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Interstitial lung disease associated with gefitinib

Kensuke Kataoka[a], Hiroyuki Taniguchi[b], Yoshinori Hasegawa[a,*], Yasuhiro Kondoh[b], Tomoki Kimura[b], Osamu Nishiyama[b], Kazuyoshi Imaizumi[a], Tsutomu Kawabe[a], Hiroaki Kume[a], Kaoru Shimokata[a]

[a]*Department of Medicine, Division of Respiratory Medicine, Nagoya University Graduate School of Medicine, Nagoya, 466-8550, Japan*
[b]*Department of Respiratory Medicine and Allergy, Tosei General Hospital, Aichi, Japan*

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Summary Although pulmonary toxicity associated with gefitinib, an epidermal growth factor receptor inhibitor, has been reported recently, the accumulation of clinical information and the underlying mechanisms of gefitinib-induced interstitial lung disease (ILD) remain insufficient and unclear. After retrospectively reviewing the clinical records and chest X-rays of 489 lung cancer patients who were treated with gefitinib, we diagnosed four cases of gefitinib-induced ILD who underwent fiberoptic bronchoscopy and bronchoalveolar lavage (BAL). We found that the period of time from starting gefitinib to the onset of ILD was short, and concluded that a careful and close observation of a chest imaging study and a collection of respiratory symptoms was recommended. All four patients were treated with a high dose of corticosteroids, and ILD was resolved. We detected high levels of interferon-inducible protein-10 in BAL fluid, although we could not demonstrate the characteristic features of laboratory findings or BAL fluid cell analysis. We speculated that a Th1 type of lung tissue inflammation or lung injury might be involved as a part of mechanisms underlying gefitinib-induced ILD.

Abbreviations: BAL, bronchoalveolar lavage; CRP, C-reactive protein; DL_{CO}, diffusing lung capacity for carbon monoxide; DLST, lymphocytes stimulating test; EGFR, epidermal growth factor receptor; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; HRCT, high resolution computed tomography; ILD, interstitial lung disease; IP-10, interferon-inducible protein-10; KL-6, Krebs von den Lungen-6; LDH, lactate dehydrogenase; NSCLC, non-small-cell lung cancer; SP-D, surfactant protein-D; TARC, thymus- and activation-regulated chemokine; UIP, usual interstitial pneumonia

*Corresponding author. Tel.: +81 52 744 2167; fax: +81 52 744 2176.
E-mail address: yhasega@med.nagoya-u.ac.jp (Y. Hasegawa).

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Introduction

Gefitinib (Iressa, AstraZeneca, Osaka, Japan), an epidermal growth factor receptor (EGFR) inhibitor, is a new molecular-targeted agent for the treatment of patients with advanced non-small-cell lung cancer (NSCLC) who fail to respond to chemotherapy. It has novel pharmacological mechanisms that affect cancer by targeting the inhibition of EGFR tyrosine kinase. Several clinical studies suggest that the drug is well tolerated and expected to possess fairly effective antitumor activity, especially for patients with EGFR mutations.[1–5] Gefitinib was approved on July 5, 2002 in Japan for the treatment of patients with advanced NSCLC previously treated with chemotherapy. The most commonly reported toxicities associated with this drug were mild and self-limiting such as eczema and diarrhea.[6] Although gefitinib was recognized as a relatively safe oral anti-cancer agent, pulmonary toxicity (interstitial lung disease; ILD) associated with gefitinib has been reported as a serious adverse effect.[7–9] The incidence of gefitinib-induced ILD was reported to be 3.2% and 6.8%, respectively, in Japan.[10,11] A multicenter prospective review reported 215 out of 3222 cases of gefitinib-induced ILD (5.81%), 83 of whom (38.6%) died of ILD.[12] However, the mechanisms of gefitinib-induced ILD remain unknown, and no clinical/physiological analysis has been reported. We report here four cases of ILD induced by gefitinib who underwent bronchoscopy and pulmonary function tests. We obtained and analyzed bronchoalveolar lavage (BAL) fluid from all four. These data will provide the clinical and biological information needed to enhance our understanding of gefitinib-induced ILD.

Patients and methods

Patients

We retrospectively reviewed the clinical records and chest X-rays of 489 lung cancer patients who were treated with gefitinib from August 2002 to September 2003. The review was performed at a meeting for the evaluation of gefitinib-induced ILD, and the diagnosis was made by the consensus of several chest physicians and one radiologist who was an expert in chest radiology. We defined gefitinib-induced ILD as an acute pulmonary syndrome with diffuse pulmonary infiltrates and without evidence of other pathologies such as infectious diseases, systemic inflammatory response syndrome, lymphangitis carcinomatosis, radiation pneumonitis, or pre-existing collagen-vascular disease. The infectious etiology of the respiratory disease was based on the microbiological evaluations, including BAL fluid culture, blood culture, cytomegalovirus antigen test, urine antigen test for *Legionella pneumophila*, polymerase chain reaction DNA test for *Pneumocystis carinii*, and paired sera (4–6-week intervals) for subsequent serology tests (chlamydia, mycoplasma, and respiratory viruses). According to the above-mentioned criteria, we diagnosed four cases of gefitinib-induced ILD who underwent fiberoptic bronchoscopy and BAL. We collected their clinical information (patient age, gender, smoking status, histological diagnosis of lung cancer, prior chemotherapy, duration of gefitinib treatment, laboratory data, and pulmonary function tests).

Bronchoalveolar lavage

BAL was performed with three (50 mL each) aliquots of sterile saline solution followed by manual aspiration using a flexible bronchoscopy. The aspirates of three consecutive aliquots were pooled, and centrifuged to separate fluid from the cells. Fluid was stored at −80 °C until conducting measurements of interferon-inducible protein-10 (IP-10) and thymus- and activation-regulated chemokine (TARC) concentrations. Cell differentials were obtained on cytospin preparations, using a Diff-Quik™ stain (Scientific Products, McGraw Park, IL). As for the analysis of cell surface markers, fluorescein isothiocyanate conjugated CD4 and CD8 monoclonal antibodies (Ortho Diagnostics Inc., Raritan, NJ) were used, and loaded on flow cytometry.

Concentrations of IP-10 and TARC were evaluated by enzyme-linked immunosorbent assay with matched antibody pairs (R&D Systems Inc., Minneapolis, MN) according to the manufacturer's recommendations. Briefly, samples were added to microtiter plates precoated with murine monoclonal antibody to IP-10 or TARC first antibody. Horseradish peroxidase-conjugated anti-IP-10 or anti-TARC second monoclonal antibody (which recognizes a different epitope from the first antibody,) was then added. After being incubated for 2 h, the plates were washed six times and a substrate solution (tetramethylbenzidine) was added. After color development was stopped, the optical density was measured with a microplate reader (EAR 400AT; SLT-Labinstruments, Salzburg, Austria) at a 450-nm wavelength. Recombinant chemokines (R&D Systems Inc., Minneapolis, MN)