Pulmonary Toxicities of Tyrosine Kinase Inhibitors

Maajid Mumtaz Peerzada, MD, Timothy P. Spiro, MD, FACP, and Hamed A. Daw, MD

Dr. Peerzada is a Resident in the Department of Internal Medicine at Fairview Hospital in Cleveland, Ohio. Dr. Spiro and Dr. Daw are Staff Physicians at the Cleveland Clinic Foundation Cancer Center, in Cleveland, Ohio.

Address correspondence to:
Maajid Mumtaz Peerzada, MD
Medicor Associates of Chautauqua
Internal Medicine
12 Center Street
Fredonia, NY 14063
Phone: 716-679-2233
E-mail: maajidpeerzada@yahoo.com

Keywords
Pulmonary toxicities, tyrosine kinase inhibitors, interstitial lung disease, imatinib, erlotinib, gefitinib

Abstract: The incidence of pulmonary toxicities with the use of tyrosine kinase inhibitors (TKIs) is not very high; however, various case reports and studies continue to show significant variability in the incidence of these adverse events, ranging from 0.2% to 10.9%. Gefitinib and erlotinib are orally active, small-molecule inhibitors of the epidermal growth factor receptor tyrosine kinase that are mainly used to treat non-small cell lung cancer. Imatinib is an inhibitor of BCR-ABL tyrosine kinase that is used to treat various leukemias, gastrointestinal stromal tumors, and other cancers. In this article, we review data to identify the very rare but fatal pulmonary toxicities (mostly interstitial lung disease) caused by these drugs.

Introduction

Tyrosine kinases are enzymes that activate the phosphorylation of tyrosine residues by transferring the terminal phosphate of ATP. Some of the tyrosine kinase inhibitors (TKIs) currently used in the treatment of various malignancies include imatinib (Gleevec, Novartis), erlotinib (Tarceva, Genentech/OSI), and gefitinib (Iressa, AstraZeneca). This article presents a basic introduction (mechanism of action and indications of use) of these TKIs and summarizes the incidence, various clinical presentations, diagnosis, treatment options, and outcomes of patients around the world that presented with pulmonary toxicities caused by these drugs. Articles were searched on PubMed using the keywords pulmonary toxicities/lung toxicities/pulmonary side effects of imatinib/erlotinib/gefitinib.

Imatinib

Imatinib inhibits BCR-ABL tyrosine kinase, the constitutive abnormal gene product of the Philadelphia chromosome (Ph+) in chronic myeloid leukemia (CML). Inhibition of this enzyme blocks proliferation and induces apoptosis in BCR-ABL– positive cell lines as well as in fresh leukemic cells in Ph+ CML. It also inhibits tyrosine kinase for platelet-derived growth factor (PDGF), stem cell factor (SCF), c-Kit, and cellular events mediated by PDGF and SCF. The US Food and Drug Administration (FDA)-approved indications for imatinib are presented in Table 1. The following are case studies and clinical reports describing various presentations of pulmonary toxicities in patients treated with imatinib.

Table 1. FDA-Labeled Indications for Imatinib

- Acute lymphoid leukemia, relapsed/refractory Philadelphia chromosome-positive
- Chronic eosinophilic leukemia
- Chronic myeloid leukemia, Philadelphia chromosome-positive, accelerated phase or blast crisis
- Chronic phase chronic myeloid leukemia, Philadelphia chromosome-positive, after failure of interferon-alpha therapy
- Chronic phase chronic myeloid leukemia, Philadelphia chromosome-positive, newly diagnosed
- Chronic phase chronic myeloid leukemia, Philadelphia chromosome-positive, recurrence after stem cell transplant
- Dermatofibrosarcoma protuberans, unresectable, recurrent and/or metastatic
- Gastrointestinal stromal tumor
- Hypereosinophilic syndrome
- Myelodysplastic syndrome, with platelet-derived growth factor receptor (PDGFR) gene rearrangement
- Myeloproliferative disorder, chronic, with PDGFR gene rearrangement
- Systemic mast cell disease, aggressive

Case Studies Reporting Pulmonary Toxicities

In 1 report, a 58-year-old man developed fulminant interstitial pneumonitis and severe skin rash 3 days after the use of low-dose imatinib (100 mg/day).[1] His symptoms included fever, dry cough, dyspnea, and extremely pruriginous skin lesions on the upper extremity. A chest X-ray showed a bilateral interstitial reticular/nodular pattern throughout both lung fields. The lung biopsies demonstrated chronic interstitial pneumonitis and pulmonary hypertension, with mild interstitial fibrosis and lymphocytic infiltration with marked pulmonary vascular mural thickening.

The patient's condition rapidly evolved into acute respiratory failure, and he was intubated. He was receiving steroids with low-dose imatinib, which was discontinued at this time. The patient's condition improved after 3 days of treatment, and antibiotics were discontinued. He was extubated after 1 week. No steroids were given after he developed respiratory failure. The skin lesion regressed after his condition improved. A follow-up chest X-ray performed 3 weeks later showed improvement, with residual infiltrates in the right lower lobe of the lung. The follow up chest X-ray after 1 month was normal.

The skin biopsy revealed perivascular lymphocytic infiltration in the dermis and exocytosis in the epidermis due to lymphocytes. These findings strongly suggested the diagnosis of a drug reaction. The features of increased alveolar macrophages with lymphocyte infiltration and interstitial fibrosis found in the lung biopsy along with the presence of spongiloid dermatitis suggested an imatinib-induced toxicity in this patient, most likely via the immune mechanism.[2]

Hypersensitivity pneumonitis was reported in a patient who was being treated with imatinib (600 mg/day) for 1 year.[3] A chest X-ray showed ground-glass opacity (GGO) that was confirmed to be bilateral and diffuse by high-resolution lung computed tomography (CT) scan. The bronchial biopsies were negative on pathology.

Eleven days after discontinuing therapy, the lung CT scan had normalized. This patient also developed diffuse lichenoid dermatosis 9 months after the use of imatinib; treatment with steroids permitted the skin lesion to only partially regress. The skin lesion had greatly improved after imatinib was discontinued.

In a report, a 77-year-old woman received imatinib (400 mg/day) for CML.[4] Four weeks after imatinib therapy, she developed progressive dyspnea on exertion after 4 weeks. Her oxygen saturation was 85% on room air, and auscultation of her lungs revealed scattered rhonchi. A chest radiograph revealed bilateral patchy infiltrates, and blood culture showed no growth. The patient did not improve even 16 days after discontinuing imatinib, at which point the prednisone dose was increased from 6 mg/day to 30 mg/day (patient was already on a tapering dose of prednisone for her polymyalgia rheumatica even before imatinib was started). Over the next 4 days, the dyspnea began to improve. A chest radiograph done approximately 2 weeks later showed improvement in pulmonary infiltrates. There was gradual resolution of dyspnea and oxygen requirement over the next 2 months. The patient had a predominance of macrophages rather than lymphocytes, with a large number of eosinophils in the bronchoalveolar lavage fluid. This report widened the spectrum of pulmonary hypersensitivity that can be associated with imatinib therapy.

Interstitial pneumonitis (clinical diagnosis) was also observed in a patient with gastrointestinal stromal tumor (GIST) after 4 weeks of imatinib (400 mg/day).[5] The patient developed hypoxia, and bilateral ground-glass infiltrates were seen on a high-resolution lung CT scan.

Two weeks after the administration of steroids, the lung scan had normalized. In another case[6] a CML patient who received imatinib 400 mg/day developed interstitial pneumonitis (clinical diagnosis, no pathology done) with bilateral interstitial infiltrates on chest X-ray 1 month after treatment. No hypoxia was present. Steroids were given and

the abnormalities improved, but they were not completely resolved after 1 year. In another report,[7] non-specific interstitial pneumonitis (transbronchial biopsy done) developed in a patient 2 months after imatinib therapy (400 mg/day). Hypoxia was present, and after the discontinuation of imatinib and use of steroids, the patient's condition improved, but GGO remained 2 months later.

In another report,[8] the result of re-administration of imatinib for long-term use was noted. In this case, a 70-year-old man with metastatic GIST was treated with imatininb. After 3 months, he developed dyspnea on exertion. His chest radiography and CT scan revealed diffuse interstitial changes with peribronchovascular bundle pattern. Imatinib-induced pneumonitis was suspected.

After discontinuation of imatinib, the pulmonary events were nearly improved. However, imatinib was re-administered because the GIST worsened. This time, imatinib was interrupted transiently while the GIST showed a marked regression; however, it was restarted, as the tumor grew larger. Four years later, the patient died of progression of GIST without fatal pneumonitis. His chest radiography and CT scan revealed more progress in peribronchovascular interstitial thickening and marked traction bronchiectasis and more prominent right pleural effusion. This report widened the spectrum of imatinib-induced pneumonitis, which clinicians should recognize following long-term imatinib administration.

A case was reported of a 74-year-old man with idiopathic pulmonary fibrosis (IPF) who developed severe dyspnea after re-administration of imatinib for CML.[9] A chest X-ray and CT scan showed GGO in both lungs in addition to preexisting honey-combing.

Discontinuation of imatinib and methylprednisolone pulse therapy followed by administration of oral prednisolone resulted in improvement both in symptoms and radiographic diagnosis. Imatinib-induced pneumonitis was diagnosed based on the patient's clinical course and findings.

Another case was reported of a 64-year-old man who had CML.[10] On the 78th day after initiation of imatinib, the patient developed dyspnea. A chest X-ray showed bilateral GGO in the lower lung fields. A CT scan revealed reticular and GGO in the subpleural area. A transbronchial lung biopsy (TBLB) revealed the destruction of alveolar, mixed intra-alveolar, and interstitial fibrosis, along with eosinophilic infiltration (eosinophilic pneumonia).

After cessation of imatinib, the dyspnea improved within 10 days without steroid therapy. A chest X-ray and CT scan performed 18 days after cessation of imatinib showed almost complete resolution of interstitial shadows.

In this case, the pathologic findings of TBLB showing prominent infiltration of eosinophils suggested an immunoallergic reaction. This case and the others noted above suggest that imatinib-induced interstitial pneumonitis may be heterogeneous, and some of these cases may likely involve an immunoallergic mechanism.

A case of lymphomatoid granulomatosis (LYG) induced by imatinib has also been reported.[11] In this case, an 89-year-old woman with liver metastasis from GIST was treated with imatinib at an initial dose of 400 mg/day. Three months later, the size of the liver tumors decreased. Three months after that, a CT scan revealed 3 intrapulmonary lesions that radiologically resembled an infectious complication or metastases of the GIST. Owing to the age of the patient and continuous decline of her physical status, a lung biopsy was excluded.

The progressing pulmonary tumors were clinically interpreted as metastases of GIST, and therefore imatinib treatment was continued. Nine months later, the patient presented with multiple subcutaneous nodules as large as 25×30 mm on both legs and the lower back. Histologic findings revealed a dense lymphocytic infiltrate, mainly of the subcutis, extending through the dermis into the epidermis, with central necrosis and scattered giant cells. The infiltrate was both angiocentric and angiodestructive. Immunohistochemically, the lymphocytes were mainly CD20 positive. Epstein-Barr virus (EBV) in situ hybridization revealed EBV RNA in a distinct population of infiltrating lymphocytes. Clonality analysis of the CDR3 region of the immunoglobulin heavy-chain gene revealed the identical clone in 2 distant biopsy specimens. A large B-cell lymphoma resembling LYG was diagnosed. In addition to hepatic GIST tumor metastasis, a whole body CT scan revealed progressive pulmonary tumors that resembled lymphomas and granulomas.

Blood cell count findings showed leucopenia and lymphopenia. Cutaneous and, most likely, pulmonary LYG was diagnosed. As the pulmonic lymphomas led to progressive dyspnea, imatinib therapy was discontinued and replaced by a symptomatic dexamethasone treatment, which was stopped by the patient after 4 weeks. Two months after discontinuation, the subcutaneous nodules had vanished completely, and the pulmonary infiltrates could be detected only as small residual nodules. The patient's physical condition continuously improved, and the leukocyte and lymphocyte counts returned to within the normal range. The liver metastasis of GIST did not show any change in size.

Bekkenk and colleagues[12] also observed the occurrence of EBV-positive, primary, cutaneous, B-cell lymphoma during imatinib treatment that resolved after treatment was discontinued. EBV-associated lymphomas occur most commonly in severely immunosuppressed patients and often spontaneously resolve after the

reconstitution of the immune system. Imatinib may act through T-cell depletion; it can inhibit T-cell proliferation and T-cell activation in vitro and reduce the expansion of cytotoxic T lymphocytes in response to EBV.[13]

A case of imatinib-associated pulmonary alveolar proteinosis has also been reported.[14] In this report, a 29-year-old woman with a 5-year history of diagnosed CML was being treated with imatinib 400 mg/day. One month after starting treatment, the patient developed dry cough and dyspnea on exertion. Chest radiography showed patchy, bilaterally symmetrical, alveolar and interstitial disease. After bronchoscopy with a typical bronchoalveolar lavage fluid and transbronchial biopsies, pulmonary alveolar proteinosis was diagnosed. Imatinib was discontinued, hydroxyurea was given, and a therapeutic lavage was performed, which led to symptomatic improvement

Clinical Reports of Pulmonary Toxicities

Imatinib-induced interstitial pneumonitis is rare.[15] The adverse effects associated with imatinib therapy in patients with CML or GIST were analyzed in a study in Japan.[16] Of 3,023 adverse events spontaneously reported during imatinib therapy, 39 cases were of interstitial lung disease (ILD), of which 27 cases were analyzed after excluding apparent cases of fluid retention owing to imatinib, infection, or lung disease induced by other causes. Chest radiographs and CT or high-resolution CT images before and after the onset of drug-induced ILD were evaluated. Drug-related ILD was categorized as 6 radiologic patterns in this study.[17,18] The first is the hypersensitivity reaction (HR) pattern, which is described as diffuse homogenous or widespread opacity, mostly composed of ground-glass attenuation. This pattern is lacking in traction bronchiectasis and structural distortion. The second pattern is the interstitial pneumonia (IP) pattern, which is represented by ground-glass attenuation and irregular linear or reticular areas of attenuation with associated bronchiectasis and bronchiolectasis. Cryptogenic-organizing pneumonia (COP) pattern is the third radiologic pattern and it is characterized by non-segmental abnormal opacity that is predominantly composed of consolidation in subpleural or peribronchovascular distribution. The fourth pattern, the nodular pattern presents as diffuse fine nodular opacity probably distributed along the bronchovascular bundle, sometimes accompanied by patchy GGO. The next pattern is the peribronchovascular bundle (PBVB) pattern, which can be described as patchy GGO predominantly distributed along the bronchovascular bundle, and the last radiologic pattern is the diffuse alveolar damage (DAD) pattern.

The median patient age was 63 years (range, 47–82 years), and the median daily dose of imatinib was 400 mg (range, 200–600 mg) at the time ILD was diagnosed. The study found no clear correlation between the development of ILD and the dose or duration of imatinib therapy. The time until development of ILD ranged from 10–282 days. In terms of safety, dyspnea was noted in 20 patients (grade 1, n=2; grade 2, n=11; grade 3, n=4; grade 4, n=3), and hypoxia was observed in 16 patients (grade 2, n=5; grade 3, n=9, grade 4, n=2). Eosinophilia developed in 5 patients (range, 7–2,701/uL). Chest radiographs and CT findings revealed HR pattern in 8 patients (30%), IP pattern in 7 patients (26%), COP pattern in 4 patients (15%), PBVB pattern in 4 patients (15%), nodular pattern in 3 patients (11%). It was unclassifiable in 1 patient (3%), and no patients showed DAD pattern. In general, a chest radiograph and a CT scan after imatinib therapy showed diffuse or patchy GGO, consolidation, and/or fine nodular opacity in bilateral lungs. Preexisting pulmonary disease was detected in 11 (41%) patients (7 chronic IP, 1 busulfan lung, 3 pneumectomy [owing to 2 lung cancer and 1 hemangioma], and 1 pleuritis) on the chest radiographs and/or CTs before imatinib therapy was initiated, though the chronic IP in 7 patients was very mild.

The prognosis of drug-induced lung injury was related to the severity of lung disease, thus patients with DAD pattern are sometimes incurable. The reason for the good prognosis in patients with imatinib-induced ILD can probably be attributed to no patients presenting with a DAD pattern.

After ILD developed, imatinib was discontinued in all patients; 19 patients were treated with high-dose corticosteroids, 5 with moderate-dose corticosteroids, and 3 were untreated. After treatment, ILD resolved completely in 7 patients and improved in 16 patients; 4 patients did not improve, and 1 patient suffered from pulmonary fibrosis. After ILD improvement, imatinib was re-administered with a reduced dose (range, 100–400 mg/day) to 11 patients. However, ILD occurred again in 4 patients.

Regarding the radiologic characteristics in this study, 8 patients (30%) showed an HR pattern, which is characterized by homogenous opacities that typically have a peripheral and upper lobe distribution, and which is sometimes associated with small areas of consolidation. The eosinophilic infiltration was seen in 2 patients; their radiographic patterns were COP and IP, respectively. A peripheral eosinophilia was present in 5 out of 27 patients (19%). These findings suggested that some of these cases are likely to involve an immunoallergic mechanism. In more than 40% of patients, chest radiographs before imatinib therapy showed mild chronic IP or pneumectomy owing to lung tumors in this study, which suggests that imatinib-related ILD is likely to develop in previously damaged lungs.

Erlotinib

The mechanism of antitumor action of erlotinib is not fully characterized. The drug is known to inhibit overall

epidermal growth factor receptor (HER1/EGFR)-tyrosine kinase. Active competitive inhibition of adenosine triphosphate inhibits downstream signal transduction of ligand-dependent HER1/EGFR activation. The FDA-approved indications for erlotinib are as follows: for treatment of carcinomas of the pancreas that are locally advanced, unresectable or metastatic, given in the first-line setting in combination with gemcitabine, and for treatment of non-small cell lung cancer (NSCLC) that is locally advanced or metastatic in patients who failed prior chemotherapy. Below are case studies and clinical reports describing patients who developed pulmonary toxicities with the use of erlotinib.

Case Studies Reporting Pulmonary Toxicities

In 1 case report, a 60-year-old former smoker was found to have cancer of the left lung.[19] Pathology results from a specimen obtained by video-assisted thoracoscopy showed a well-differentiated adenocarcinoma and demonstrated the pattern of usual interstitial pneumonia. The patient began therapy with erlotinib 150 mg/day. In the fourth week of treatment, the patient had acutely worsening dyspnea and hypoxemia without fever, chills, or cough. He was afebrile and tachypneic, with a resting oxygen saturation of 94% while breathing ambient air, which decreased to 88% with ambulation. Breath sounds were decreased, with crackles bilaterally. The patient also had a maculopapular rash that was consistent with a drug effect. A chest CT scan revealed new extensive bilateral GGO and alveolar air space densities throughout both lungs.

Erlotinib therapy was discontinued, and therapy with methylprednisolone and an antibiotic was initiated. No pathogens were isolated. Despite therapy, respiratory failure developed, requiring mechanical ventilation, and after several weeks of intensive care, the patient died. Histologic analysis postmortem showed a pattern of diffuse alveolar damage.

Given the data for gefitinib and the findings in this case, the authors recommended that patients with evidence of usual interstitial pneumonia present on resected lung specimens or a clinical diagnosis of pulmonary fibrosis should not be treated with erlotinib or, for that matter, gefitinib. Patients receiving erlotinib should have their baseline respiratory symptoms well documented prior to the administration of medication. Should pulmonary symptoms worsen, erlotinib therapy should be stopped immediately, and empiric corticosteroids should be administered until erlotinib-induced ILD can be excluded as the cause.

In another case report,[20] a 55-year-old smoker with no evidence of preexisting interstitial disease developed bilateral ILD and respiratory failure, which could be explained only as a toxicity of erlotinib. He had a history of stage IV left upper lobe squamous-cell carcinoma for which he had received 3 successive regimens of chemotherapy (ifosfamide plus gemcitabine, docetaxel, mitomycin plus navelbine), followed 5 months later by erlotinib. At initiation of erlotinib treatment, there were no radiologic signs suggestive of ILD disease or apparent clinical signs of respiratory distress. While the patient was completing 2 months of erlotinib therapy, he presented with nonproductive cough and a facial exanthema and developed bilateral diffuse GGO.

Despite discontinuation of erlotinib, he was admitted with respiratory failure 2 weeks later. Diagnostic work-up for other causes of pneumonitis, including infectious diseases, congestive cardiac failure, and pulmonary infarction, was negative. The patient was started on supplemental oxygen and intravenous methylprednisolone (1 mg/kg daily and then 3 g bolus after 1 week), and empiric therapy was expanded 1 week later to include cyclophosphamide (500 mg). Despite transient clinical improvement, hypoxemia persisted and oxygen requirements increased. The patient progressively deteriorated and died 3 weeks later. The autopsy was suggestive of the organizing stage of diffuse alveolar damage.

The diagnosis of drug-induced ILD relies on typical radiologic signs and exclusion of other potential causes. The incidence of ILD was less than 1% in erlotinib pivotal trials.[21] However, the incidence could be higher since ILD diagnosis requires diagnostic work-up that may not always be feasible in patients with advanced lung cancer and/or comorbidities.

Two cases of erlotinib-associated acute pneumonitis were reported.[22] The first patient was started on erlotinib treatment for metastatic NSCLC. The second patient was treated with erlotinib for metastatic adenocarcinoma of unknown origin. Both patients developed dyspnea and hypoxemia 5–6 days after initiation of erlotinib treatment. Physical examination in the first patient revealed a temperature of 37.7°C, a blood pressure of 127/65 mmHg, a respiratory rate of 24 breaths/min, and a heart rate of 88 beats/min. Chest auscultation was significant for bilateral diffuse crackles, and jugular venous distension was not present.

In the second case, physical examination revealed a temperature of 37.0°C, a blood pressure of 99/64 mmHg, a respiratory rate of 30 breaths/min, and a heart rate of 120 beats/min. Chest auscultation was significant for bilateral diffuse crackles, and jugular venous distension was not present. Diffuse alveolar hemorrhage was excluded by bronchoscopy in both cases. CT scans of the chest in the patients showed extensive bilateral ground-glass infiltrates consistent with pneumonitis. In both patients, acute pneumonitis resulted in respiratory failure, requiring intubation and mechanical ventilation.

Bronchoalveolar lavage cultures were negative. Erlotinib treatment was stopped and both patients were treated with corticosteroids. The first patient was given 250 mg of methylprednisolone intravenously, every 6 hours for 3 days. Corticosteroid therapy was continued with 60 mg of prednisone daily thereafter. Hypoxemia improved after 4 days, and the patient was extubated. A repeat chest radiograph showed marked reduction of the bilateral lung opacities. Two weeks after presentation, the patient was transferred to a rehabilitation center on tapering prednisone. The second patient also received 250 mg of methylprednisolone intravenously, every 6 hours for 3 days. Methylprednisolone was gradually tapered. Transient improvement in pulmonary status and oxygenation was achieved with corticosteroid therapy, but the patient developed *Klebsiella* sepsis that resulted in septic shock with multiorgan failure and eventual death. An autopsy revealed diffuse alveolar damage of the lungs, which most likely represents acute lung injury secondary to septic sock.

In 1 report,[23] there were 2 patients who presented with fatal ILD after treatment with erlotinib. The first patient was a 62-year-old woman with NSCLC and intracranial metastasis. On day 43 of erlotinib treatment, she developed progressive shortness of breath without a cough or fever. A chest CT scan showed a new ground-glass attenuation pattern located peripherally in the right upper zone. The patient was hospitalized on day 49 after no improvement with steroids, antibiotics, and bronchodilator inhalers. CT pulmonary angiography showed a widespread ground-glass attenuation pattern and alveolar consolidation without signs of pulmonary emboli or a tumor. A clinical diagnosis of ILD was made. Despite discontinuing erlotinib on day 52 and treatment with supplemental oxygen, nebulizers, intravenous dexamethasone (12 mg/day), and intravenous antibiotics, the patient's condition deteriorated and she died 54 days after commencing erlotinib. The findings from the autopsy of the lungs were consistent with diffuse alveolar damage.

The second patient was a 62-year-old nonsmoker who was diagnosed with NSCLC. After 4 weeks of erlotinib treatment, she developed a transient, grade 1, acneiform rash. On examination, she was in respiratory distress with bilateral fine inspiratory crepitations on auscultation. Serial chest radiographs showed progressive consolidation of the lower zones. A high-resolution CT scan showed new extensive bilateral ground-glass attenuation and bilateral pleural effusions (in addition to the preexisting pulmonary fibrosis, lung tumor, and mediastinal and hilar lymphadenopathy). A clinical diagnosis of erlotinib-induced ILD was made. Despite discontinuation of erlotinib on day 31, administration of supplemental oxygen, and treatment with oral prednisolone (60 mg/day) and intravenous antibiotics, her condition deteriorated. She died 34 days after commencing erlotinib. The autopsy revealed a pattern consistent with diffuse alveolar damage. The limited histopathologic data from cases of EFGR TKI-induced ILD indicate that the most common pathologic diagnosis is one of diffuse alveolar damage, as was the case in the above-mentioned report.[24]

Management includes discontinuing erlotinib, supportive therapy (including supplemental oxygen and mechanical ventilation when necessary), and high dose steroids. Although resolution has been reported, many patients die of progressive respiratory failure.

A case was reported of a 43-year-old man with NSCLC was given erlotinib (150 mg/day).[25] The patient initially tolerated the medication well, but reported minimal dyspnea on exertion. In December 2005, a CT scan of the lungs was performed to assess response; it showed bilateral focal ILD with a reticular pattern. The patient developed increasing dyspnea, and in January 2006, he presented with dyspnea at rest. A CT scan revealed severe thickening of the interstitium, which was present in the right lung, but also in the entire lung, which had been normal before erlotinib treatment. High-resolution CT was pathognomonic for ILD. Erlotinib therapy was discontinued and therapy with oral steroids was initiated. The dyspnea improved, and the patient was discharged 5 days later. The onset of related ILD following small molecule EGFR inhibitors has been reported to occur as early as 5 days after starting therapy, and symptoms typically include dyspnea, cough, hemoptysis, and fever.[26] The mechanism by which erlotinib causes ILD is unknown. Most cases of ILD occur in patients who have other confounding or contributing factors, including pre-existing parenchymal lung disease, metastatic cancer, pulmonary infections, prior radiotherapy, or concomitant/prior chemotherapy.[26]

One report[27] showed severe lung toxicity during treatment with gemcitabine and erlotinib for metastatic pancreatic cancer. Discontinuation of erlotinib and treatment with prednisolone (900 mg/day) for 3 days initially showed improvement in the patient's condition and a CT scan 7 days after initiation of steroid treatment showed a complete recovery of ILD when compared to the CT that was done after the patient became symptomatic. Prednisone was subsequently reduced and stopped after 16 days of treatment. It could not be ruled out if both drugs (gemcitabine and erlotinib) or an interaction between the 2 drugs contributed to the development of severe ILD.

Clinical Reports of Pulmonary Toxicities

In an open-label phase II trial, stage III/IV NSCLC patients who had progressive disease after at least 1 prior platinum-based chemotherapy regimen were enrolled.[28]

Erlotinib was administered orally at a dose of 150 mg/day until disease progression or intolerable toxicities. A total of 62 patients were enrolled and all but 2 were evaluated for efficacy. Four patients (6.5%) had ILD-like events, including worsening of radiation pneumonitis in 1 patient and 1 death. The incidence of ILD, which is the most clinically problematic adverse effect associated with erlotinib, tended to be higher than that reported in other clinical studies of erlotinib.[29,30]

In a phase III trial of erlotinib combined with carboplatin and paclitaxel chemotherapy in advanced NSCLC (TRIBUTE), patients were randomly assigned to receive either a daily dose of 150 mg of erlotinib or placebo concurrently with chemotherapy. There were 5 (1.0%) severe ILD cases in the erlotinib arm versus 1 (0.2%) ILD case in the placebo arm. All 6 cases of ILD were fatal. The clinical presentation and the nature of these ILDs were not reported.[31]

Pulmonary toxicities have been infrequently reported in patients receiving erlotinib for the treatment of advanced solid tumors.[24,29,32-36] A double-blind, multicenter, randomized trial that was performed by the National Cancer Institute of Canada Clinical Trials Group compared orally administered erlotinib (150 mg/day) with placebo. Patients with locally advanced or metastatic NSCLC after failure of at least 1 previous chemotherapy regimen were enrolled in the study. Overall, the incidence of ILD in this study was approximately 0.8%. Patients in the placebo group had a similar incidence of ILD. In this report, cases were described in nonspecific terms, such as interstitial pneumonia, alveolitis, pneumonitis, and pulmonary fibrosis.[21]

Erlotinib treatment in the management of previously treated stage IIIB or IV NSCLC was evaluated in another randomized, placebo-controlled, double-blind trial.[29] Patients were enrolled in the study at least 21 days after chemotherapy and 1 week after radiotherapy. The patients were randomly assigned to the erlotinib arm (150 mg/day of erlotinib) or the placebo arm. Three cases of pneumonitis were reported in each of the 2 groups.[29] Risk factors for EFGR tyrosine kinase inhibitor-associated ILD are not well defined.

Limited data from phase I clinical trials of 157 patients reported no recognized cases of ILD, but 1 patient reportedly died of undefined toxicity.[24,37,38]

In the BR21 trial, in which erlotinib was compared with placebo, the term ILD was not used, but the overall incidence of pulmonary fibrosis plus pneumonitis was reported to be 6% in each arm. One death from pneumonitis was observed in each study arm, resulting in an incidence of 0.2% for erlotinib and 0.4% for placebo.[29]

A phase IB trial included 1 NSCLC patient (previously treated with chemoradiation) who developed a lethal adult respiratory distress syndrome 7 days after initiation of treatment with gemcitabine and erlotinib (100 mg/day). This event was interpreted by investigators as an erlotinib- and/or gemcitabine-induced pneumonitis: however, no statement regarding the clinical course and treatment of this fatal pneumonitis was given by the authors.[39]

Gefitinib

The mechanism of antineoplastic action is not fully understood. Gefitinib inhibits tyrosine kinases associated with transmembrane cell surface receptors found on both normal and cancer cells. One such receptor is epidermal growth factor receptor. Tyrosine kinase activity appears to be vitally important to cell proliferation and survival. The FDA approved gefitinib as continued monotherapy in patients with locally advanced or metastatic NSCLC who have failed both platinum and docetaxel-based chemotherapies or patients who are benefiting or have benefited from gefitinib. Below is a review of cases and clinical reports of gefitinib-treated patients who presented with pulmonary toxicities.

Case Studies Reporting Pulmonary Toxicities

One case report[40] showed a 41-year-old man with adenocarcinoma of the lung with intrapulmonary metastases receiving gefitinib who developed a bilateral spontaneous pneumothorax. Twenty-one days after receiving gefitinib, he had spontaneous pneumothorax in the left lung, followed 4 days later by pneumothorax in the right lung. The extent of the pneumothorax was slight; therefore, he recovered without drainage within several days. The patient had also received paclitaxel and carboplatin previously. Spontaneous pneumothorax, especially bilateral pneumothorax, is a rare complication of chemotherapy used to treat lung cancer.

Another case report[41] described a 55-year-old man with advanced adenocarcinoma of the lung who received gefitinib. After administration of gefitinib for 7 months, a CT scan of the chest demonstrated diffuse GGO, and the patient was suspected to have developed gefitinib-induced ILD. However, TBLB revealed tumor cells in the middle-size lung vessels. Afterwards, multiple infarctions of the brain, spleen, and left kidney were detected. The patients was then considered to have developed systemic tumor emboli, a rare complication. The clinical presentation in this patient was difficult to distinguish from that of ILD, and TBLB was useful in the differential diagnosis.

Four cases were reported wherein the patients developed GGO on CT scans of the chest.[42] One case occurred during the second week of treatment, 2 occurred in the second month, and 1 in the fourth

month. In all 4 cases, gefitinib withdrawal and steroid use showed marked improvement in the patients. Dyspnea on exertion, shortness of breath, and cough were the usual presenting features in the patients.

In 1 case, a patient presented with symptoms of progressive and exertional dyspnea and a cough with hemoptysis 4 weeks after gefitinib administration.[43] Withdrawal of gefitinib and administration of methylprednisolone and other supportive treatment helped improve the patient's respiratory function.

In this report, a patient developed dyspnea on exertion with a dry cough 6 weeks after initiation of gefitinib.[44] A chest CT scan showed focal areas of GGO. Discontinuation of gefitinib and treatment with methylprednisolone and supportive treatment improved the patient's respiratory status.

There have also been case reports[45-47] of gefitinib-induced pulmonary toxicity that resulted in a fatal outcome despite treatment discontinuation and use of steroids and supportive treatment. Before diagnosing ILD, other possible causes of pulmonary distress should be ruled out, including infection, pulmonary embolism, cancer progression, radiation-related injury, fluid overload, and congestive heart failure.[41,42,48,]

Clinical Reports of Pulmonary Toxicities

Various reports have been published about the incidence of ILD in gefitinib-treated patients. The data from 1 report[49] is presented in Table 2.

In a series of 8 patients who underwent autopsy following death from acute lung injury associated with the use of gefitinib, the pathologic diagnosis of DAD was made (AstraZeneca and Iressa Expert committee, 2003). Pre-existing ILD, including usual IP, was found in 3 of the 8 patients. Clinical examination of the total population of 152 patients with ILD suggested that the presence of IPF affected outcome from ILD. There was pre-existing IP in 23 of 48 patients. In a group of 29 (of 152 patients) patients for whom CT scans were available before and after onset of ILD, 12 had pre-existing IPF and 7 (58%) died; 17 did not have pre-existing IPF, and only 3 (18%) of these patients died. Hence, the presence of IPF seems to be an important risk factor. Clinical examinations of 152 patients with ILD were performed. In a series of 47 patients from this population for whom high-resolution CT was available, the characteristic images of gefitinib-associated ILD were of patchy, diffuse, ground-glass shadows. Several characteristic high-resolution CT patterns that are seen in other drug-associated ILDs were also observed in the gefitinib-associated condition (eg, acute IP-like pattern, COP-like pattern, eosinophilic pneumonia–like pattern, and localized infiltration pattern).

Table 2. Incidence of ILD in Gefitinib-Treated Patients

	Gefitinib-treated patients (n)	Incidence of ILD, death (%)
Globally	92,750	0.99 (0.36)
Japan marketed use	39,600	1.86 (0.69
Outside Japan	53,150	0.34 (0.11)
US EAP	24,200	0.39 (0.08)
Rest of the world EAP	15,000	0.38 (0.021)

EAP=expanded access program; ILD=interstitial lung disease.

Data from Forsythe and Faulkner.[78]

In 1 report,[50] of the 18 patients with NSCLC who had been treated with gefitinib for 2 months, 4 developed severe acute interstitial pneumonia. Fever, dyspnea, hypoxemia, and anorexia were noted. The range for onset of symptoms after gefitinib administration was between 4 and 19 days. Chest CTs showed that GGOs were distributed diffusely, which was consistent with interstitial pneumonia.

The level of serum KL-6, a marker of pulmonary injury and fibrosis, was 1,043–1,422 U/mL (normal range, <500 U/mL) at diagnosis of interstitial pneumonia. The sputum culture of bacteria and fungi were collected, and general blood tests, including levels of fungal antigen (serum β-D-glucan) and cytomegalovirus antigen, were assessed in all 4 patients. Only 1 patient was positive for serum β-D glucan at the start of acute interstitial pneumonia and for cytomegalovirus antigen after repeated high-dose steroid treatment. These infections were immediately treated with an antifungal agent (fluconazole) and an antiviral agent (ganciclovir). After the disease developed, all patients were given high-dose steroids and oxygen. Two patients responded to the steroids, whereas the other 2 patients died from progressive respiratory dysfunction. Autopsies in the 2 deceased patients showed diffuse alveolar damage with hyaline membranes distributed in the lungs and no evidence of lymphangitis carcinomatosa, pulmonary embolus, or pulmonary hemorrhage.

In another report, 67 patients with NSCLC who had been treated with gefitinib were selected.[51] Of these 67 patients, 5 who developed dyspnea after gefitinib treatment were selected. Chest radiographs and CT findings, along with the clinical course, were evaluated.

All patients presented with dyspnea. The first patient had fever, cough, and sputum along with dyspnea, and

another patient had cough with dyspnea. The time of symptom onset varied from 20 days to 3 months after the administration of gefitinib. Arterial blood gas analysis revealed severe hypoxia. All patients required supplementary oxygen administration by nasal cannula or facial mask. Pulmonary function test was not performed in any of the patients. In patient 1, unilateral GGO was seen in plain radiography, and unilateral homogenously distributed GGO was seen on CT. In patients 2 and 3, plain radiographs showed unilateral GGO, and CT showed unilateral GGO with interlobular septal thickening. Patient 4 had bilateral GGO on plain radiographs, and bilateral GGO and pleural effusion on CT. In patient 5, plain radiographs showed bilateral GGO, and CT showed bilateral patchy GGO.

Administration of gefitinib was discontinued in 4 patients (patients 1, 3, 4, 5) just after symptoms developed. Four patients (patients 1, 2, 3, and 5) were treated with oral or intravenous steroid therapy. Dyspnea and hypoxia improved following the discontinuation of gefitinib and the start of steroid therapy in 3 patients (patients 1, 2, and 3), but there was no response in the other 2 patients (patients 4 and 5). Three of 5 patients (patients 1, 2, and 3) were discharged and transferred to other hospitals, and 2 patients (patients 4 and 5) died of respiratory failure within 10 days of symptom onset. In all patients, the findings of GGO and interlobular septal thickening were new, as compared with prior studies before the administration of gefitinib.

According to an official notice by the Japanese ministry of Health, Labor, and Welfare, 291 of 17,500 patients with NSCLC who were treated with gefitinib had suspected interstitial pneumonia or acute lung injury associated with gefitinib, including 81 deaths.[52] In this above mentioned report, 5 of the 67 patients suffered from acute lung injury. The mechanism of interstitial pneumonitis induced by gefitinib is not known. However, several cytokines are known to be associated with IP induced by gefitinib, like EGFR and transforming growth factor-alpha (TGF-alpha).[53,54] TGF-alpha is a secreted mitogen that shares 42% homology with HER and binds to EGFR. TGF-alpha stimulates the proliferation of cultured epithelial cells, fibroblasts, and endothelial cells. In addition, TGF-alpha protects against acute lung injury, at least in part, by attenuating inflammatory response and by reducing pulmonary edema. Therefore, inhibition of EGFR-mediated signaling by gefitinib probably impairs the repair mechanism by TGF-alpha and exacerbates lung injury.[55,56] Some studies have identified specific serum markers and risk factors that can facilitate the diagnosis of gefitinib-induced pneumonitis and some studies have shown specific serum markers of pulmonary fibrosis, such as surfactant protein (SP)-A, SP-D, and KL-6, a mucin-like glycoprotein expressed in type II pneumocytes. These markers can become overexpressed during gefitinib treatment in patients with acute lung injury and therefore may be predictors of gefitinib-induced ILD.[57,58] Epidemiologic studies by Inoue and coauthors[50] and Inomata and colleagues[57] showed that risk factors for gefitinib-induced lung injury included smoking habits, male gender, and the coexistence of idiopathic pulmonary fibrosis or interstitial pneumonia. In addition, they found that the risk factors for death due to lung injury were early onset (within 2 weeks) and poor performance status.

A review of a safety information database containing over 50,000 patients treated worldwide with gefitinib found 408 patients who had ILD, 324 of who were from Japan.[52] This resulted in a global incidence of approximately 1%, with a higher incidence in Japan (2%) and a lower incidence in the United States (0.3%). Of the cases reported, 31% received prior radiation therapy and 57% had prior chemotherapy. One-third of cases were fatal.

Smaller studies conducted in Asia have reported higher incidences, ranging from 4–6%.[59,60] These differences point to risk factors that are probably related to ethnicity. Patients with existing pulmonary fibrosis or other pulmonary comorbidities may be at greater risk of developing ILD.[50,52,60] The first signs of ILD are often dyspnea with or without cough or low-grade fever, which rapidly become worse and require hospitalization. Symptoms typically appear in the first 1–2 months of treatment; the median onset of ILD was 24 days in Japan and 42 days in the United States.[61] Characteristic CT chest findings include bilateral diffuse GGO.[50] At the first signs of respiratory changes during treatment with gefitinib, treatment should be interrupted and a thorough investigation of pulmonary symptoms should be initiated. If ILD is confirmed, treatment should be discontinued.[52,62-64] This review also demonstrated that methylprednisolone can be used to treat respiratory symptoms, and most symptoms resolve after anti-EGFR therapy has been discontinued.[42,48] The presence and extent of parenchymal lung disease is best determined by high-resolution CT and pulmonary function tests.[65] Definitive diagnosis of ILD requires a lung biopsy, which is not routinely performed in lung cancer patients. The use of clinical criteria and high-resolution CT can rule out other possible diseases with a high degree of sensitivity (72–79%) and specificity (84–87%).[66] In this review, gefitinib-related ILD was found to be fatal in one-third of cases.[52] Death due to ILD can be prevented by promptly recognizing new onset respiratory symptoms, discontinuing treatment, performing radiographic assessments, and starting glucocorticosteroid treatment when ILD is suspected.[65]

In 1 study,[67] a total of 1,976 patients with NSCLC from 84 of 112 (75%) institutions surveyed were reported. Among these patients, 102 individuals developed pulmonary infiltrates after treatment initiation, which were reported as potential causes of gefitinib-induced ILD. The central review committee evaluated the clinical data of these 102 patients and determined that 70 cases of ILD and 31 deaths were attributable to gefitinib, corresponding with a prevalence of 3.5% (95% CI, 2.8–4.5%) and a mortality rate of 1.6% (95% CI, 1.1–2.2%) for gefitinib-induced ILD. All ILD patients had been treated with gefitinib monotherapy, with the exception of 1 patient who received gefitinib concurrently with cisplatin. None of the ILD patients received radiotherapy simultaneously with gefitinib treatment. The median time from the start of gefitinib treatment to the development of ILD was 31 days (interquartile range, 18–50 days), and the median duration of gefitinib treatment before ILD development was 29 days (interquartile range, 18–49 days).

Among the 70 patients with gefitinib-induced ILD, 9 (13%) underwent bronchoscopic examination, comprising 6 lung biopsies and 4 bronchoalveolar lavages; all the lung biopsy specimens showed interstitial inflammation and fibrosis, and bronchoalveolar lavage revealed no signs of infection (eg, neutrophilia). Cultures of blood or other specimens were performed for 49 patients with ILD (70%), with no infection detected.

After the development of gefitinib-induced ILD, 66 patients (94%) received corticosteroids; additional treatment with antibiotics in 17 of the patients did not increase the proportion of individuals with improved ILD (18% and 61% with and without antibiotics, respectively).

Multivariate logistic regression analysis revealed that sex, smoking status, and coincidence of interstitial pneumonia as independent risk factors for gefitinib-induced ILD.

An analysis was performed of the risk factors for development of ILD and the prognostic factors seen after ILD in patients with NSCLC who received gefitinib.[68] In total, 330 patients were eligible for ILD evaluation, and 15 (4.5%) were finally confirmed to have developed ILD by blinded expert review. The analysis found that the overall incidence of ILD was 4.5%, and no obvious interinstitutional variability was observed in the incidence of ILD among institutions. It was also noted that pre-existing pulmonary fibrosis, poor performance status at the time of initial gefitinib treatment, and prior thoracic irradiation were independent risk factors for ILD. Further, pre-existing pulmonary fibrosis, a short interval from the initiation of gefitinib treatment to the onset of ILD, and ILD with an acute IP pattern were poor prognostic factors.

Another report[69] that elucidated risk factors for ILD in Japanese patients with NSCLC during treatment with gefitinib or chemotherapy showed that the mortality rate in patients who developed acute ILD after gefitinib treatment was 31.6%.

The study confirmed and further defined risk factors for developing ILD with gefitinib or chemotherapy. The factors included: older age, poor World Health Organization performance status, smoking, short duration from diagnosis of NSCLC, reduced normal lung on CT scan, preexisting ILD, and concurrent cardiac disease.

During the study follow-up, the average incidence rate for acute ILD events in patients treated with gefitinib was 3.2-fold higher compared to that seen with other chemotherapy treatments. The increased risk of ILD associated with gefitinib treatment was seen most clearly in the first 4 weeks after treatment initiation. Interestingly, the issue of ILD in patients with NSCLC, after gefitinib or other treatments, appears to be a problem largely limited to Japan. Data from the AstraZeneca Global Drug Safety Database showed that the reporting rate of ILD-type events in patients receiving treatment with gefitinib was only 0.23% in the rest of the world excluding Japan, based on more than an estimated 215,000 patients worldwide that were exposed to gefitinib.[70] Even for neighboring countries, the pattern differs from Japan: the rate in East Asian countries, including Korea and Taiwan but excluding Japan, was 0.17%.[70] However, the proportion of ILD-type events with a fatal outcome was similar: 37% in Japan and 31% in the rest of the world. The reasons for this difference in incidence of ILD between Japan and other countries remain unclear, but may be related to either constitutional or environmental factors specific to Japan or Japanese patients.

In one study,[71] a retrospective analysis of 112 patients with NSCLC who received gefitinib monotherapy was performed. The incidence of ILD was as high as 5.4%. The risk of ILD appears to be around 2–5% if gefitinib is given to patients without careful risk assessment. The study also showed preexisting PF as a strong risk factor. Of the 112 patients in the study, 12 had PF at the start of gefitinib administration. Four (33%) of these patients subsequently developed ILD, 3 (25%) died as a result, and no response was seen in any of the 12 patients.

Another retrospective review[72] of the clinical records and chest X-rays of 489 lung cancer patients who were treated with gefitinib was conducted. The authors identified 4 cases of gefitinib-induced ILD.

Patients visited the hospital complaining of dyspnea (4/4), dry cough (3/4), and cyanosis (1/4) after the start of gefitinib. Their median length of treatment with gefitinib was 15 days. High-resolution CT of the chest showed bilateral diffuse ground-glass infiltrates (4/4), honeycombing (1/4), emphysema (1/4), and some areas of patchy consolidation (3/4).

The bilateral diffuse ground-glass infiltrates and patchy consolidation resolved after the discontinuation of gefitinib and treatment with corticosteroids. After diagnosis of ILD, all 4 patients stopped taking gefitinib and were treated with high-dose corticosteroids (2 mg/kg/day up to 1 g/day of intravenous methylprednisolone). After starting corticosteroid therapy, oxygenation and interstitial shadows began to gradually improve in all patients. Corticosteroids were subsequently reduced to a maintenance dose (20–30 mg/day of oral prednisolone). All 4 patients were discharged from the hospital, and only 1 patient required home oxygen therapy. All 4 continued to take oral steroids and showed no evidence of recurrent ILD.

As indicated by this report and others, the period of time from starting gefitinib to the onset of interstitial pneumonia was short (within 1 week to 1 month, median 15 days in this report).[73] Three cases of postmortem histopathology of lung tissues from the patients with gefitinib-induced ILD have been reported,[50,74] and they showed a pattern of DAD.

In another study,[57] 110 NSCLC patients who were treated with gefitinib were selected. The most serious complication was acute lung injury. Of the 110 patients with NSCLC, 12 patients developed this disorder and 5 of these 12 died as a result.

The highest risk factor was the complication of chronic pulmonary fibrosis, which appeared to remain stable. The postmortem autopsy conducted on one of the patients who died of acute lung injury revealed histopathologic findings of DAD, which were the same as the findings seen in previous gefitinib studies.[50,74] DAD is known to be the most severe histopathologic characteristic of acute lung injury, and patients are poor responders in intensive care. The overall incidence of acute lung injury in this study was 10.9%, which was higher than incidence seen in the previous studies.[75-77] For this reason, it was speculated that the high incidence was caused mainly by the enrollment of many patients with preexisting pulmonary fibrosis and/or poor performance status, which were risk factors of lung injury during treatment with gefitinib. The other cause seemed to be the difference in genetic factors. Even when 9 patients with pulmonary fibrosis were excluded as subjects, the incidence was still high (6.9%, 7/101).

Final Summary

In summary, this review demonstrates that pulmonary toxicities associated with TKI therapy are rare, with ILD being the most prominent. In 1 large study of imatinib in Japanese patients, of the 3,023 adverse events spontaneously reported during treatment, 39 cases were of ILD. Besides this study, there have been individual case reports (10) of ILD patterns. For erlotinib-treated patients, the incidence of ILD ranged between 0.2% and 1.1%, except in 1 study that showed an incidence of 6.5%. In gefitinib-treated patients the incidence of ILD ranged from 0.38% to 2%. Other studies have shown the incidence varying from 3.35% to 10.9%.

There seems to be a higher incidence of TKI-induced ILD (in gefitinib studies) in Japanese patients. The reasons for this difference in incidence of ILD between Japan and other countries remain unclear, but may relate to either constitutional or environmental factors specific to Japan or Japanese patients.

Risk factors for developing ILD in patients receiving gefitinib include poor World Health Organization performance status, smoking, short duration from time of diagnosis of NSCLC, reduced normal lung on CT scan, preexisting ILD, and concurrent cardiac disease. In terms of safety, dyspnea appears to be the main presenting complaint. The time range between TKI administration and symptom presentation was very variable (10–282 days with imatinib).

Doctors should be aware of pulmonary toxicities, and any patient on TKIs presenting with dyspnea should discontinue TKIs and start steroid therapy, especially if suspicion for TKI-induced ILD is high. From the data that were presented, immediate cessation of TKI therapy and use of steroids caused significant improvement (with imatinib, 23/27 patients analyzed in the first study and numerous patients in the 10 other individual cases that were reported).

Immediate imaging studies (chest X-ray or CT scan of the chest) should be performed; in most cases of ILD that were reviewed, imaging demonstrated bilateral infiltrates. Overall, the mortality rate that was observed in the patients was extremely variable.

References

1. Lin JT, Yeh KT, Fang HY, Chang CS. Fulminant, but reversible interstitial pneumonitis associated with imatinib mesylate/ *Leuk Lymphoma*. 2006;47:1693-1695.
2. Akoun GM, Cadranel J, Rosenow EC 3rd. Bronchoalveolar lavage cell data in drug-induced pneumonitis. *Allerg Immunol*. 1991;23:245-252.
3. Bergeron A, Bergot E, Vilela G, et al. Hypersensitivity pneumonitis related to imatinib mesylate. *J Clin Oncol*. 2002;20:4271-4272.
4. Rajda J, Pathak PD. Reversible drug-induced interstitial pneumonitis following imatinib mesylate therapy. Division of hematology and oncology, Rochester General Hospital, Rochester, New York. Published online in Wiley Interscience (www.interscience.wiley.com). DOI:10.1002/ajh.20319.
5. Ma CX, Hobday TJ, Jett JR. Imatinib mesylate-induced interstitial pneumonitis. *Mayo Clin Proc*. 2003;78:1578-1579.
6. Isshiki I, Yamaguchi K, Okamoto S. Interstitial pneumonitis during imatinib therapy. *Br J Haematol*. 2004;125:420.
7. Rosado MF, Donna E, Ahn YS. Challenging problems in advanced malignancy: case 3. Imatinib mesylate-induced interstitial pneumonitis *J Clin Oncol*. 2003;78:3171-3173.
8. Seki N, Ito A, Watanabe K, et al. Irreversible imatinib-induced pneumonitis following long-term imatinib administration. *Intern Med*. 2007;46:1941-1942.
9. Yamasawa H, Sugiyama Y, Bando M, Ohno S. Drug-induced pneumonitis associated with imatinib mesylate in a patient with idiopathic pulmonary fibrosis. *Respiration*. 2008;75:350-354.

10. Yokoyama T, Miyazawa K, Kurakawa E, Nagate A, et al. Interstitial pneumonia mesylate: pathologic study demonstrates alveolar destruction and fibrosis with eosinophilic infiltration. *Leukemia*. 2004;18:645-646.
11. Yazdi AS, Metzler G, Weyrauch S, et al. Lymphomatoid granulomatosis induced by imatinib-treatment. *Arch Dermatol*. 2007;143:1222-1223.
12. Bekkenk MW, Vermeer MH, Meijer CJ, et al. EBV-positive cutaneous B-cell lymphoproliferative disease after imatinib mesylate. *Blood*. 2003;102:4243.
13. Seggewiss R, Loré K, Greiner E, et al. Imatinib inhibits T-cell receptor-mediated T-cell proliferation and activation in a dose-dependent manner. *Blood*. 2005;105:2473-2479.
14. Wagner U, Staats P, Moll R, Feek U, Vogelmeier C, Groneberg DA. Imatinib-associated pulmonary alveolar proteinosis *Am J Med*. 2003;115:674.
15. Kantarjian H, Sawyers C, Hochhaus A, et al. Hematologic and cytogenetic responses to imatinib mesylate in chronic myelogenous leukemia. *N Engl J Med.* 2002;346:645-652.
16. Ohnishi K, Sakai F, Kudoh S, Ohno R. Twenty-seven cases of drug-induced interstitial lung disease associated with imatinib mesylate. *Leukemia*. 2006;20:1162-1164.
17. Rossi SE, Erasmus JJ, McAdams HP, Sporn TA, Goodman PC. Pulmonary drug toxicity: radiologic and pathologic manifestations. *Radiographics*. 2000;20:1245-1259.
18.Sakai F, Noma S, Kurihara Y, et al. Leflunomide related lung injury in patients with rheumatoid arthritis: imaging features. *Modern Rheumatol*. 2005;15:173-179.
19. Liu V, White DA, Zakowski MF, et al. Pulmonary toxicity associated with erlotinib. Interstitial lung disease in patients with non-small-cell lung cancer treated with epidermal growth factor receptor inhibitors. *Chest*. 2007;132:1042-1044.
20. Makris D, Scherpereel A, Copin MC, et al. Fatal interstitial lung disease associated with oral erlotinib therapy for lung cancer. *BMC Cancer*. 2007;7:150.
21. Cohen MH, Johnson JR, Chen YF, Sridhara R, Pazdur R. FDA drug approval summary: erlotinib (Tarceva) tablets. *Oncologist*. 2005;10:461-466.
22. Vahid B, Esmaili A. Erlotinib-associated acute pneumonitis: report of two cases. *Can Respir J*. 2007;14:167-170.
23. Lind JS, Smit EF, Grünberg K, Senan S, Lagerwaard FJ. Fatal interstitial lung disease after erlotinib for non-small cell lung cancer. *J Thorac Oncol.* 2008;3:1050-1053.
24. 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;2:537-543
25. Bach JP, Kiessling AM, Kleinhans A, et al. Pulmonary fibrosis in a patient treated with erlotinib. *Onkologie*. 2006;29:342-343.
26. Tarceva [product information]. Genentech, South San Francisco, CA; 2004.
27. Boeck S, Hausmann A, Reibke R, Schulz C, Heinemann V. Severe lung and skin toxicity during treatment with gemcitabine and erlotinib for metastatic pancreatic cancer. *Anticancer Drugs*. 2007;18:1109-1111.
28. Kubota K, Nishiwaki Y, Tamura T, et al. Efficacy and safety of erlotinib monotherapy for Japanese patients with advanced non-small cell lung cancer: a phase II study. *J Thorac Oncol*. 2008;3:1439-1445.
29. Shepherd FA, Rodrigues Pereira J, et al. Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med*. 2005;353:123-132.
30. Tsuboi M, Le Chevalier T. Interstitial lung disease in patients with non-small-cell lung cancer treated with epidermal growth factor receptor inhibitors. *Med Oncol*. 2006;23:161-170.
31. Herbst RS, Prager D, Hermann R, et al. TRIBUTE: a phase III trial of erlotinib hydrochloride (OSI-774) combined with carboplatin and paclitaxel chemotherapy in advanced non-small-cell lung cancer. Interstitial lung disease in patients with non-small-cell lung cancer treated with epidermal growth factor receptor inhibitors. *J Clin Oncol*. 2005;23:5892-5899.
32. Tammaro KA, Baldwin PD, Lundberg AS. Interstitial lung disease following erlotinib (Tarceva) in a patient who previously tolerated gefitinib (Iressa). *J Oncol Pharm Pract*. 2005;11:127-130.
33. Dragovich T, Patnaik A, Rowinsky EK et al. A phase I B trial of gemcitabine and erlotinib HCL in patients with advanced pancreatic adenocarcinoma and other potentially responsive malignancies. *Proc Am Soc Clin Oncol.* 2003;22: Abstract 223.
34. Yamamoto N, Yamada Y, Shimoyama T, et al. A phase I study of erlotinib HCl in Japanese patients with various types of solid tumors. *Proc Am Soc Clin Oncol* 2003;22: Abstract 225.
35. Tan AR, Yang X, Berman A, et al. Evaluation of epidermal growth factor receptor signaling in tumor and skin biopsies after treatment with OSI-774 in patients with metastatic breast cancer. *Proc Am Soc Clin Oncol.* 2003;22:196.
36. Takano T, Ohe Y, Kusumoto M, et al. Risk factors for interstitial lung disease and predictive factors for tumor response in patients with advanced non-small cell lung cancer treated with gefitinib. *Lung Cancer*. 2004;45:93-104.
37. Kris MG, Sandler A, Miller V. Cigarette smoking history predicts sensitivty to erlotinib: results of a phase II trial in patients with bronchoalveolar carcinoma (BAC) . *Proc Am Soc Clin Oncol.* 2004;22: Abstract 7062.
38. Johnson BE, Lucca J, Rabin M. Preliminary results from a phase II study of the EGFR tyrosine kinase inhibitor erlotinib in patients >70 years of age with previously untreated advanced non-small cell lung carcinoma. *Proc Am Soc Clin Oncol.* 2004;22: Abstract 7080.
39. Dragovich T, Huberman M, Von Hoff DD, et al. Erlotinib plus gemcitabine in patients with unresectable pancreatic cancer and other solid tumors: phase IB trial. *Cancer Chemother Pharmacol*. 2007;60:295-303.
40. Mori M, Nakagawa M, Fujikawa T, et al. Simultaneous bilateral spontaneous pneumothorax observed during the administration of gefitinib for lung adenocarcinoma with multiple lung metastases. *Intern Med*. 2005;44:862-864.
41. Umemura S, Kishino D, Tabata M, et al. Systemic tumor embolism mimicking gefitinib ('IRESSA')-induced interstitial lung disease in a patient with lung cancer. *Intern Med*. 2005;44:979-982.
42. Shih YN, Chiu CH, Tsai CM, Perng RP. Interstitial pneumonia during gefitinib treatment of non-small-cell lung cancer. *J Chin Med Assoc*. 2005;68:183-186.
43. Ieki R, Saitoh E, Shibuya M. Acute lung injury as a possible adverse drug reaction related to gefitinib. *Eur Respir J*. 2003;22:179-181.
44. Seto T, Seki N, Uematsu K, et al. Gefitinib-induced lung injury successfully treated with high-dose corticosteroids. *Respirology*. 2006;11:113-116.
45. Sumpter K, Congleton J, Harper-Wynne C, O'Brien M. Severe acute interstitial pneumonia and gefitinib. *Lung Cancer*. 2004;43:367-368.
46. Rabinowits G, Herchenhorn D, Rabinowits M, Weatge D, Torres W. Fatal pulmonary toxicity in a patient treated with gefitinib for non-small cell lung cancer after previous hemolytic-uremic syndrome due to gemcitabine. *Anticancer Drugs*. 2003;14:665-668.
47. Ohyanagi F, Ando Y, Nagashima F, Narabayashi M, Sasaki Y. Acute gefitinib-induced pneumonitis. *Int J Clin Oncol*. 2004;9:406-409.
48. Müller NL, White DA, Jiang H, Gemma A. Diagnosis and management of drug-associated interstitial lung disease. *Br J Cancer*. 2004;91:S24-30. Review.
49. Camus P, Kudoh S, Ebina M. Interstitial lung disease associated with drug therapy. *Br J Cancer*. 2004;91:S18-23.
50. Inoue A, Saijo Y, Maemondo M, et al. Severe acute interstitial pneumonia and gefitinib. *Lancet*. 2003;361:137-139.
51. Park HS, Lee HJ, Im JG, et al. Gefitinib-induced pneumonitis in non-small cell lung cancer: radiological and clinical findings in five patients. *Clin Imaging*. 2007;31:306-312.
52. Cohen MH, Williams GA, Sridhara R, Chen G, Pazdur R. FDA drug approval summary: gefitinib (ZD1839) (Iressa) tablets. *Oncologist*. 2003;8:303-306.
53. Madtes DK, Rubenfeld G, Klima LD, et al. Elevated transforming growth factor-alpha levels in bronchoalveolar lavage fluid of patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 1998;158:424-430.
54. Madtes DK, Busby HK, Strandjord TP, Clark JG. Expression of transforming growth factor-alpha and epidermal growth factor receptor is increased following bleomycin-induced lung injury in rats. *Am J Respir Cell Mol Biol*. 1994;11:540-551.
55. Hardie WD, Prows DR, Piljan-Gentle A, et al. Dose-related protection from nickel-induced lung injury in transgenic mice expressing human transforming growth factor-alpha. *Am J Respir Cell Mol Biol*. 2002;26:430-437.
56. Hardie WD, Prows DR, Leikauf GD, Korfhagen TR. Attenuation of acute lung injury in transgenic mice expressing human transforming growth factor-alpha. *Am J Physiol*. 1999;77:L1045-1050.
57. Inomata S, Takahashi H, Nagata M, et al. Acute lung injury as an adverse event of gefitinib. *Anticancer Drugs*. 2004;15:461-467.
58. Kitajima H, Takahashi H, Harada K, et al. Gefitinib-induced interstitial lung disease showing improvement after cessation: disassociation of serum markers. *Respirology*. 2006;11:217-220.
59. Chiu CH, Tsai CM, Chen YM, Chiang SC, Liou JL, Perng RP. Gefitinib is active in patients with brain metastases from non-small cell lung cancer and response is related to skin toxicity. *Lung Cancer*. 2005;47:129-138.
60. Takano T, Ohe Y, Kusumoto M, et al. Risk factors for interstitial lung disease and predictive factors for tumor response in patients with advanced non-small cell lung cancer treated with gefitinib. *Lung Cancer.* 2004;45:93-104.
61. Kaneda H, Tamura K, Kurata T, Uejima H, Nakagawa K, Fukuoka M. Retrospective analysis of the predictive factors associated with the response and survival benefit of gefitinib in patients with advanced non-small-cell lung cancer. *Lung Cancer*. 2004;46:247-254.
62. Iressa [package insert]. AstraZeneca Pharmaceuticals. Wilmington, DE; November 2004.
63. Tarceva [package insert]. Genentech. South San Francisco, CA and OSI Pharmaceuticals, Melville, NY; 2004.

64. Nagaria NC, Cogswell J, Choe JK, Kasimis B. Side effects and good effects from new chemotherapeutic agents. Case 1. Gefitinib-induced interstitial fibrosis. *J Clin Oncol*. 2005;23:2423-2424.
65. Raghu G, Nyberg F, Morgan G. The epidemiology of interstitial lung disease and its association with lung cancer. *Br J Cancer*. 2004;91:S3-10. Review.
66. Hunninghake GW, Zimmerman MB, Schwartz DA, et al. Utility of a lung biopsy for the diagnosis of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med*. 2001;164:193-196.
67. 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;24:2549-2556.
68. Hotta K, Kiura K, Tabata M, et al. Interstitial lung disease in Japanese patients with non-small cell lung cancer receiving gefitinib: an analysis of risk factors and treatment outcomes in Okayama Lung Cancer Study Group. *Cancer J*. 2005;11:417-424.
69. Kudoh S, Kato H, Nishiwaki Y, et al. Interstitial lung disease in Japanese patients with lung cancer: a cohort and nested case-control study. *Am J Respir Crit Care Med*. 2008;177:1348-1357.
70. Armour A. Gefitinib in advanced non-small cell lung cancer: clinical experience in patients of Asian origin. *Asia Pac J Clin Oncol*. 2007;3:66-78.
71. Takano T, Ohe Y, Kusumoto M, et al. Risk factors for interstitial lung disease and predictive factors for tumor response in patients with advanced non-small cell lung cancer treated with gefitinib. *Lung Cancer*. 2004;45:93-104.
72. Kataoka K, Taniguchi H, Hasegawa Y, et al. Interstitial lung disease associated with gefitinib. *Respir Med*. 2006;100:698-704.
73. AstraZeneca. In-house data; result and discussion document concerning the prospective investigation on Iressa tablet 250 (special investigation). 2004.
74. Okamoto I, Fujii K, Matsumoto M, et al. Diffuse alveolar damage after ZD1839 therapy in a patient with non-small cell lung cancer. *Lung Cancer*. 2003;40:339-342.
75. Fukuoka M, Yano S, Giaccone G, et al. Multi-institutional randomized phase II trial of gefitinib for previously treated patients with advanced non–small-cell lung cancer. *J Clin Oncol*. 2003;21:2237-2246.
76. Herbst RS, Maddox AM, Rothenberg ML, et al. Selective oral epidermal growth factor receptor tyrosine kinase inhibitor ZD1839 is generally well-tolerated and has activity in non–small-cell lung cancer and other solid tumors: results of a phase I trial. *J Clin Oncol*. 2002;20:3815-3825.
77. Pallis AG, Mavroudis D, Androulakis N, et al. ZD1839, a novel, oral epidermal growth factor receptor-tyrosine kinase inhibitor, as salvage treatment in patients with advanced non-small cell lung cancer. Experience from a single center participating in a compassionate use program. *Lung Cancer*. 2003;40:301-317.
78. Forsythe B, Faulkner K. Safety and tolerability of gefitinib ('Iressa', ZD1839) in advanced NSCLC: overview of clinical experience Poster presented at: European Respiratory Society; September 27-October 1, 2003; Vienna, Austria. Poster number P327.