

# Fatal interstitial lung disease associated with icotinib

Jiexia Zhang\*, Yangqing Zhan\*, Ming Ouyang, Yinyin Qin, Chengzhi Zhou, Rongchang Chen

Department of Respiratory Medicine, The First Affiliated Hospital of Guangzhou Medical University, State Key Laboratory of Respiratory Disease (Guangzhou Medical University, China), Guangzhou Institute of Respiratory disease, Guangzhou 510120, China

\*These authors contributed equally to this work.

Correspondence to: Rongchang Chen, MD, Professor, FCCP. No.151 Yanjiang Road, Guangzhou Ct, 510120 China. Email: chenrc@vip.163.com.

**Abstract:** The most serious, and maybe fatal, yet rare, adverse reaction of gefitinib and erlotinib is drug-associated interstitial lung disease (ILD), which has been often described. However, it has been less well described for icotinib, a similar orally small-molecule tyrosine kinase inhibitor (TKI). The case of a 25-year-old female patient with stage IV lung adenocarcinoma who developed fatal ILD is reported here. She denied chemotherapy, and received palliative treatment with icotinib (125 mg po, three times daily) on March 1, 2013. One month after treatment initiation, the patient complained of continuous dry cough and rapid progressive dyspnea. Forty one days after icotinib treatment, icotinib associated ILD was suspected when the patient became increasingly dyspnoeic despite of treatment of pericardial effusion, left pleural effusion and lower respiratory tract infection, and X-ray computed tomography (CT) of chest revealed multiple effusion shadows and ground-glass opacities in bilateral lungs. Then, icotinib was discontinued and intravenous corticosteroid was started (methylprednisolone 40 mg once daily, about 1 mg per kilogram) respectively. Forty three days after icotinib treatment, the patient died of hypoxic respiratory failure. ILD should be considered as a rare, but often fatal side effect associated with icotinib treatment.

**Keywords:** Icotinib; interstitial lung disease (ILD); lung cancer; pulmonary toxicity; epidermal growth factor receptor (EGFR); tyrosine kinase inhibitor (TKI)

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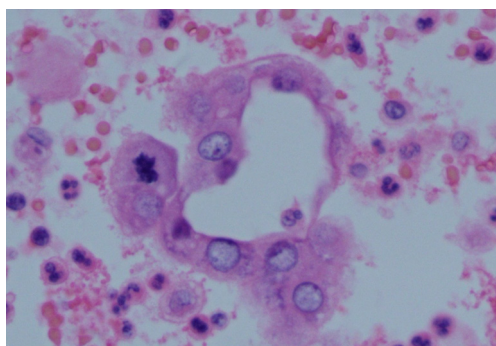
## Introduction

In June 2011, icotinib (Conmana<sup>®</sup>, Zhejiang Beta pharmaceutical Co., Ltd., Hangzhou, China), a new Chinese made, orally active, small-molecule tyrosine kinase inhibitor (TKI) targeting the epidermal growth factor receptor (EGFR), was approved by China Food and Drug Administration (CFDA) and added to the treatment of non small cell lung cancer (NSCLC) in China. Similar to gefitinib and erlotinib, icotinib is an effective drug in recommended dose (125 mg, 3 times daily). However, its recommended dose is far from its tolerated dose. It shows potential superiority to erlotinib in a case report, in which a patient with lung adenocarcinoma after erlotinib failure responded to high dose icotinib (1). Additionally, it is a relatively safer drug compared with erlotinib (2). The most common adverse effects associated with icotinib are rash and diarrhea (3-8).

The most serious, and maybe fatal, yet rare, adverse reaction of gefitinib and erlotinib is drug-associated interstitial lung disease (ILD), which has been often described (9-11). However, it has only been few documented in the clinical trials of icotinib. We present a fatal case of icotinib-associated ILD in a patient with lung adenocarcinoma and discuss it in the context of icotinib-associated ILD.

## Case report

A 25-year-old female Chinese was diagnosed with stage IV lung adenocarcinoma with lymphangitis carcinomatosa and hydropericardium. Icotinib treatment was initiated once diagnosis of lung adenocarcinoma was made. Forty three days later, the patient died of hypoxic respiratory failure. Written consent was obtained from the patient's parents for publication of this case report and any accompanying images.



**Figure 1** Pathological images of pericardial fluid sediment, showing heterogenic gland (Hematoxylin-eosin, original  $\times 400$ ).

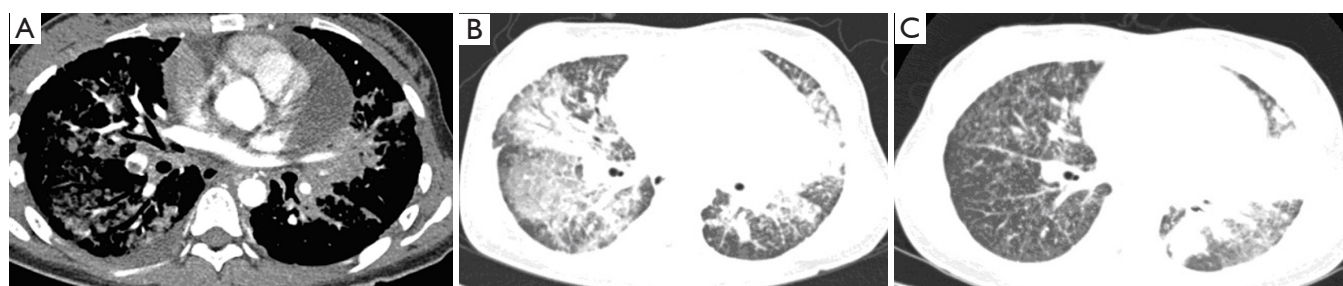
The patient was healthy before the onset of illness. She had no history of smoking. She was admitted to other hospital for a complaint of dry cough and dyspnea. X-ray computed tomography (CT) of chest revealed multiple thickened bronchial wall and bronchiectasia in segment bronchus of left lung, mass shadows in apicoposterior segment and left posterior basal segment and diffuse nodular shadows in both lungs, with evidence for enlarged mediastinal, bilateral hilar and axillary lymph nodes (images were discarded by her parents after the patient was dead and were not available). There was irregular thickening of interlobular septal in bilateral lungs too. Diagnosis of stage IV lung adenocarcinoma with lymphangitis carcinomatosa was made when tranbronchial lung biopsy revealed adenocarcinoma. EGFR mutation in biopsy of lung tissue was tested negative by sequencing polymerase chain reaction. However, she had a poor World Health Organization (WHO) performance status (score 3). Chemotherapy was not reasonable and palliative treatment with icotinib (125 mg po, 3 times daily) was initiated. Ten days after treatment initiation, the patient developed a rash, a common adverse reaction of icotinib. Follow-up radiographs in our hospital 3 weeks after treatment initiation showed stable disease (SD) with no enlargement in the size of mass shadows and no increase in the number of nodular shadows.

One month after icotinib treatment, while still on icotinib therapy, the patient was admitted to our hospital with continuous dry cough and rapid progressive dyspnea, denying lying down. Chest pain and haemoptysis was denied. Physical examination revealed decreased breath sounds in left lower lobe, some inspiratory crackles in right lower lobe and distant heart sounds. Oxygen saturation was 85% in room air and supplemental oxygen was given

via nasal cannula. Leukocyte count was elevated with  $15.92 \times 10^9$  cells/L. Blood cultures and sputum analysis initially was tested negative. Precursor of B-type natriuretic peptide was normal. Arterial blood gas analysis indicated presence of hypoxemic respiratory failure. Hence, pericardial effusion, left pleural effusion and lower respiratory tract infection was suspected. Ultrasound revealed massive pericardial effusion and left pleural effusion. Percutaneous pericardial drainage and chest catheter closed drainage was conducted. Pathological examination of pericardial fluid sediment revealed metastatic adenocarcinoma from lung (*Figure 1*). Intracavitary chemotherapy with etoposide (0.3 g) and cisplatin (100 mg) was administrated in the treatment of pericardial effusions. Antimicrobial therapy was pragmatically initiated with intravenous levofloxacin (500 mg once daily). Other medications included furosemide 20 mg, asmeton 2 tablets and selenious yeast tablets 100  $\mu$ g (3 times daily).

However, clinical symptoms (including cough, dyspnea) and oxygen saturation was only partially improved and accompanied by fever 5 days after hospital admission. D-dimers were elevated with 5,467 ng/mL. Leukocyte count recovered to normal with  $8.53 \times 10^9$  cells/L and procalcitonin was elevated with 0.81 ng/mL 1 week after admission. Multi-layer spiral CT angiography of pulmonary artery confirmed suspicion of pulmonary artery embolism (*Figure 2A*). Multiple effusion shadows and ground-glass opacities were also found in bilateral lungs (*Figure 2B*). Hence, nadroparin (3,075 anti-Xa units twice daily) was initiated and warfarin was added later. Antibiotic was empirically changed to piperacillin-sulbactam (2,000/1,000 mg three times daily), and changed to meropenem (500 mg 3 times daily) together with intravenous voriconazole (200 mg twice daily) later.

Forty days after icotinib treatment, ILD was suspected when the patient still became increasingly dyspnoeic, despite of treatment of pericardial effusion, left pleural effusion and lower respiratory tract infection. The onset of continuous cough and dyspnea and characteristic newly emerged diffuse ground-glass opacities in bilateral lobe both supported the diagnosis of ILD (*Figure 2B,C*). The case scored 5 by using the Naranjo scale (12). Hence, it is probable that ILD was associated to icotinib. Icotinib was discontinued and intravenous corticosteroid was started (methylprednisolone 40 mg once daily, about 1 mg per kilogram) respectively. The condition of patient went worse even under the above medication. Forty-three days later, the patient died of hypoxic respiratory failure. Autopsy was not performed due to lack of permission from her parents.



**Figure 2** Newly emerged diffuse ground-glass opacities in bilateral lungs and pulmonary embolism after the onset of continuous cough and dyspnea. (A) Image of CT angiography of pulmonary artery 5 weeks after initiation of icotinib, showing pulmonary embolism in basal stem right lower lobe pulmonary artery. CT, computed tomography; (B) CT image of chest five weeks after initiation of icotinib, showing newly emerged diffuse ground-glass opacities in bilateral lungs; (C) CT image of chest three weeks after initiation of icotinib, showing mass shadow and obstructive pneumonia in left lower lobe, diffuse nodular shadows and irregular thickening of interlobular septal in bilateral lungs.

**Table 1** Summary of ILD characteristics in clinical trails

Case number	Sex	Age	Stage	Dose	Onset of ILD	ILD symptoms	CT findings	Disease progression	Treatment	ILD outcome (time after onset)	Reference
1	NR	NR	NR, NSCLC	150 mg bid	9 days	Dyspnea	Pneumonitis	Yes	ID	Fatal [31]	(2)
2	NR	NR	NR, NSCLC	200 mg bid	7 days	Dyspnea	NR	Yes	ID, CS	Fatal [30]	(2)
3	Male	49	IV, Lung Adenocarcinoma	125 mg tid	4 months	Deteriorated cough, dyspnea	Ground-grass opacities and interstitial fibrosis in bilateral lungs	NR	ID, CS	Cure	(6)

ILD, interstitial lung disease; NR, not reported; ID, icotinib discontinuation; CS, corticosteroids.

A PubMed and Google Scholar search was conducted using the keywords “pulmonary toxicity”, “ILD”, “icotinib” and “conmana®”. Similar Search was also conducted in a Chinese data-Wangfang Data. Relevant case reports and case-series were included and references of retrieved publications were screened for relevant literature. Until now, except for our case, a total of three cases of icotinib-associated ILD were reported in the clinical trial (*Table 1*). Two cases of ILD occurred within one month of icotinib treatment. Pathological examination showed that two cases of icotinib-associated ILD in phase I study of icotinib were accompanied with disease progression (4). One was considered disease-related and the other was considered both drug-related and disease-related. The third case appeared in phase IV study and diagnose of ILD was made based on ground-grass opacities and pulmonary fibrosis in CT scan, without evidence of biopsy (8). Other initial studies of icotinib leading to its approval and retrospective

studies did not report pulmonary toxicity (3,6,7,13-15). There was no case report.

## Discussion

The present case showed that icotinib may be associated with fatal ILD. To our knowledge, this is the first case report of fatal ILD associated with icotinib. Similar to other orally small molecule EGFR-TKIs, such as gefitinib and erlotinib, icotinib can cause or contribute significantly to the pulmonary toxicity, and thus this drug also must be considered among the EGFR-TKIs drugs which can cause fatal ILD. Respiratory symptoms should be carefully monitored for the first month period of icotinib treatment.

Severe ILD, including fatalities had been reported in clinical studies and case series with other EGFR-TKIs (16-18). For gefitinib-treated patients, FDA reported that incidence of ILD was 1% worldwide, of which more than

30% were fatal (10). The incidence of ILD varied with countries. It was higher in Japan (2%) than in the United States (0.3%) (19). In the FDA approval report, overall incidence of ILD in erlotinib-treated patients was about 0.8%, which was similar to patients in the placebo group (11). Overall incidence of ILD in icotinib treated patients was still unknown. However, results of another phase IV study in which more than 10,000 patients were enrolled are round the corner.

Thus far, no risk factors for the development of icotinib-associated ILD have been described. However, several risk factors were considered to be related to gefitinib-associated ILD, including older age, poor World Health Organization (WHO) performance status ( $\geq 2$ ), smoking, recent NSCLC diagnosis, reduced normal lung on CT scan, preexisting chronic ILD, concurrent cardiac disease and Japanese ethnicity (20). The higher incidence of ILD in Japanese patients was considered to be contributed to the larger percentage of patients with EGFR mutations and clinical responses to gefitinib (21). Other studies have suggested recent radiation therapy and chemotherapy as risk factors for ILD (22). Most of ILD occur within 3–7 weeks after initiation of gefitinib and one third of cases are fatal. Risk factors of erlotinib-associated ILD were similar to gefitinib, with a median of 47 days after initiation therapy (11,17,23). Several of these risk factors were present in our case, including recent NSCLC diagnosis (1 month), poor WHO performance status, reduced normal lung on CT scan (diffuse nodular shadows in bilateral lungs, left pleural effusion, multiple pulmonary artery embolisms) and concurrent cardiac disease (massive pericardial effusion). Including our cases, disease progression was confirmed by pathological examination in three out of four cases of icotinib-associated ILD and it maybe consider as one of the risk factors of icotinib-associated ILD. Overall, three out of four cases of ILD occurred within one month of initiation of icotinib. Two cases of ILD reported in clinical trials of icotinib were treated with chemotherapy before initiation of icotinib. Whether risk factors of icotinib-associated ILD have its uniqueness or are similar to gefitinib and erlotinib, it remains to be investigated.

However, the mechanism for developing icotinib-associated ILD is still unknown. Phase I study of icotinib demonstrated that there was no obvious relationship between advert effects/severe advert effects and dose (3,4,24). Pharmacology and clinical evaluation revealed that the therapeutic window for icotinib-defined as the tolerable and effective dose range was 100–625 mg three times per day (24).

Dose of icotinib in all of four cases of icotinib-associated ILD ranged 300–400 mg per day, which was lower than highest tolerable and effective dose. Hence, icotinib-associated ILD may seem unlikely to be dose dependent. Considering the similarities of EGFR-TKIs in chemical structure and pharmacological effects, it is likely that the mechanism for development of icotinib-associated ILD is comparable with gefitinib and erlotinib. However, whether icotinib can induce pulmonary toxicity by a mechanism related to its unique properties or similar to other EGFR-TKIs (gefitinib and erlotinib), it remains to be studied.

It is worth to note that, three out of four cases of icotinib-associated ILD were fatal. Fatality of ILD induced by icotinib was higher than that of gefitinib and erlotinib, although all three fatal cases were accompanied by disease progression. In view of poor information concerning risk factors and mechanism of icotinib-associated ILD, prevention and treatment of icotinib-associated ILD should borrow from gefitinib and erlotinib associated ILD. Medical history, including respiratory symptoms, signs, chemotherapy or radiation, etc., should be well reviewed prior to the prescription of medication. Icotinib-associated ILD should be highly suspected once respiratory symptoms (especially dry cough and dyspnea) worsen. Discontinuation of medication, initiation of high dose corticosteroids and supportive therapy with oxygen therapy or mechanical ventilation was reported in case series as the only useful interventions in the treatment of gefitinib and erlotinib associated ILD (9,25,26).

Limitation of our report was that cytomegalovirus CMV infection and pneumocystis jiroveci pneumonia could not be ruled out. Serological test for CMV infection was not performed. Because the condition of the patient was going bad rapidly, bronchoscopy could not be performed and sputum from deep position or bronchoalveolar lavage was not available for bacterial and fungal culture or detection of CMV and *pneumocystis jiroveci*. Additionally, biopsy of lung also could not be done to confirm pathology of ILD.

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Authors Z.YQ and Z. JX participated in the PubMed and Google Scholar search for cases of icotinib associated ILD.



All authors participated in the discussion of the data and contributed to the drafting of the manuscript.

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