—Review—

# Drug-Induced Interstitial Lung Diseases Associated with Molecular-Targeted Anticancer Agents

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**Abstract**

Little was known about drug-induced interstitial lung disease (ILD) when acute ILD-type events developed in several Japanese patients treated with gefitinib. A better understanding of drug-induced ILD is required, including more reliable data about the incidence of events associated with different treatments and identification of the risk factors for this type of ILD. Recent advances in imaging, molecular examination, and pathology have been used in postmarketing surveillance studies designed and conducted by an independent academic team to define the risk and to increase the amount of evidence about ILD related to various molecularly targeted anticancer agents. These studies may shed light on the underlying mechanisms of drug-induced ILD and appropriate evidence-based strategies that can be used to prevent or manage these events.
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**Key words:** anticancer agents, molecular target, interstitial lung disease

## Introduction

The development of molecularly targeted agents has been a key factor in recent advances in cancer therapy, and some of these agents are now considered standard therapies for various types of carcinoma. The toxicity of many of these agents is different from that of other kinds of antitumor agents. In Japan, cases of lung diseases presumably induced by gefitinib (Irresa®) have provided important findings, including evidence about racial differences in the adverse reactions and pathological variety of the lung diseases, as well as enhanced understanding of the diseases. Recently, a surveillance system has been established for detailed analysis of these adverse events in Japan. In this paper, I would like to present an outline of drug-induced lung diseases based on the current situation involving the development of molecularly targeted agents. The present status of new agents and measures for monitoring adverse events are also discussed.

## Present Status of Lung Diseases Induced by Molecularly Targeted Anticancer Agents in Japan

Because information about drug-induced lung disease was obtained mainly from clinical trial reports submitted to regulatory agencies and

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spontaneous reporting of adverse events by health professionals, it was difficult to accurately determine the number of affected persons in the general population. Thus, it is questionable how to interpret the study results and other reported data as they were presented. In Japan, however, the quality of information on drug-induced lung diseases has drastically changed after public attention was heightened by media coverage related to lung diseases apparently caused by molecularly targeted agents, such as gefitinib and imatinib. As a result, a surveillance system has been established to collect sufficient information on lung diseases associated with drugs, mainly new drugs and frequently prescribed drugs, and the system provides objective analysis of these adverse reactions. With the establishment of this system, we have entered a new era in which the manifestations of drug-induced lung diseases can be examined in detail using up-to-date image analysis techniques, laboratory data, pathological classification, and molecular biological techniques[1–3]. In this enhanced research environment, detailed studies are underway to assess data on recently developed molecularly targeted agents. The current status of these studies is reviewed in this article. The outline of the diagnosis and treatment of drug-induced lung diseases have been reviewed in other articles[4,5].

**1. Gefitinib**

Gefitinib is an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor extensively used for the treatment of non-small-cell lung cancer (NSCLC), and lung diseases thought to be caused by this drug attracted public attention, as mentioned above. A large-scale prospective case-control study of risk factors and relative risks of acute lung diseases/ interstitial pneumonia was performed in a cohort of patients with NSCLC who had or had not been treated with gefitinib[3]. The study had two main objectives: 1) estimation of the relative risk of acute lung diseases/interstitial pneumonia in patients with progressive/recurrent NSCLC treated with gefitinib compared with the risk of patients treated with other chemotherapeutic agents, and analysis of the risk factors for the development of treatment-induced interstitial lung disease (ILD); and 2) estimation of the incidence of ILD during the treatment of patients with advanced/recurrent NSCLC. The cohort comprised 3,159 analyzed patients; ILD developed in 59 (3.98%) of the 1,482 patients treated with gefitinib and in 35 (2.09%) of the 1,677 patients treated with other chemotherapeutic agents. The risk factors identified were: 1) treatment with gefitinib, 2) history of smoking, 3) pre-existing interstitial pneumonia, 4) time between the first diagnosis of NSCLC and development of ILD $\geq$6 months, 5) performance status $\geq$2, 6) reduced normal lung ($\leq$50%), 7) age $\geq$ 55 years, and 8) complications of cardiovascular disease. The adjusted overall odds ratio for gefitinib versus chemotherapy was 3.23, and the risk of ILD was particularly elevated (3.8 times higher) 4 weeks after the start of treatment. The mortality rates were 31.6% and 27.9% in gefitinib-treated patients and other patients, respectively. The following risk factors were identified by logistic regression analysis to be most commonly associated with a poor prognosis: 1) age $\geq$65 years, 2) smoking habit, 3) pre-existing interstitial pneumonia, 4) reduced normal lung $\leq$50%, and 5) extensive area adherent to pleura $\geq$50%. It is extremely important that accurate information has now been obtained on the incidence of ILD and factors relating to the development of drug-induced lung diseases in this large-scale prospective study[3].

**2. Erlotinib**

Like gefitinib, erlotinib is a molecularly targeted agent that inhibits EGFR tyrosine kinase. In large-scale international phase III studies of erlotinib, the incidence of severe drug-induced lung disease has not been high. In one study of the effects of erlotinib used in combination with gemcitabine, the incidence of drug-induced lung diseases was 2.5%. In a clinical study in Japan, however, ILD-like events were observed in 6 (4.8%) of 126 patients, and 3 patients (2.4%) died[6]. Because patients with pre-existing interstitial pneumonia developed ILD and died in a phase I study, the phase II study excluded patients with pre-existing interstitial pneumonia. Patients in whom an ILD-like adverse event occurred during

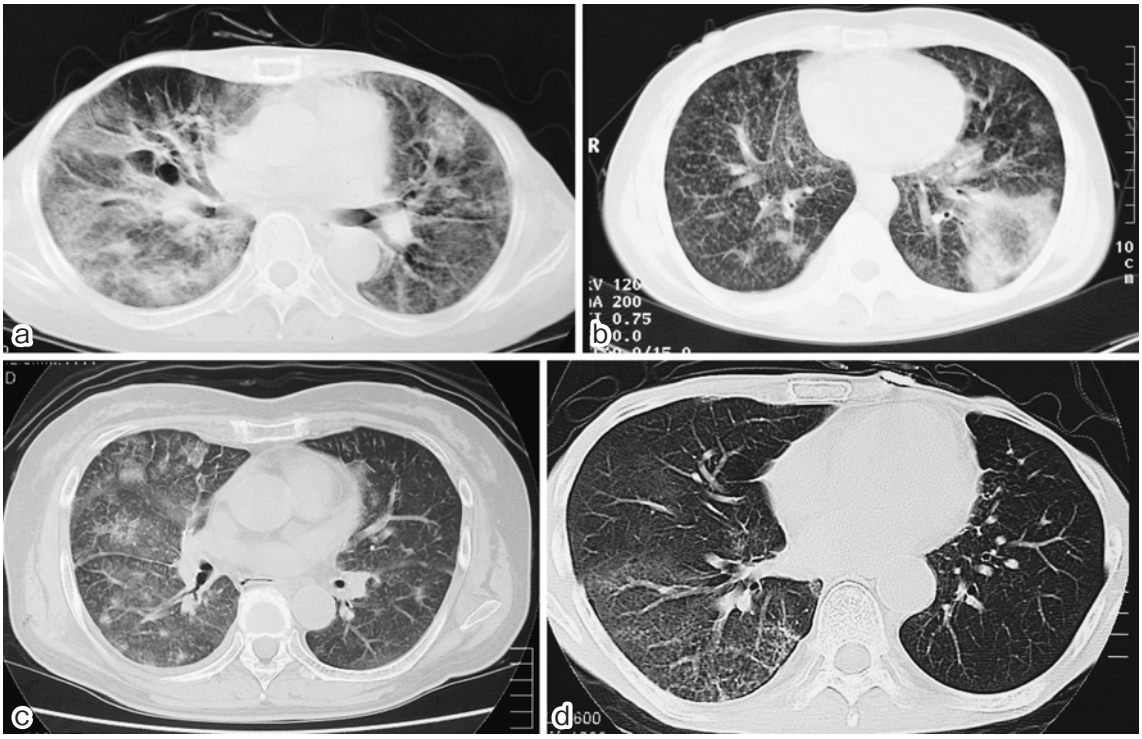


Fig. 1 **a**: Acute interstitial pneumonia/acute respiratory distress syndrome-type findings. Patchy or diffuse infiltrate shadows in both lungs and ground-glass opacity with structural distortion, such as traction bronchiectasis[1]. **b**: Organizing pneumonia/chronic eosinophilic pneumonia-type findings. Peripherally dominant infiltrate shadows in image with lung window setting[1]. **c**: Acute eosinophilic pneumonia-type findings. Coexistence of patchy or diffuse ground-glass opacity and invasive shadows in image with bilateral lung windows, often distributing multilobularly and associated with thickening of the interlobular septum and rare structural distortion, such as traction bronchiectasis[1]. **d**: Faint ground-glass opacity. Faint ground-glass opacity in image with bilateral lung windows, without reduction in lung volume or traction bronchiectasis[1].

the study were evaluated by a third-party assessment committee. One case was judged as an exacerbation of radiation pneumonitis, considered unlikely to be an ILD adverse event. The sample size of this study was small, so further accumulation of information is necessary. However, because this study included many patients with risk factors for drug-induced lung diseases identified in the aforementioned study of gefitinib[3], patient selection for treatment with erlotinib should take into account the above findings about gefitinib.

There may be racial differences in the incidence of drug-induced lung diseases. In addition, the incidence of events in different groups is too low to be determined conclusively during the drug-development stage. For drugs exhibiting a risk of these types of adverse events, to assure the drug's safety it is important to establish a system for collecting postmarketing information. Currently, the postmarketing surveillance of erlotinib is being performed in medical institutions that meet specific predetermined criteria, with all the patients in the institutions included as study subjects. When erlotinib had been administered to 3,320 patients, drug-induced lung diseases had been reported in 125 patients (3.8%), and the mortality rate was reported to be 0.8%.

### 3. Imatinib

The characteristics of drug-induced ILD in patients treated with imatinib (Glivec®) have been studied in detail, although the data cited were primarily from spontaneous reports. An estimated 5,500 patients have been treated with imatinib, and lung diseases were reported in 27 patients (0.49%). No deaths were reported. In contrast, imaging findings of lung diseases in 37 patients treated with gefitinib demonstrated DAD in 7 patients (19%), all

of whom died **(Fig. 1)**[2]. In addition, the images of some patients suggested the presence of acute eosinophilic pneumonia-like or organizing pneumonia / chronic eosinophilic pneumonia-like image, or ground-glass opacity, although the mortality rate of these patients was low **(Fig. 1)**[2]. On the other hand and consistent with other clinical experience, no patient treated with imatinib showed diffuse alveolar damage.

### 4. Bortezomib

Bortezomib (Velcade®) is a proteasome inhibitor prescribed for multiple myeloma. Lung diseases associated with this drug were first reported in Japan in patients who were treated with bortezomib that had been imported personally or who were enrolled in the clinical study[7]. As a result, the Japanese Society of Hematology and the Japanese Society of Clinical Hematology jointly conducted an urgent questionnaire survey related to this issue and found that lung diseases developed in 7 (15.2%) of 46 patients who were treated with bortezomib[8]. Six of these 7 patients had received hematopoietic stem cell transplantation, which was suggested by multivariate analysis to be a possible risk factor[8]. The concomitant use of corticosteroids, on the other hand, was identified as a risk-reduction factor[8]. The lung diseases in 5 patients were reviewed by a third-party assessment committee consisting of respiratory specialists, radiologists, and pathologists[9]. Three of the 5 patients died, and diffuse alveolar damage was found in 2 patients at autopsy. Of the 4 patients who underwent computed tomography, 4 showed pericardial fluid and 3 showed wall thickening and luminal narrowing of the bronchi (indicating edema of the airway mucosa)[9]. These findings, which are not found with other antitumor agents, are considered to be characteristic side effects of bortezomib[10]. As for erlotinib, a special postmarketing surveillance survey for bortezomib is now being performed in all patients in Japanese medical institutions meeting specific criteria. According to the interim analysis of 666 cases, interstitial pneumonia and other lung diseases have occurred in 3.6% of the patients with coexisting ground-glass opacity and nonspecific lung damage[10].

## Current Issues in Lung Diseases Induced by Molecularly Targeted Anticancer Agents

Finally, I would like to summarize the current issues in "interstitial pneumonia induced by molecularly targeted anticancer agents". The first issue is how to evaluate the safety of novel agents that will be developed in the future. It is suspected that there are racial differences in the incidence of drug-induced lung diseases. However, it is difficult to determine the relative incidences of these diseases during the drug-development phase, because the events are too rare and the sample sizes are too small to make reliable estimates from the results of clinical studies in Japan. Therefore, in the current situation of increasing globalization of drug development, how to cope with these adverse events is a crucial subject, and it is important to establish a system for collecting postmarketing data about drugs so that their safety can be continually monitored and optimized. Accordingly, it is considered to be essential to carefully evaluate the safety of all newly developed drugs in the way that erlotinib and bortezomib were evaluated.

The second issue involves the difficulty of diagnosing drug-induced interstitial pneumonia in clinical practice. In the survey on the use of gefitinib, the assessment committee reviewed reported cases of lung diseases and differentiated drug-induced lung diseases from diseases with other causes. In patients for whom imaging results were available, 22 (15.7%) of 140 cases were diagnosed, not as acute lung diseases/interstitial pneumonia but as other causes[2]. Molecularly targeted anticancer agents will be increasingly used to treat various types of tumors in the future. Therefore, it is necessary to establish an environment in which patients can consult respiratory specialists.

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