis for T790M was not done in this case as T790M inhibitors, which could have been an option here, were not available to us for this patient.

Afatinib is an orally available, irreversibly binding ErbB family blocker with the ability to block signaling from EGFR (ErbB1), human EGFR 2 (HER2/ErbB2), ErbB4, and all relevant ErbB family dimers.<sup>[18]</sup> *In vitro*, the median inhibitory concentration is lower than those of currently available EGFR TKIs.<sup>[18]</sup>

In a similar study published by Hoffknecht *et al.*, 35% (11 of 31) of evaluable patients had a cerebral response, 5 (16%) responded exclusively in brain. Response duration (range) was 120 (21–395) days. 66% (21 of 32) of patients had cerebral disease control on afatinib. Data from one patient with an impressive response showed an afatinib concentration in the cerebrospinal fluid of nearly 1 nMol, which is twice as much as the concentration required to inhibit EGFR activity as demonstrated by the *in-vitro* studies.<sup>[14]</sup> This is probably the reason why afatinib was able to show response in this patient who had brain metastasis, where first generation EGFR-TKIs failed.

According to a study published by Schuler *et al.*, afatinib confers longer PFS versus chemotherapy (8.2 versus 5.4 months; hazard ratio [HR] = 0.50;  $P = 0.0297$ ) in patients with brain metastases who harbored common EGFR mutations. The outcomes were particularly promising in patients with a Del19 mutation (9.5 versus 4.7 months, HR = 0.24, 95% confidence interval: 0.09–0.62,  $P = 0.0012$ ), a subgroup for whom afatinib is the only TKI to demonstrate superior OS versus chemotherapy.<sup>[10]</sup>

In this case study, the patient had also shown improvement in liver function test. This may be due to the tumor shrinkage as well as due to the fact that only 2% of metabolism of afatinib takes place in the liver as compared to significant metabolism of erlotinib and gefitinib by the liver. The first generation EGFR-TKIs, erlotinib, and gefitinib can also cause drug-

induced liver injury (DILI) and thereby may cause grade 3 (>10 times the upper limit of normal) liver enzyme elevation in some cases. Grade 3 enzyme elevations and hence, DILI are extremely rare with Afatinib. Interactions with CYP 450 enzymes are also common with first generation EGFR-TKIs, erlotinib and gefitinib, which is absent with afatinib. The absence of these interactions, DILI and reduced need for the liver to metabolize the drug must have allowed the liver function to normalize as represented by the improvement in liver function test. Importantly, smoking history, alcohol consumption or presence of liver metastases seems to have no significant impact on the pharmacokinetics of afatinib.<sup>[18]</sup>

The patient's general condition also improved, with the patient re-attaining the appetite. This led to increase in the patient's weight and also a visible improvement in ECOG performance status from 4 to 2. The patient did not experience any major adverse effects. All these factors contributed to improvement in the patient's quality of life.

## Conclusion

Afatinib may be useful treatment option in patients with advanced adenocarcinoma of the lung, with brain metastasis and an actionable EGFR mutation and also those who may have progressed on first generation TKIs.

## References

1. Travis WD. Pathology of lung cancer. *Clin Chest Med* 2011;32:669-92.
2. Reck M, Popat S, Reinmuth N, De Ruyscher D, Kerr KM, Peters S; ESMO Guidelines Working Group. Metastatic non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2014;25 Suppl 3:iii27-39.
3. Sequist LV, Yang JC, Yamamoto N, O'Byrne K, Hirsh V, Mok T, *et al.* Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. *J Clin Oncol* 2013;31:3327-34.
4. Sharma SV, Bell DW, Settleman J, Haber DA. Epidermal growth factor receptor mutations in lung cancer. *Nat Rev Cancer* 2007;7:169-81.
5. Mok TS, Wu YL, Thongprasert S, Yang CH, Chu DT, Saijo N, *et al.* Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med* 2009;361:947-57.
6. Mitsudomi T, Morita S, Yatabe Y, Negoro S, Okamoto I, Tsurutani J, *et al.* Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): An open label, randomised phase 3 trial. *Lancet Oncol* 2010;11:121-8.
7. Maemondo M, Inoue A, Kobayashi K, Sugawara S, Oizumi S, Isobe H, *et al.* Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. *N Engl J Med* 2010;362:2380-8.
8. 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.
9. 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.
10. Schuler M, Wu YL, Hirsh V, O'Byrne K, Yamamoto N, Mok T, *et al.* First-line afatinib versus chemotherapy in patients with non-small cell lung cancer and common epidermal growth factor receptor gene mutations and brain metastases. *J Thorac Oncol* 2016;11:380-90.
11. Langer CJ, Mehta MP. Current management of brain metastases, with a focus on systemic options. *J Clin Oncol* 2005;23:6207-19.
12. Eichler AF, Loeffler JS. Multidisciplinary management of brain metastases. *Oncologist* 2007;12:884-98.
13. Fan Y, Huang Z, Fang L, Miu L, Lin N, Gong L, *et al.* Chemotherapy and EGFR tyrosine kinase inhibitors for treatment of brain metastases from non-small-cell lung cancer: Survival analysis in 210 patients. *Oncotargets Ther* 2013;6:1789-803.
14. Hoffknecht P, Tufman A, Wehler T, Pelzer T, Wiewrodt R, Schütz M, *et al.* Efficacy of the irreversible ErbB family blocker afatinib in epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI)-pretreated non-small-cell lung cancer patients with brain metastases or leptomeningeal disease. *J Thorac Oncol* 2015;10:156-63.
15. Khuntia D, Brown P, Li J, Mehta MP. Whole-brain radiotherapy in the management of brain metastasis. *J Clin Oncol* 2006;24:1295-304.
16. Ruderman NB, Hall TC. Use of glucocorticoids in the palliative treatment of metastatic brain tumors. *Cancer* 1965;18:298-306.
17. Zimm S, Wampler GL, Stablein D, Hazra T, Young HF. Intracerebral metastases in solid-tumor patients: Natural history and results of treatment. *Cancer* 1981;48:384-94.
18. Prescribing information of Afatinib. Available from: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2013/201292s0001bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/201292s0001bl.pdf). [Last accessed on 2016 Apr 03].

**How to cite this article:** Mehta P, Bhajoni PS, Mehta SP. Response to afatinib, after gefitinib and erlotinib, in a patient with advanced adenocarcinoma of lung with brain metastasis: A case report. *Int J Mol Immuno Oncol* 2017;2:22-24.

**Source of Support:** Nil. **Conflict of Interest:** None declared.