AZD9291-induced Acute Interstitial Lung Disease

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To the Editor: A 32-year-old Chinese male patient with 1 week cough and dyspnea on exertion was presented to hospital. He was a metastatic lung adenocarcinoma patient with 3 years treatment history. In October 2012, the patient complained cough, short of breath, and thoracic computerized axial tomography scan (CAT-scan) revealed left lung hilum mass with the right lung multismall patches or opacities. Core needle biopsy on supraclavicular lymph nodes was performed and diagnosis of Stage IV (T3N3M1a) lung adenocarcinoma was made by radiologist, pathologist, and oncologist. Chemotherapy with cisplatin and pemetrexed was initiated and a partial response (PR) was reached. After 6 cycles of double-bullet chemotherapy, maintenance therapy with pemetrexed was used. In January 2014, positron emission tomography-computed tomography scan showed the right lung disease progression and bone metastasis. Fine needle aspiration (FNA) was performed on right lung node and genetic sequencing study showed epidermal growth factor receptor (EGFR) 19 del erlotinib (Tarceva, Roche, Switzerland) was administrated orally and both lung lesions became shrunk and a good PR was achieved after 1 month of erlotinib treatment. This result maintained 9.5 months until patient's lung disease progression and liver metastasis which were confirmed by CAT-scan and FNA. The 3rd line treatment with docetaxel (Qilu Pharmaceutical Co., China) and bevacizumab (Avastin, Roche, Switzerland) was administered, PR was reached. Patient's symptoms got severe and CAT-scan showed disease progression on both lungs after 4 months of above treatment. FNA was performed on the right lung lesion and gene panels were tested, it showed EGFR T790M, 19 del, and TP53 mutation. AZD9291 (Tagrisso, Osimertinib, AstraZeneca, UK) was used at a dose of 80 mg oral daily. The patient performed well and CAT-scan showed PR at 1 month follow-up, and the lesions continued remission on the last follow-up at 5.5 months therapy. The patient complained light cough and short of breath on exertion at 4.5 months of AZD9291 therapy. Physical examination was unremarkable; there were no rales or wheezes on chest auscultation. Oxygen saturation was 98%, blood works results were all within normal range. CAT-scan revealed interstitial lung fibrosis change on both lungs and obvious ground-glass opacities on the right upper lung [Figure 1a]. After carefully reviewed patient's history and series CAT-scans, drug-induced acute interstitial lung disease (ILD) was confirmed by pathologist, radiologist, and oncologist.

Because AZD9291 was the 4th line therapy of this patient, stop taking it to avoid worsening ILD was quite dangerous for him.

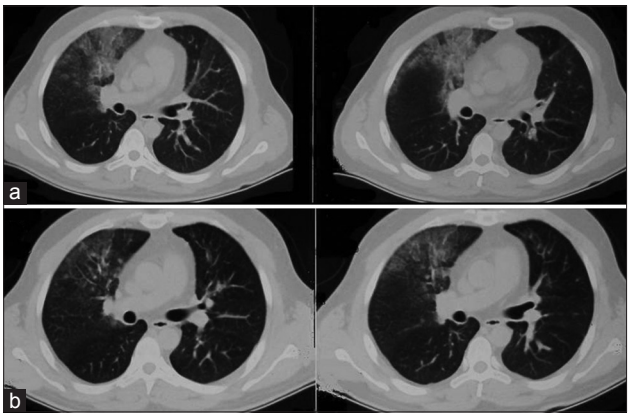

Figure 1: CAT-scan revealed interstitial lung fibrosis change on both lungs. (a) 4.5 months after AZD9291 treatment, right upper lung interstitial fibrosis. (b) One month after AZD9291 dose reduction and dexamethasone treatment.

The aggressive treatment plan was immediately initiated with dose reduction to 80 mg every other day, low-dose continued oxygen inhalation, and high-dose corticosteroid (10 mg dexamethasone infusion once a day for 10 days). Patient's symptoms got improved, ground-glass opacities on the right lung were remarkable attenuated, and both lung fields got clearer on CAT-scan at 1 month follow-up [Figure 1b].

AZD9291 is an oral, potent, irreversible 3rd generation EGFR tyrosine kinase inhibitor (TKI), inhibits kinase activity. *In vitro* and *in vivo* studies, it showed strong inhibition lung cancer cells with EGFR sensitizing mutation or with T790M resistance mutation, but less activity on wild-type compare to the 1st generation gefitinib or erlotinib.[1] In patients with relapsed or metastasized disease after 1st generation TKI, its overall response rate (ORR) was around 50%; and patients with EGFR T790M mutation positive or negative had a 60% ORR and PFS 9.6 months or 21% ORR and PFS 2.8, respectively.[2]

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ILD is a rare complication during EGFR-TKI therapy, about 1–3% patients will acquire it. The mechanism of TKI-induced ILD is not very clear, TKI interrupting type II pneumocytes and alveolar wall repair may play an important role.[3]

There is no standard guideline for the treatment of TKI-induced ILD; current management includes oxygen inhalation, drug discontinuation, and high-dose and prolongs corticosteroids or immunosuppressive. High-dose *N*-acetylcysteine alleviates pulmonary fibrosis in rats but needs further study in human.[4] The patient had been treated with multiline therapies, maintenance 3rd generation EGFR-TKI is the most reliable method to sustain patient's survival. We reduced 50% dosage of the drug administration according to the half-life and metabolic characters of it,[1] to maintain effective blood drug concentration and maximally reduce its side effects.

Drug-induced ILD is a severe and a fatal complication if not intervened promptly. This case showed that early diagnosis and early intervention of this complication is critical important during TKI treatment of advanced nonsmall cell lung cancer. AZD9291 dose reduction and aggressive corticosteroid treatment could be a promising treatment option for patient who required 3rd generation TKI to maintain disease remission. Clinical physicians must cautiously weigh the benefits and risks of targeted therapies causing ILD in order to provide optimal treatments and favorable outcomes.

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Conflicts of interest

There are no conflicts of interest.

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