Erlotinib induced fatal interstitial lung disease in a patient with metastatic non-small cell lung cancer: case report and review of literature

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Abstract

Erlotinib is one of the most widely used tyrosine kinase inhibitor targeting human epidermal growth factor receptor. Since its introduction, it has revolutionized the treatment of advanced non-small cell lung cancer. Skin rashes and diarrhea are the most often reported side effects of erlotinib however it is also associated with interstitial pneumonitis or interstitial lung disease, which often turns out to be fatal complication of using this medicine. Though reported scarcely in the western world, the association of interstitial lung disease with epidermal growth factor receptor has attracted a lot of attention in the recent times. Various researches working with murine models of bleomycin-induced pulmonary fibrosis have found a *pro* and *con* role of the receptor in development of the interstitial lung disease. We present the case of a patient diagnosed with stage IV adenocarcinoma of the lung with metastasis to brain. He was found to be positive for the human epidermal growth factor mutation and was hence started on erlotinib. Within a few weeks of starting the medicine the patient was admitted with diarrhea. During the course of this admission he developed acute shortness of breath diagnosed as interstitial pneumonitis. The purpose of this case report is to review the literature associated with erlotinib induced interstitial pneumonitis and make the practicing oncologists aware of this rare yet fatal complication of erlotinib. Here we will also review literature, pertaining to the role of epidermal growth factor receptor in development of interstitial lung disease.

Introduction

Non-small cell lung cancer (NSCLC) is the most common cause of cancer death in the world.[1] Newer agents based on molecular targeting have been developed over time to tackle this formidable challenge. Targeting human epidermal growth factor receptor (EGFR), expressed by a variety of solid organ tumors, has been central to development of molecular therapies for lung cancer.[1] Erlotinib, a low molecular weight tyrosine kinase inhibitor (TKI), is one of the most popular molecular-targeted therapies widely used as a first line treatment in patients in whom the NSCLC expresses EGFR mutation.[2] Erlotinib acts by inhibiting the tyrosine kinase activity of the EGFR, generally by competing with adenosine tri-phosphate (ATP) for the ATP-binding site.[1] The most common adverse events (AE) associated with erlotinib include skin rash, diarrhea, fatigue and other constitutional symptoms.[3,4] Pulmonary toxicity, especially interstitial lung disease (ILD) is one of the rarer AE of erlotinib with reported incidence of nearly 0.3% in US population.[5] The use of steroids has met with partial success in management of patients in the acute phase of ILD, who developed ILD as a complication of erlotinib.[4] We present the case of a middle aged patient, with recent diagnosis of stage IV NSCLC (pathology favoring adenocarcinoma) who was treated with erlotinib (150 mg PO/day) as first line therapy and developed dyspnea, cough and pulmonary infiltrates diagnosed as ILD, which proved fatal. It is important for treating oncologists to remember this rare but critical pulmonary complication of erlotinib, as timely recognition of the pathology may prevent fatal outcomes.

Case Report

A 72-year-old man with no significant past medical was referred to oncology clinic after he was found to have a right upper lobe lung mass. The patient presented to primary care physician with history of dull aching right side chest pain along with noticing specks of blood in his phlegm. A chest X-Ray (CXR) showed an ill-defined 60×45 mm mass in the right upper lobe. Computed tomography (CT) of the chest showed 87×63 mm mass in the right upper lobe with multiple small nodules in both lobes of the lungs (Figure 1). Histopathology of the sample obtained via a transbronchial biopsy showed NSCLC favoring adenocarcinoma. Mutation analysis of the sample was positive for EGFR mutation (exon-19 deletion) and negative for K-ras and ALK rearrangement. As part of metastatic workup, CT head with contrast was obtained, which showed a 9×8 mm mass in the gray matter of right insular cortex suggestive of metastatic deposit. Magnetic resonance imaging brain showed a bilobed nodular contrast enhancing lesion in the right anterior inferior frontal cerebral cortex measuring 12.2×8.6×4.7 mm, confirming the lesion as metastasis from a distant primary (which was lung adenocarcinoma in this patient). The bone scan showed a blastic lesion in the T8 vertebrae and *manubrium sterni*. Radiation oncology evaluated the patient and planned for palliative external beam radiation therapy (EBRT) to whole brain (30 Gy in 10 fractions). However, prior to starting the EBRT, patient developed a single episode of significant hemoptysis (around 2 weeks from initial presentation) for which he was admitted to the hospital. Repeat CXR showed stable changes from previous CXR done at the time of admission. A decision was made to administer palliative EBRT to chest targeting the tumor, including the blastic lesions on the spine (T6-T8). Soon after completion of EBRT patient was started on erlotinib 150 nmg PO once daily. Three weeks after starting erlotinib, the patient presented to the emergency room (ER) with weakness, fatigue and diarrhea (3-4 watery stools per day) for 3 days. The patient was also reporting cough associated with occasional white phlegm over last 3-4 days. Vital signs on admission were significant for tachycardia to a rate of 107/min and a temperature of 100.4°C. The laboratory results, at the time of admission, are shown in Table 1. A CXR done in the ER (Figure 2A) showed improvement in the lung mass and interstitial opacities seen on previous study, however it also

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Key words: Non small cell lung cancer; Tyrosine kinase inhibitors; Interstitial pneumonitis.

Contributions: AM and NA wrote the manuscript. CC edited the manuscript and provided critique. TL edited the manuscript and provided critique.

Conflict of interest: the authors declare no potential conflict of interest.

Received for publication: 13 January 2016.
Revision received: 16 April 2016.
Accepted for publication: 13 May 2016.

Rare Tumors 2016; 8:6410
doi:10.4081/rt.2016.6410

reported a lingular infiltrate, which was new from the comparison study. The patient was diagnosed provisionally with health care associated pneumonia and was started on vancomycin and levofloxacin. The stool sample was tested for toxigenic *Clostridium difficile* using polymerase chain reaction based assay, which returned back negative. Vancomycin was stopped 24 hours after admission due to absence of any growth in the blood culture and resolution of fever. Two days after admission, the patient reported worsening of shortness of breath and was noted to have increased oxygen requirement. His vital signs at this point were significant for the heart rate of 108 beats/min, respiratory rate of 32/min and the oxygen saturation of 87% on 5 L of oxygen via nasal cannula. Patient was shifted to medical intensive care unit (MICU) for this acute onset respiratory distress. A portable CXR, done at this point, showed progression of diffuse bilateral pulmonary opacities since admission (Figure 2B). The patient was started on broad-spectrum antibiotics (azithromycin, piperacillin-tazobactam and vancomycin). His labs at the time of admission to MICU are shown in Table 1. The patient was also started on non-invasive positive pressure ventilation but was unable to tolerate it. As part of his advance directives, the patient has signed a *Do-not resuscitate and Do-not intubate* form. He did not wish to change his CODE status at the time of admission to MICU. In tandem with his code status, he was not intubated and was given oxygen via a non-rebreather mask. Patient and his family opted for comfort care after discussion with palliative care team. The patient expired on 4th day of admission to the hospital.

Discussion and Conclusions

EGFR is a 170-kDa transmembrane glycoprotein consisting of extracellular ligand binding site, transmembrane hydrophobic region and intracellular tyrosine kinase domain.[1] It belongs to a family of receptor tyrosine kinase which includes EGFR (ErbB-1), human epidermal growth factor receptor (HER) 2/c-neu (ErbB-2), Her-3 (ErbB-3) and Her-4 (ErbB-4).[6] Though EGFR mutant tumors were first discovered in 2004, anti-EGFR therapies were being developed since early 1990's against wild type EGFR, which was known to be overexpressed in many epithelial cancers.[7] Gefitinib and erlotinib are the 2 most widely used receptor TKIs' which selectively inhibit the EGFR tyrosine kinase domain.[8] In May of 2013, erlotinib was approved by Food and Drug administration as first line treatment of patients with metastatic NSCLC whose tumors had EGFR exon 19 deletions or exon 21 (L858R) substitution mutations.[2] Skin rash is one of the most common AE's noted in the clinical trials, where its' appearance has been associated with better overall survival.[9] Since the first report of gefitinib associated ILD from Japan, ILD has become a focus of considerable attention.[10] ILD is a very rare complication associated with EGFR-TKI's with said incidence of 0.2 to 1.1% in patients treated with erlotinib and 0.38 to 2% in patients treated with gefitinib.[11] Furthermore, significant difference occurs amongst ethnic groups. Where, the incidence

Table 1. Labs at the time of admission and on medical intensive care unit (MICU) admission.

	Hospital admission (day 1)	MICU admission (day 3)
Bone morphogenetic protein		
Sodium (mEq/L)	128	129
Potassium (mEq/L)	3.7	4.4
Chloride (mEq/L)	102	104
Bicarbonate (mEq/L)	19	17
Blood urea nitrogen (mg/dL)	10	13
Creatinine (mg/dL)	0.8	1.0
Glomerular filtration rate	95	73
Calcium (mg/dL)	6.6	6.3
Phosphorus (mg/dL)	1.5	-
Magnesium (mg/dL)	2.3	2.0
Complete blood count		
Hemoglobin (g/dL)	8.6	7.9
Hematocrit (%)	24.7	23.5
Platelet (k/uL)	227	223
Total leucocyte count (k/uL)	4.1	3.2
Absolute neutrophil count (k/uL)	3.9	3.0
Liver function tests		
Total protein (g/dL)	5	-
Albumin (g/dL)	2.5	-
Total bilirubin (mg/dL)	1.5	-
Direct bilirubin (mg/dL)	0.4	-
Alkaline phosphatase (U/L)	54	-
Gamma glutamyl transferase (U/L)	23	-
Alanine transaminase (U/L)	15	-
Aspartate transaminase (U/L)	23	-
Lactate dehydrogenase (U/L)	227	-
Blood gas (venous)		
pH	7.441	-
pCO2 (mmHg/L)	35.9	-
Bicarbonate (mmHg/L)	24	-
Blood gas (arterial)		
pH	-	7.409
pCO2 (mmHg/L)	-	28
Bicarbonate (mmHg/L)	-	17.7

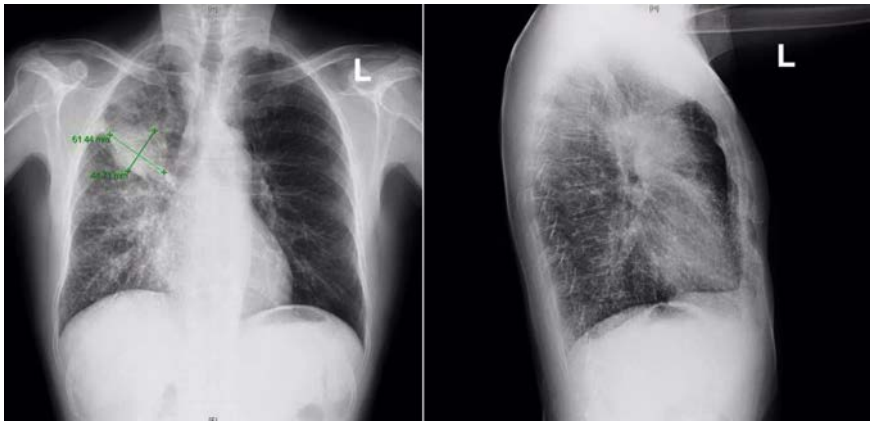

Figure 1. Initial chest X-ray (AP/Lat) showing right upper lobe lung mass diagnosed as non-small cell carcinoma of the lung.

of EGFR-TKI associated ILD was not only higher in Japanese patients (1.7%) *versus* their American counterparts (0.3%), the median time to onset of the ILD was also less in the Japanese patients (24 *vs.* 42 days).[12] Male gender, smoking history and previous evidence of lung fibrosis have been somewhat predictive of risk of developing ILD in patients treated with EGFR-TKI.[13]

The role of EGFR signaling in the development of fibrotic lung or interstitial lung disease is very debatable. EGFR and its' ligands, particularly EGF and transforming growth factor-α (TGF-α), are highly expressed on bronchial epithelial cells, smooth muscle cells and fibroblasts and play a central role in functioning of these cells under both normal and fibrotic conditions.[14,15] Several researchers have attempted to explain the role of EGFR and its' ligands by studying the murine models of bleomycin induced pulmonary fibrosis (BIPF). Studies on mouse models have shown that gefitinib augments interstitial pneumonitis and increases the severity of the BIPF, a finding, which is in tandem with the observations made in humans.[16,17] On the contrary, mouse models with either constitutive or conditional expression of TGF-α in lung epithelial cells were shown to develop fibrosis and TGF-α knockout mice had significantly reduced fibrosis.[18] Furthermore in another model of bitransgenic mice with constitutional expression of TGF-α but genetically disrupted EGFR did not develop pulmonary fibrosis.[19] Some studies have also shown that gefitinib has a protective effect against BIPF and even reduces the overexpression of TGF-α in BIPF mice.[20,21] At this point, though we have clear evidence of the involvement of EGFR and TGF-α in development of ILD at genetic level, the exact role of the receptor stays unclear.

Though our current understanding of the role of EGFR in pathogenesis of ILD remains anecdotal, the association of ILD with EGFR-TKI has been proven beyond doubt. Shi and colleagues in their systematic review of clinical trials, including 15,618 patients have show that relative risk of developing all grades of ILD and fatal interstitial pneumonitis is significantly higher in patients who are treated with EGFR-TKI's upfront.[22] The management of acute phase of erlotinib-induced ILD begins with being aware of this rare but crippling and sometimes even fatal complication of EGFR-TKI therapy. Unfortunately, due to rarity of the presentation, no randomized controlled trials have been possible.[4] Immediate discontinuation of the EGFR-TKI, supplemental oxygen, empirical antibiotics (to cover for superimposing infections) and supportive ventilation (invasive or non-invasive) should be provided upfront.[4] Infection, which is a common cause of respiratory failure in lung cancer patients, must be ruled out with appropriate cultures and serological tests.[4,12] Systemic corticosteroids have been tried in patients with acute phase of erlotinib induced-ILD in the past with mixed results.[4,11] Pre-existing pulmonary fibrosis has been listed as a risk factor for development of ILD in patients treated with EGFR-TKI.[4,13,23] High resolution CT scan, performed to detect pre-existing pulmonary fibrosis, may serve as a good screening tool in the future, which has shown to be diagnostic in up to 50-60% patients when performed in the correct clinical context.[24]

In conclusion, EGFR-TKI induced pulmonary toxicity is a challenging and often fatal complication of treatment of patients with EGFR positive NSCLC. Review of literature shows that maintaining a high index of suspicion and detecting subtle signs of pulmonary toxicity may prove beneficial in stopping this fatal process in its tracks. Early discontinuation of the EGFR-TKI and initiation of corticosteroids remains the main modality of treatment. This report serves as an important reminder to the treating oncologist regarding the potential complication of erlotinib therapy, which if not treated, may prove to be fatal in a very short time. This report also raises the pertinent question of screening and/or monitoring NSCLC patients for ILD when considering EGFR-TKI drug for therapy. More research is required in an attempt to develop a risk stratification for patients who are candidates for EGFR-TKI therapy.

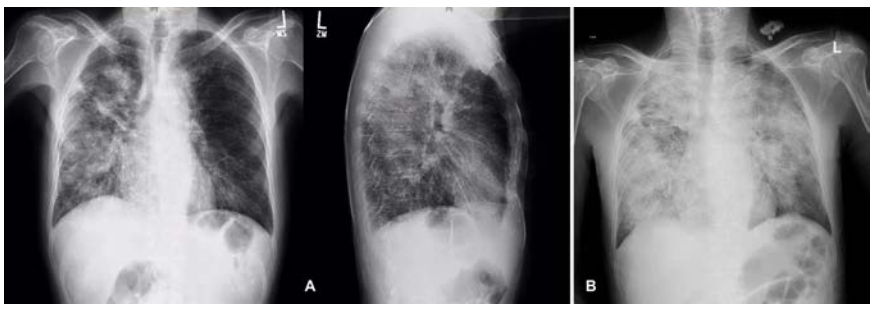

Figure 2. A) Chest X-ray (AP/Lat) at the time of admission (day 1); B) chest X-ray (portable film) showing extensive infiltrates bilaterally (day 3).

References

1. Gridelli C, Bareschino MA, Schettino C, et al. Erlotinib in non-small cell lung cancer treatment: current status and future development. Oncologist 2007;12:840-9.
2. Khozin S, Blumenthal GM, Jiang X, et al. U.S. Food and Drug Administration approval summary: erlotinib for the first-line treatment of metastatic non-small cell lung cancer with epidermal growth factor receptor exon 19 deletions or exon 21 (L858R) substitution mutations. Oncologist 2014;19:774-9.
3. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med 2005;353:123-32.
4. Min JH, Lee HY, Lim H, et al. Drug-induced interstitial lung disease in tyrosine kinase inhibitor therapy for non-small lung cancer: a review on current insight. Cancer Chemother Pharmacol 2011;68:1099-109.
5. Li C, Wei R, Jones-Hall YL, et al. Epidermal growth factor receptor (EGFR) pathway genes and interstitial lung disease: an association study. Sci Rep 2014;4:4893.
6. King TE Jr, Pardo A, Selman M. Idiopathic pulmonary fibrosis. Lancet 2011;378:1949-61.
7. Pao W, Chmielecki J. Rational, biologically based treatment of EGFR-mutant non-small-cell lung cancer. Nat Rev Cancer 2010;10:760-74.
8. Sakao S, Tatsumi K. Molecular mechanisms of lung-specific toxicity induced by epidermal growth factor receptor tyrosine kinaseinhibitors. Oncol Lett 2012;4:865-7.
9. Fiala O, Pesek M, Finek J, et al. Skin rash as useful marker of erlotinib efficacy in NSCLC and its impact on clinical practice. Neoplasma 2013;60:26-32.
10. Inoue A, Saijo Y, Maemondo M, et al. Severe acute interstitial pneumonia and gefitinib. Lancet 2003;361:137-9.
11. Peerzada MM, Spiro TP, Daw HA. Pulmonary toxicities of tyrosine kinase inhibitors. Clin Adv Hematol Oncol 2011;9:824-36.
12. Yoneda KY, Shelton DK, Beckett LA, Gandara DR. Independent review of interstitial lung disease associated with death in TRIBUTE (paclitaxel and carboplatin with or without concurrent erlotinib) in advanced non-small cell lung cancer. J Thorac Oncol 2007;2:537-43.

13. Ando M, Okamoto I, Yamamoto N, et al. Predictive factors for interstitial lung disease, antitumor response, and survival in non small cell lung cancer patients treated with gefitinib. J Clin Oncol 2006;24:2549-56.
14. Baughman RP, Lower EE, Miller MA, et al. Overexpression of transforming growth factor alpha and epidermal growth factor receptor in idiopathic pulmonary fibrosis. Sarcoidosis Vasc Diffuse Lung Dis 1999;16:57-61.
15. Hetzel M, Bachem M, Anders D, et al. Different effects of growth factors on proliferation and matrix production of normal and fibrotic human lung fibroblasts. Lung 2005;183:225-37.
16. Miyake K, Tani K, Kakiuchi S, et al. Epidermal growth factor receptor-tyrosine kinase inhibitor (gefitinib) augments pneumonitis, but attenuates lung fibrosis in response to radiation injury in rats. J Med Invest 2012;59:174-85.
17. Suzuki H, Aoshiba K, Yokohori N, Nagai A. Epidermal growth factor receptor tyrosine kinase inhibition augments a murine model of pulmonary fibrosis. Cancer Res 2003;63:5054-9.
18. Madtes DK, Elston AL, Hackman RC, et al. Transforming growth factor-alpha deficiency reduces pulmonary fibrosis in transgenic mice. Am J Respir Cell Mol Biol 1999;20:924-34.
19. Le Cras TD, Hardie WD, Fagan K, et al. Disrupted pulmonary vascular development and pulmonary hypertension in transgenic mice overexpressing transforming growth factor-alpha. Am J Physiol Lung Cell Mol Physiol 2003;285:L1046-54.
20. Wang P, Tian Q, Liang ZX, et al. Gefitinib attenuates murine pulmonary fibrosis induced by bleomycin. Chin Med J (Engl) 2010;123:2259-64.
21. Hardie WD, Davidson C, Ikegami M, et al. EGF receptor tyrosine kinase inhibitors diminish transforming growth factor-alpha-induced pulmonary fibrosis. Am J Physiol Lung Cell Mol Physiol 2008;294:L1217-25.
22. Shi L, Tang J, Tong L, Liu Z. Risk of interstitial lung disease with gefitinib and erlotinib in advanced non-small cell lung cancer: a systematic review and meta-analysis of clinical trials. Lung Cancer 2014;83:231-9.
23. Muller N, Fraser R, Lee K, Johkoh T. Diseases of the lung: radiologic and pathologic correlations. Philadelphia: Lippincott Williams & Wilkins; 2003.
24. Gotway MB, Freemer MM, King TE Jr. Challenges in pulmonary fibrosis. 1: use of high resolution CT scanning of the lung for the evaluation of patients with idiopathic interstitial pneumonias. Thorax 2007;62:546-53.