

Fatal Interstitial Lung Disease after Addition of Sorafenib to a Patient with Lung Adenocarcinoma Who Had Failed to Improve with Erlotinib Alone

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Key Words

Erlotinib · Interstitial lung disease · Non-small cell lung cancer · Sorafenib

Abstract

Interstitial lung disease (ILD) induced by epidermal growth factor receptor tyrosine kinase inhibitors has been extensively documented with decreasing incidence after appropriate patient selection due to increasing awareness over the years. However, ILD induced by sorafenib was mentioned with lower frequency only in patients with hepatocellular and renal cell carcinoma living in Japan but not in patients with other carcinomas or living outside Japan, and it has been overlooked in clinical practice. In the present case, sorafenib was added to the treatment of a 60-year-old non-smoking patient with non-small cell lung cancer (NSCLC). After his failing to improve with erlotinib alone, erlotinib was continued to be given in combination with sorafenib as a salvage therapy. Although clinical signs of ILD were observed 2 weeks after the addition of sorafenib, the radiological diagnosis of ILD was only made 41 days after the initiation of the combination treatment, and the patient died 56 days after treatment onset. It was concluded that ILD was indeed induced by sorafenib. This is the first report of ILD induced by sorafenib in a patient with NSCLC living outside Japan. Oncologists should be aware of this fatal complication for its early detection in order to avoid a severe course of ILD leading to a decrease in the ILD mortality rate.

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Sorafenib, a multikinase inhibitor approved for the treatment of advanced renal cell carcinoma and unresectable hepatocellular carcinoma, also shows antitumor activity in non-small cell lung cancer (NSCLC). The combination of sorafenib and erlotinib may improve overall survival and is one of the treatment options for previously treated patients with NSCLC, especially those with wild-type epidermal growth factor receptor (EGFR) mutation. Adverse events (AEs) of this combination treatment including fatigue, hand-foot skin reaction, rash, diarrhea, oral mucositis, anorexia and even fatal pulmonary hemorrhage have been reported [1–3].

Interstitial lung disease (ILD), a serious and sometimes fatal AE, induced by EGFR tyrosine kinase inhibitors (TKIs), has been extensively documented with decreasing incidence after appropriate patient selection due to increasing awareness over the years [4, 5]. However, sorafenib-induced ILD was mentioned with a lower frequency only in patients with hepatocellular and renal cell carcinoma living in Japan but not in patients with other carcinomas or living outside Japan and it has been overlooked in clinical practice [6]. Here, we describe the case of a fatal ILD that occurred after adding sorafenib to the treatment with erlotinib of a patient with lung adenocarcinoma.

Case Report

Erlotinib (150 mg, once daily) was given to a 60-year-old non-smoking man who was diagnosed with stage IV lung adenocarcinoma with unknown status of EGFR mutation after failing to respond to the first-line chemotherapy with pemetrexed 500 mg/m² and cisplatin 75 mg/m² (every 3 weeks for 4 cycles) in September 2009 (fig. 1a). His performance status (PS) score was 1. Partial remission was revealed by a chest computed tomography (CT) in October 2009 (fig. 1b) with limited grade II rash, and stable disease was confirmed by a follow-up chest CT until the progression of the disease shown in January 2010 with a PS score 1 (fig. 1c).

The patient denied any further chemotherapy. Therefore, sorafenib (400 mg twice daily) was added to his treatment with erlotinib as a salvage therapy after a complete informed consent had been obtained on January 29, 2010. Gradual aggravation with symptoms of cough, dyspnea, fever and fatigue was observed 2 weeks after the initiation of the combination treatment; however, the patient insisted and came back to the hospital until March 9, 2010. A chest CT scan the 2nd day after his hospitalization revealed a great mass in the lower lobe of the right lung with atelectasis, obstructive pneumonia and multiple patchy ground-glass opacities in the left lung (fig. 1d). Arterial blood gas measurements at a cardiac output of 8 l/min revealed a pH of 7.50, PaCO₂ of 32 mm Hg, PaO₂ of 55 mm Hg, HCO₃ of 25 mmol/l and base excess of 3.4 mmol/l. A clinical and radiological diagnosis of ILD was made and the combination treatment was discontinued straightway. Although treatment with supplemental oxygen, methylprednisolone, antibiotics (Meropenem) and best supportive care was initiated immediately, the patient's condition deteriorated and he died on March 25, 2010.

Discussion

EGFR TKIs have significant antitumor activity in NSCLC patients with sensitive EGFR mutation. However, discontinuation of TKIs after disease progression may result in a disease flare-up [7]. Therefore, our patient continued to receive erlotinib after adding sorafenib. Unfortunately, he died 8 weeks after the initiation of the combination treatment due to a fatal ILD.

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ILD may be induced by the combined action of erlotinib and sorafenib. However, the pharmacokinetics of sorafenib may not be affected by the coadministration of erlotinib, while the clearance of erlotinib may be enhanced by concomitant sorafenib [2, 8]. Moreover, the median time to the onset of ILD induced by erlotinib is 47 days (range from 5 days to 9 months) [9], while the overall peak time to onset of sorafenib-induced ILD is 2–4 weeks [6]. So, we conclude that ILD occurred after the addition of sorafenib but not during the previous treatment course with erlotinib. To our knowledge, this is the first report on sorafenib-induced fatal ILD in a patient with NSCLC and living outside Japan.

There are no specific and effective treatments for ILD except for immediate discontinuation of the suspected drug and empirical corticosteroid treatment with early recognition of the disease. Without early awareness of ILD, the clinical signs of ILD are not observed until 7 weeks later, after a chest CT scan; however, this was too late in our case to improve the syndrome of ILD. The mortality rate of sorafenib-induced ILD is about 50% [6]. We should be aware of this high-mortality AE and seek its early detection in order to avoid a severe course of ILD leading to a decrease in the ILD mortality rate.

EGFR TKI-induced ILD has been documented extensively in Japan. Risk factors of developing EGFR TKI-induced ILD include male sex, smoking, a poor PS and the existence of pulmonary fibrosis [4, 5]. In our case, the patient had a good PS and no pulmonary fibrosis or smoking history, and grade II rash was the only AE during the period of erlotinib administration. Further investigation of the exact mechanism and the risk factors of developing sorafenib-induced ILD is warranted.

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Disclosure Statement

None declared.

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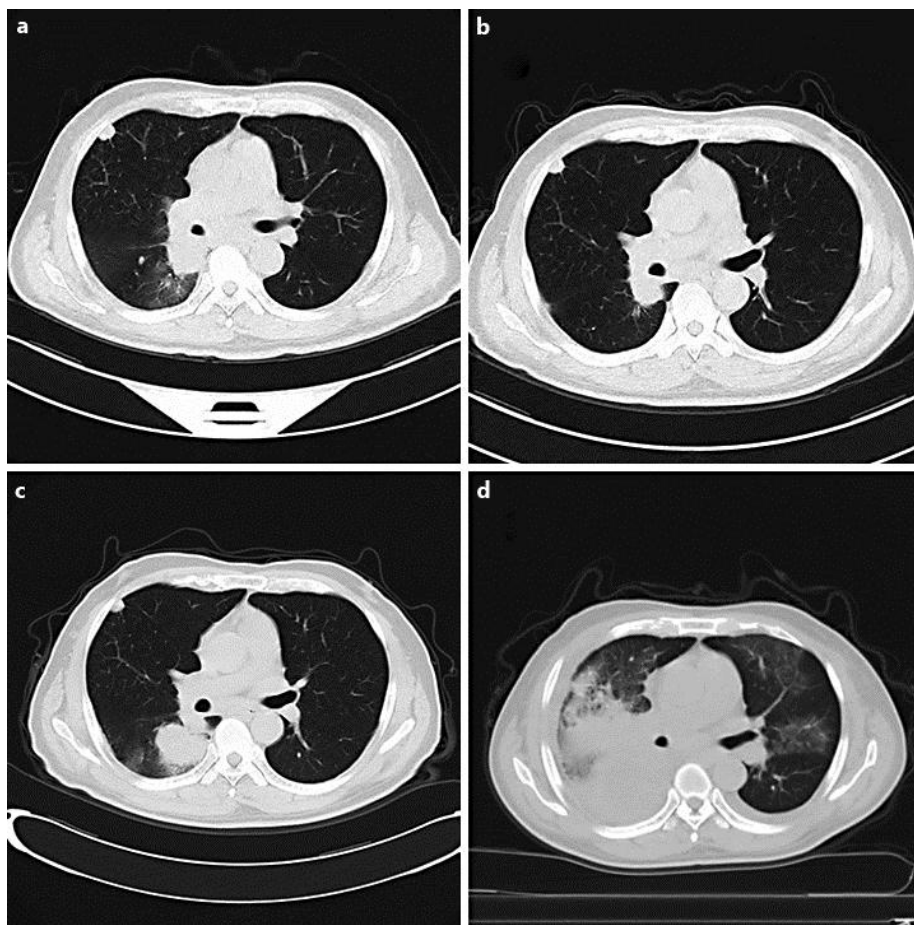


Fig. 1. Chest CT images before (a) and after (b) erlotinib treatment, and before (c) and after (d) the addition of sorafenib. **a** Lesions of the right lung before the initiation of erlotinib treatment. **b** Partial remission of lower lobe lesions of the right lung 1 month after the initiation of erlotinib treatment. **c** Relapse of lower lobe lesions of the right lung with pachy shadows 4 months after the initiation of erlotinib. **d** Great mass in the lower lobe of the right lung with atelectasis, obstructive pneumonia and multiple patchy ground-glass opacities in the left lung 41 days after the addition of sorafenib.