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

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Introduction: A rare but serious complication of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) therapy is a lung injury syndrome commonly referred to as a drug-induced interstitial lung disease (ILD). It has a typical clinical presentation of rapidly progressive acute or subacute dyspnea and a histopathology of diffuse alveolar damage (DAD). The incidence, severity, and risk factors for EGFR TKI-induced ILD remain poorly understood. Whether concurrent chemotherapy increases its risk is also unclear. The primary focus of this blinded review was to determine the incidence of ILD leading to death in 1059 TRIBUTE patients randomized to chemotherapy plus erlotinib or placebo.

Methods: All fatal serious adverse events (SAEs) were reviewed by an independent three-person panel composed of a medical oncologist, radiologist, and pulmonologist not associated with the study and without knowledge of treatment assignment. Fatal respiratory SAEs were identified and assigned to one of four potential attributions: progressive cancer, concurrent illness, drug-induced ILD, or other toxicities not related to ILD. Each panel member first made an independent assignment; then each case was discussed jointly. If needed, consensus was reached by vote.

Results: Fatal SAEs were reported in 80 of 1059 patients (7.6%); 53 of 526 patients on erlotinib (10.1%) and 27 of 533 on placebo (5.1%) (p < 0.05). Consensus assignation for 41 fatal respiratory SAEs was as follows: cancer, 18 (44%); concurrent illness, 15 (37%); other toxicities not related to ILD, five (12%); ILD, three (7%). All three ILD cases occurred in the erlotinib arm (3/526; 0.6%). The one biopsy-confirmed case of ILD revealed bronchiolitis obliterans organizing pneumonia, a histopathologic finding that has not previously been reported. All three cases of fatal ILD had a typical clinical presentation of acute or subacute onset of dyspnea with rapid progression to respiratory failure.

Conclusions: This independent blinded analysis of the TRIBUTE study identified fatal ILD in 0.6% of cases treated with the combination of erlotinib plus chemotherapy, possibly higher than previous reports of EGFR TKIs alone in the non-Japanese population. Fatal ILD alone does not fully account for the imbalance in fatal SAEs observed in TRIBUTE. EGFR TKI-induced fatal ILD typically presents with acute or subacute dyspnea with rapid progression and a typical histopathology of diffuse alveolar damage both consistent with the acute respiratory distress syndrome, but can also be associated with a histopathology of bronchiolitis obliterans organizing pneumonia. Further studies designed to better understand the underlying pathophysiology and risk factors for ILD are needed.

Key Words: Erlotinib, Tarceva, Epidermal growth factor receptor, tyrosine kinase inhibitor, non-small cell lung cancer, interstitial lung disease, acute respiratory distress syndrome, TRIBUTE.
concurrent chemotherapy, the TRIBUTE study was independently reviewed.

Lung cancer is the leading cause of cancer death in the United States, where it accounts for more deaths than colon, breast, and prostate cancer combined. Although recent improvements in chemotherapy for advanced stage NSCLC are well documented, the survival impact of this therapeutic approach remains limited, and chemotherapy is still associated with considerable side effects. Therefore, novel approaches to the treatment of NSCLC are the focus of intense basic science and clinical research interest. Recent advances in understanding the underlying molecular biology of lung cancer have facilitated development of new therapies directed against gene targets important in NSCLC growth and survival pathways. For example, EGFR, a member of the HER or Erb-B family of receptor TKs, is implicated in the development and progression of cancer and is expressed in many human malignancies, including NSCLC. Small molecule TKIs of EGFR, such as gefitinib (Iressa, AstraZeneca, London, UK) and erlotinib (Tarceva) have demonstrated antitumor activity against NSCLC in preclinical models and response rates of 9% to 26% in patients failing initial chemotherapy. Moreover, a recent phase III trial (BR21) comparing erlotinib with placebo as second- or third-line therapy reported a survival benefit for the EGFR TKI. Conversely, ISEL, a placebo controlled phase III trial for refractory NSCLC, failed to demonstrate a survival advantage for gefitinib, and phase III trials of chemotherapy with or without concurrent gefitinib (INTACT 1 and INTACT 2) or erlotinib (TRIBUTE and TALENT) showed no benefit in response rate or survival with the addition of the EGFR TKIs and in fact suggest a negative interaction.

Although generally well tolerated, EGFR TKIs have been associated with the development of severe or fatal ILD. EGFR TKI-induced ILD presents at approximately 24 and 42 days after starting gefitinib in Japanese and the non-Japanese populations, respectively, and approximately 47 days after starting erlotinib. It is characterized by the acute or subacute onset of dyspnea with or without cough or low-grade fever, rapid progression requiring hospitalization, and often respiratory failure requiring mechanical ventilation. Chest radiographs and high-resolution computed tomography (CT) reveal bilateral opacifications, often resembling acute interstitial pneumonitis, but the radiographic findings are variable and nonspecific. Although referred to as an ILD syndrome, the histopathology has been incompletely characterized, revealing diffuse alveolar damage, consistent with the acute respiratory distress syndrome (ARDS). Nevertheless, pathologic confirmation is rarely obtained, and the syndrome has been characterized mainly on clinical grounds.

Whether the two EGFR TKIs differ in the propensity to induce ILD is unclear. Furthermore, whether concurrent chemotherapy increases toxicities such as ILD has not been specifically assessed. In this regard, in TRIBUTE, more serious adverse events (SAEs) leading to death were reported in patients on the erlotinib arm. Such events were experienced by 53 of 526 patients in the erlotinib arm (10.1%) and 27 of 533 patients in the placebo arm (5.1%), \( p < 0.05 \).

In light of the imbalance in fatal SAEs observed in the TRIBUTE study (with fatal ILD as a potential explanation), a blinded review of SAEs leading to death in TRIBUTE was performed. An independent three-person panel, the TRIBUTE review committee (TRC) focused this review on fatal respiratory SAEs. Fatal respiratory SAEs were attributed to the following categories: ILD, progression of underlying NSCLC, concurrent illness, or other toxicities not related to ILD. The primary focus of this study was to determine the incidence of fatal ILD in patients treated for NSCLC with chemotherapy plus erlotinib or placebo and to estimate whether chemotherapy increased the risk of erlotinib-induced ILD.

**METHODS**

Details of the TRIBUTE study are as previously described. Adverse events had been previously coded by the original TRIBUTE investigators using the Medical Dictionary for Regulatory Activities (MedDRA), Version 6.0. Event severity was graded using the National Cancer Institute–Common Toxicity Criteria (NCI-CTC), Version 2.0. All cases that had been previously coded as fatal SAEs by the TRIBUTE investigators were forwarded to the TRC. The TRC consisted of three physicians (a medical oncologist, a pulmonologist, and a thoracic radiologist) not associated with TRIBUTE.

For the current analysis, all fatal SAEs from both study arms of TRIBUTE were reviewed. Fatal SAEs that had been coded by the original TRIBUTE investigators to the MedDRA system organ class (SOC) as respiratory were classified as respiratory-related fatal SAEs and identified for further review by the TRC. Additionally, fatal SAEs coded by the TRIBUTE investigators as being associated with pneumonia (which appears in the MedDRA SOC of Infections and infestations) and neoplasm were also classified as respiratory-related fatal SAEs and identified for further review by the TRC. All other fatal SAEs deemed not related to a respiratory event were not subject to further review by the TRC.

The three TRC members, blinded to study arm and whether patients under review had been randomized to erlotinib or placebo, independently assessed and assigned causality for each case of fatal SAE under investigation, using the case report forms and source documents available to the original TRIBUTE investigators. Baseline patient characteristics in regards to preexisting ILD, asbestos exposure, and pulmonary function tests were not specifically recorded as a part of the study protocol but were noted as available from the source documents. Fatal SAEs were first categorized as due to either progression of NSCLC or to an unexpected SAE. The unexpected fatal SAEs were then subclassified as due to either ILD possibly/probably related to study drug, concurrent illness, or other toxicities not thought to be related to ILD. For the assignment of ILD, four specific findings were required: (1) progressive dyspnea with or without cough or fever, (2) lack of evidence of infection, (3) radiographic findings consistent with drug-induced ILD (i.e., bilateral, diffuse, or patchy interstitial and/or alveolar opacifications without evidence of marked progression of underlying lung...
cancer), and (4) consistent pathologic findings if available. These criteria were designed with the intention of being more specific than sensitive for identifying a drug-induced phenomenon. After individual assessment by each TRC member, the team then met to determine consensus assignations. Where there was not initial unanimous consensus, the TRC revisited the case as a group to formalize consensus. When deemed necessary, additional information such as additional radiographs, laboratory data, and medical records were requested. If a unanimous consensus assignation was not reached after completion of this process, the final determination of causality was based on a majority vote.

RESULTS

Of a total of 80 fatal SAEs, 22 were respiratory as coded according to the MedDRA SOC and were identified for TRC review. Additionally, 12 fatal SAEs associated with pneumonia and seven cases attributed to neoplasm were identified for additional review. In total, there were 41 cases identified as SAEs potentially due to respiratory events. Nonrespiratory fatal SAEs not subject to further review consisted of acute myocardial infarction \((n = 7)\), acute cardiac or cardiopulmonary arrest \((n = 5)\), cerebral vascular accident \((n = 4)\), sepsis or septic shock \((n = 4)\), dehydration \((n = 2)\), asthenia \((n = 2)\), intestinal perforation \((n = 2)\), arrhythmia \((n = 2)\), intestinal ischemia \((n = 1)\), deep vein thrombosis \((n = 1)\), cardiac tamponade \((n = 1)\), pericardial effusion \((n = 1)\), congestive heart failure \((n = 1)\), superior vena cava occlusion \((n = 1)\), gastrointestinal hemorrhage \((n = 1)\), diarrhea \((n = 1)\), thrombocytopenia \((n = 1)\), aortic aneurysm rupture \((n = 1)\), and mental status change \((n = 1)\).

Of 41 respiratory fatal SAEs reviewed (Figure 1), by consensus assignation, 18 were definitively attributed to progression of NSCLC, leaving 23 unexpected SAEs. Of the 23 unexpected SAEs, 15 were definitively attributed to concurrent illness (e.g., progression of a preexisting disorder) and five to toxicity other than ILD (e.g., neutropenia with sepsis). In one of the 15 cases of concurrent illness, the TRC believed the fatal SAE to be due to progression of bronchiolitis obliterans organizing pneumonia (BOOP) with fibrosis, but not attributable to study drug as the patient had biopsy-proven BOOP and fibrosis with symptomatic and radiographic progression requiring escalating doses of systemic corticosteroids just before beginning study drug. In three cases, the investigators determined that the fatal SAE was due to ILD and possibly/probably related to study drug. With unblinding, it was apparent that all three cases of fatal ILD occurred in the erlotinib arm. There were no cases of fatal ILD identified in the chemotherapy alone arm. These results represent a rate of fatal ILD of 0.6% \((3/526)\) in association with the use of erlotinib and concurrent chemotherapy in this trial.

The three cases of ILD attributed to study drug are briefly presented below and summarized in Table 1. After review of the chest CT scans and other source documents by the TRC, the consensus was that the findings in each case were most consistent with ILD and not with progressive cancer or infection.

Case 1

The patient was a 56-year-old African American male, active smoker, with stage IV adenocarcinoma. Thirteen days after beginning study drug at 100 mg, chest radiography and CT scan performed to evaluate increasing dyspnea revealed new extensive interstitial infiltrates throughout the majority of the right lung and mild interstitial infiltrates at the left base. He was treated with intravenous corticosteroids and intravenous antibiotics empirically for an exacerbation of underlying chronic obstructive pulmonary disease (COPD) and infection. A bronchoscopy with bronchoalveolar lavage (BAL) was negative for pathogens. Twenty-eight days after beginning study drug and while continuously maintained on intravenous corticosteroids, the dose was increased to 150 mg, per protocol specifications. Twenty-nine days after starting study drug, a repeat CT scan noted extensive bilateral interstitial and alveolar infiltrates. Forty days after beginning study drug, the patient died and the original TRIBUTE investigator had reported his death as due to progressive NSCLC. Neither lung biopsy nor autopsy was performed.

Case 2

The patient was a 70-year-old white woman, former smoker, with bronchioalveolar cell lung cancer. Serial chest CT scans while on study revealed a progressive bilateral alveolar filling process consistent with either bronchioalveolar carcinoma or pneumonitis; 124 days after beginning study drug, a repeat CT scan noted extensive bilateral interstitial and alveolar infiltrates. Forty days after beginning study drug, the patient died and the original TRIBUTE investigator had reported his death as due to progressive NSCLC. Neither lung biopsy nor autopsy was performed.
**Case 3**

The patient was a 43-year-old African American woman, recent ex-smoker, with stage IIIB NSCLC with a right-sided malignant pleural effusion. Before starting on study drug, she was noted to have right-sided lung nodules and ground-glass opacifications in the left upper and lower lobes. Five days after starting study drug, the patient was hospitalized with hypoxemia, dyspnea, fever, chest pain, and a worsening chest CT. There was no improvement with empirical intravenous antibiotics. Bronchoscopy with BAL was negative for pathogens. With progressive decline, 20 days after starting study drug, a surgical biopsy revealed BOOP without evidence of infection. Study drug was discontinued at day 23 and high-dose systemic corticosteroids were started. The patient had symptomatic improvement and was discharged home on oxygen on day 36, but was rehospitalized with increasing dyspnea. With progressive respiratory failure, she was placed under hospice care and died on day 51.

**DISCUSSION**

The EGFR TKIs erlotinib and gefitinib are active anticancer agents in the treatment of patients with NSCLC and are generally well tolerated. In the recent BR21 trial, erlotinib improved survival compared with placebo in chemotherapy-pretreated patients with advanced stage NSCLC. Although ISEL, a similar trial with gefitinib, failed to demonstrate a survival advantage, subgroup analysis of this study suggested a survival benefit for never smokers and Asian patients who received gefitinib. Conversely, four large phase III trials in

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**TABLE 1. Characteristics of the Three Patients with ILD Attributed to Study Drug**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Race/Ethnicity</th>
<th>Smoking Status</th>
<th>NSCLC Subtype</th>
<th>Stage</th>
<th>Results of CT Scan</th>
<th>Clinical Symptoms</th>
<th>No. of Days in Study at Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>56</td>
<td>African American</td>
<td>Active</td>
<td>Adenoca</td>
<td>IV</td>
<td>ILD with mixed interstitial and airspace opacities</td>
<td>Increasing dyspnea</td>
<td>40</td>
</tr>
<tr>
<td>2</td>
<td>70</td>
<td>White</td>
<td>Former smoker</td>
<td>BAC</td>
<td>IV</td>
<td>Progressive alveolar filling</td>
<td>Fever, dyspnea</td>
<td>128</td>
</tr>
<tr>
<td>3</td>
<td>43</td>
<td>African American</td>
<td>Recent ex-smoker</td>
<td>NSCLC</td>
<td>IIIB (pleural effusion)</td>
<td>ILD</td>
<td>Hypoxemia, dyspnea, chest pain</td>
<td>51</td>
</tr>
</tbody>
</table>

Adenoca, adenocarcinoma; BAC, bronchioloalveolar carcinoma; CT, computed tomography; ILD, interstitial lung disease; NSCLC, non-small cell lung cancer.

**FIGURE 2.** (A) Chest radiograph at baseline (case 2). (B) Chest radiograph at the time of respiratory decompensation. (C) Computed tomography scan at the time of respiratory decompensation (case 2).
the first-line therapy of advanced NSCLC comparing chemotherapy alone to the concurrent administration with either gefitinib or erlotinib showed no advantage for the combination and in fact suggest a negative interaction.\(^9\)\(^–\)\(^12\)\(^,\)\(^18\) Possible explanations for these negative results include failure to select for an EGFR-targeted population, a negative interaction between EGFR TKIs and chemotherapy, and additive toxicities.\(^19\) An increased incidence of fatal SAEs in TRIBUTE for patients in the combination arm is particularly concerning for additive toxicities as a cause of increased mortality. In this review, we focused on fatal ILD as a potential cause of the imbalance in fatal SAEs observed in TRIBUTE.

EGFR TKI-induced ILD has been most extensively described in regards to gefitinib. In two different randomized phase II trials, ILD was reported in 0.47% (2/425) of patients, with both cases occurring at the 500-mg dose.\(^4\)\(^,\)\(^5\) In INTACT 1 and INTACT 2 combining gefitinib with standard first-line chemotherapy for advanced NSCLC, ILD was reported in 0.86% of patients receiving placebo, 1.14% of patients receiving 250 mg gefitinib, and 1.14% of patients receiving 500 mg gefitinib.\(^9\)\(^,\)\(^10\) A report by the U.S. Food and Drug Administration of 50,005 patients receiving gefitinib (18,960 from Japan and 23,000 from the United States) revealed an overall incidence of ILD of approximately 1%. Interestingly, in Japanese patients, the incidence was 1.7%, whereas in U.S. patients, it was 0.3%. The median time to onset of ILD was 24 days in Japan and 42 days in the United States. Approximately one third of cases were fatal.\(^14\) A safety report by AstraZeneca, the makers of gefitinib, on approximately 185,000 patients revealed similar findings.\(^8\) The ISEL trial revealed a higher incidence of ILD in Japanese patients compared with non-Japanese patients (3%–4% versus 1%).\(^8\) Most recently, the West Japan Thoracic Oncology Group convened an expert panel review of 1976 consecutive patients treated with gefitinib, specifically focusing on the development of ILD. They found an incidence of 3.5% with an attributed mortality of 1.6%. Male sex, a smoking history, and concurrent interstitial pneumonia were identified as independent risk factors for the development of ILD.\(^21\)

The incidence of ILD associated with erlotinib is less well defined. Limited data from phase I clinical trials with a total of 157 patients reported no recognized cases of ILD, but one patient reportedly died of undefined lung toxicity.\(^6\)\(^,\)\(^22\)\(^,\)\(^23\) 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.\(^7\) The recently published TRIBUTE trial reported a 1% (5/526) incidence of ILD in the erlotinib plus chemotherapy arm and a 0.2% (1/533) incidence in the placebo plus chemotherapy arm. All reported cases of ILD were fatal. However, reports of ILD were based on case reporting of adverse events and not systematically verified by an independent blinded panel as in our review of these data.\(^11\)

Establishing a diagnosis of ILD is often difficult and is particularly challenging in the absence of a confirmatory surgical lung biopsy. Even with a surgical lung biopsy, assigning causality remains a difficult challenge. Chemotherapy and radiotherapy, either alone or in combination, have been associated with the development of ILD. Of reported cases of ILD in association with gefitinib use, 31% of patients had received previous radiation therapy and 57% had received previous chemotherapy.\(^14\) In INTACT 1 and 2 combined, the overall incidence of ILD was 1.14% with gefitinib plus chemotherapy. In addition, infections, medications, and other environmental exposures can mimic ILD or potentially increase the susceptibility to ILD. As demonstrated in the current analysis, it may sometimes be difficult to distinguish progressive cancer, particularly of the bronchioloalveolar subtype, from EGFR TKI-induced ILD. Accordingly, in this study, particular care was taken in assigning a diagnosis of ILD. All suspected cases of fatal ILD were meticulously reviewed by an independent expert panel consisting of a medical oncologist, a pulmonologist, and a thoracic radiologist, who performed a thorough and detailed review of the clinical history and radiographic findings.

Our study focused on identifying fatal cases of ILD, derived as a subset of fatal SAEs identified in TRIBUTE. If ILD due to erlotinib is fatal in approximately one third of cases, as previously described for gefitinib, then we estimate that the overall incidence of ILD was approximately 1.8% in patients receiving the combination of chemotherapy plus erlotinib in TRIBUTE. Unfortunately, the retrospective nature of this analysis, the variability in radiographic presentation, and the paucity of pathologic confirmation confound our ability to draw firm conclusions. Underscoring these uncertainties, it is reported that findings on CT scanning correlate with histopathology in less than 60% of cases of drug-induced ILD.\(^24\) Of interest is one patient in our study (classified as concurrent illness and not ILD) who had biopsy-proven ILD before enrolling in TRIBUTE and who developed worsening and eventually fatal ILD in the erlotinib-chemotherapy arm. As described above, the West Japan Thoracic Oncology Group reported concurrent interstitial pneumonia as a risk factor for the development of gefitinib-induced ILD. In addition, among a case series of 110 patients treated with gefitinib in Japan were nine patients with preexisting pulmonary fibrosis. Five of the nine patients developed acute lung injury during treatment, and of those, three died.\(^13\) A retrospective analysis of 12 patients with gefitinib-induced ILD and preexisting idiopathic pulmonary fibrosis also suggests a high mortality rate of 58%.\(^16\)

Although a variety of medications and chemotherapeutic agents have been implicated in the development of ILD, EGFR TKI–induced ILD may represent a unique clinical syndrome. ILD attributed to EGFR TKIs has been described as an acute lung injury syndrome (ALI), an acute respiratory distress syndrome (ARDS), pneumonitis, interstitial pneumonia, interstitial fibrosis, drug-induced pulmonary toxicity, and alveolar hemorrhage, but the clinical presentations are invariably similar. Typical pulmonary symptoms are acute onset of dyspnea with or without cough or low-grade fever, followed by a rapid worsening of symptoms invariably requiring hospitalization.\(^14\) In a retrospective analysis of gefitinib-induced
inflammatory response syndrome. In addition, the West ALI/ARDS associated with the broadly defined systemic manifestations of EGFR TKI–induced ILD are very similar to from our case of BOOP, the lung histology, and the clinical manifestations of EGFR TKI–induced ILD are very similar to ALI/ARDS associated with the broadly defined systemic inflammatory response syndrome. In addition, the West Japan Thoracic Oncology Group has described four different patterns of gefitinib-induced ILD including nonspecific ground-glass attenuation (47% of cases), extensive bilateral ground-glass attenuation or airspace consolidations with trac-tbronchiectasis (24%), multifocal airspace consolidations (14%), and patchy distribution of ground-glass attenuation with interlobar septal thickening (2%), all of which are consistent with radiographic patterns of ARDS.

Treatment of EGFR TKI–induced ILD is largely supportive, including supplemental oxygen, empirical antibiot-ics, and mechanical ventilation. Immediate discontinuation of the drug is recommended and systemic corticosteroids are usually prescribed, although no controlled trials have been conducted to evaluate their benefit. Approximately one third of the patients with EGFR TKI–induced ILD die. The clinical course, radiographic findings, lung pathology, and mortality of EGFR TKI–induced ILD is most consistent with ALI/ ARDS and with the exception of empirical corticosteroids, the treatment is identical. EGFR TKI–induced ILD should therefore be considered in the differential diagnosis as a potential cause of ARDS in any patient who is on an EGFR TKI who presents with acute or subacute dyspnea.

CONCLUSION

In this blinded review of the TRIBUTE trial, the incidence of fatal ILD in association with the administration of erlotinib and concurrent paclitaxel and carboplatin was determined to be 0.6%, with an overall incidence estimated at approximately 1.8%. Given the uncertainties in diagnosing and assigning causality to ILD, these results may be higher than those previously reported in association with gefitinib alone in the non-Japanese population. The possibility of a synergistic effect between chemotherapy and EGFR TKIs in the development of ILD cannot be ruled out. The histopatho-logic finding in EGFR TKI–induced ILD is invariably DAD, although we report a case with BOOP. Patients receiving EGFR TKIs, particularly those with preexisting pulmonary fibrosis or a diagnosis of underlying ILD, should be moni-tored closely for development or worsening of ILD. EGFR TKI–induced ILD has a high associated mortality, and when it is suspected, the drug should immediately be withdrawn, hospitalization and systemic corticosteroids considered, and infection ruled out. EGFR TKI–induced ILD should be con-sidered as a potential cause of ALI/ARDS and the manage-ment of these patients should therefore be consistent with contemporary ALI/ARDS management.

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