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Imaging of gefitinib-related interstitial lung disease: Multi-institutional analysis by the West Japan Thoracic Oncology Group

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Summary Gefitinib (Iressa™) is an epidermal growth factor receptor tyrosine kinase inhibitor that has been approved for the treatment of lung cancer in Japan, however, after marketing several cases of severe pulmonary toxicity were reported. The West Japan Thoracic Oncology Group conducted an independent survey of acute pulmonary toxicity and interstitial lung disease (ILD) caused by gefitinib in its member's institutions. The purpose of this study was to clarify the image characteristics of ILD caused by the molecular-targeting drug gefitinib. A total of 1976 patients had been treated with gefitinib between August and December 2002, and 102 of them were suspected of having acute pulmonary toxicity and ILD. A final definite diagnosis of gefitinib-induced ILD was made by at least three radiologists based on a review and analysis of the chest radiography and CT findings plus the clinical data in the medical records. The imaging findings were classified into four patterns: (A) a nonspecific area with ground-glass attenuation, (B) a multifocal area of airspace consolidations, (C) patchy distribution of ground-glass attenuation accompanied by interlobar septal thickening, and (D) extensive bilateral ground-glass attenuation or airspace consolidations with traction bronchiectasis. CT as well as chest radiography had been performed in 65 of the 102 patients at the onset of ILD, and chest radiography alone had been performed in 26. After excluding 11 cases with insufficient data and 21 cases

Abbreviations: AEP, acute eosinophilic pneumonia; AIP, acute interstitial pneumonia; BOOP, bronchiolitis obliterans organizing pneumonia; CT, computed tomography; DAD, diffuse alveolar damage; EGFR, epidermal growth factor receptor; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; WJTOG, West Japan Thoracic Oncology Group

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concluded to be other pulmonary diseases, 70 patients were diagnosed with gefitinib-induced ILD. Finally, the diagnostic image findings were classified as pattern A in 29 cases, pattern B in 7 cases, pattern C in 3 cases, pattern D in 20 cases and others in 11 cases. The CT images were classified as pattern A, B, C, and D in 24, 7, 1, and 12 cases, respectively. The mortality rate was significantly higher in the patients with pattern D than the other patterns. Pattern D were thought to represent the features of diffuse alveolar damage. In conclusion, the molecular-targeting drug gefitinib induces pulmonary toxicity at a certain rate and the imaging findings of ILD induced by gefitinib are similar to those of pulmonary toxicity induced by conventional antineoplastic agents.

1. Introduction

Lung cancer is the leading cause of cancer deaths among both females and males in Japan and worldwide. The epidermal growth factor receptor tyrosine kinase inhibitor gefitinib (Iressa™) was recently approved in Japan for the treatment of recurrent non-small cell lung cancer, before being approved in the United States. Clinical trials have revealed significant variability in response to gefitinib, showed higher response rate in Japanese patients than in a predominantly European-derived population (27.5% versus 10.4%, respectively in a multi-institutional phase II trial) [1]. The good responders in Japan were women, patients with adenocarcinoma, and non-smokers. Adverse drug reactions in the pre-approved trials were frequent, but mild, and included an acne-like skin rash and diarrhea. However, some cases of gefitinib-related life-threatening interstitial lung disease (ILD) have been reported since the marketing of the drug [2—6], and the incidence of ILD was considered higher than that of ILD caused by pre-existing anticancer drugs. Based on these considerations, the West Japan Thoracic Oncology Group (WJTOG) independently investigated the incidence of acute pulmonary toxicity and ILD, the risk factors for their development, and the outcome. The radiological diagnosis of acute pulmonary toxicity and ILD in that survey was made by the participating radiologists. The purpose of this study was to clarify the characteristics of pulmonary toxicity induced by the molecular-targeting drug gefitinib based on an analysis of diagnostic images alone.

2. Materials and methods

We observed the guidelines for the retrospective epidemiological analysis in Japan using encoded data of patients in order to survey the incidence and risk factors of gefitinib-related ILD, and the survey by the WJTOG was approved by the review board of each institution.

2.1. Patients

The chest computed tomography (CT) scans and chest radiographs obtained in the 102 patients with suspected gefitinib-related ILD were retrospectively reviewed. The patients were identified as follows.

We requested to examine the number of patients who had begun to receive gefitinib between August 31, 2002 (when the drug was put on the National Health Insurance Drug List) and December 31, 2002, and the number of patients who were suspected of acute pulmonary toxicity and ILD to the 112 centers that were members of the WJTOG at the end of December 2002, and responses were obtained from 84 centers. A total of 1976 patients had been treated with gefitinib, and 102 of them were suspected of having acute pulmonary toxicity and ILD. In addition, a thorough clinical history and record of the patients and their chest radiography and CT scans taken about 1 month before the onset of ILD, at the onset, and serially after the onset, were obtained from each institution. Chest radiography and CT scans taken about 1 month before the onset were obtained for 97 and 92 patients, respectively, and chest radiography and CT scans taken at the onset were obtained for 92 and 65 patients, respectively. Serial chest radiography and CT scans after the onset were obtained for 89 and 32 patients, respectively. The patients consisted of 15 females and 87 males, and their mean age was 67 years (range, 38—90 years). All patients had non-small cell lung cancer including adenocarcinoma in 69 patients, squamous cell carcinoma in 27 patients, large cell carcinoma in 2 patients, and others in 4 patients. No patients had undergone lung biopsy and/or bronchoalveolar lavage to diagnose ILD.

2.2. Radiography and CT scanning methods

The chest radiographs obtained were the original films taken at each institution and included conventional films and computed radiographs. The CT scans were performed with a CT unit at each institution. All CT scans were obtained with 5—10 mm collimation at 5—10 mm intervals and with the patient in the supine position and at maximal inspiration. In 40 cases thin-section CT was performed with 1—2 mm collimation at 10 mm intervals at the onset of ILD. Scanning extended from the apices of lungs to the costophrenic angles. Thin-section CT images were reconstructed with a high-spatial-frequency algorithm. CT scans were obtained with window settings for lung parenchyma (window width, 1600—1800 HU; window level, −600 to −700 HU) and mediastinum (window width, 300—350 HU; window level, 25—40 HU).

2.3. Image analysis

The chest radiography and CT images were reviewed by at least three chest radiologists together, and final decisions regarding the findings were made by consensus, in conference with pulmonary physicians and medical oncologists. Gefitinib-related ILD was defined as an acute respiratory disorder that developed during gefitinib therapy in which ILD