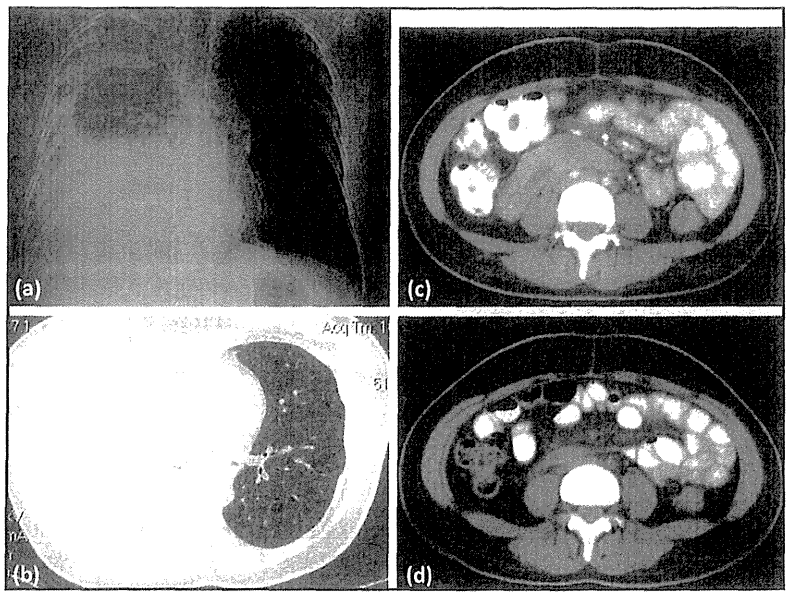

Fig. 4. Chest radiograph (a) and HRCT (b) images of a 37 year old female with a right-sided chylous pleural effusion and cystic changes due to LAM. CT of the abdomen (c) revealed a retroperitoneal mass with hypodense center that was associated with a protein losing enteropathy, suggesting communication with the gut. Needle aspiration showed HMB-45 positive cells consistent with LAM. 1 year of Sirolimus therapy resulted in resolution of retroperitoneal mass (d).

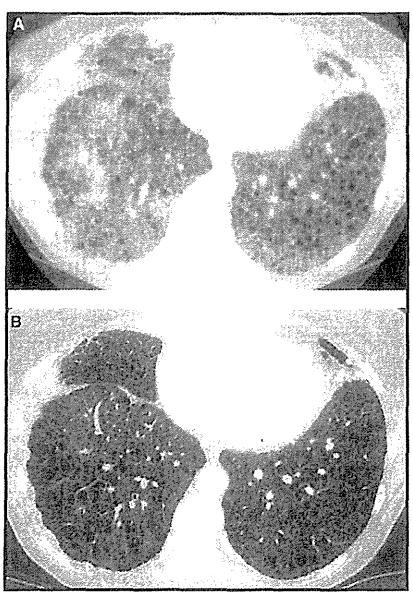

Fig. 5: Pulmonary lymphatic congestion (A) due to chylous reflux is a cause of worsening dyspnea and hypoxemia in LAM. Note the diffuse reticular and ground glass densities. Treatment with Sirolimus has been demonstrated to improve the congestion (B). Reprinted with permission of the American Thoracic Society from Moua et al (2012): Resolution of Chylous Pulmonary Congestion and Respiratory Failure in Lymphangioleiomyomatosis with Sirolimus Therapy. Am. J. of Resp. Crit. Care Med. 186(4): page 390.

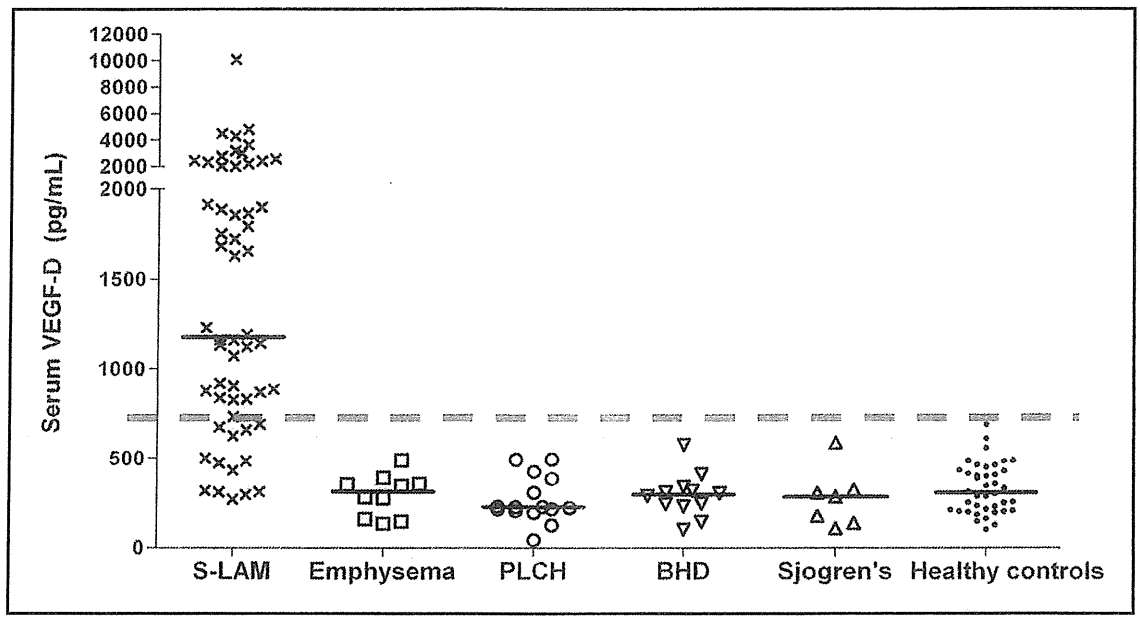

Fig. 6. A serum VEGF-D level >800pg/ml differentiates sporadic LAM (S-LAM) from other cystic diseases of the lung, including emphysema, pulmonary Langerhans cell histiocytosis (PLCH), Birt Hogg Dube (BHD) Syndrome, and Sjogren's cystic lung disease. (Modified with permission from Young et al) (65)

Diagnosis

The average age at the time of diagnosis of LAM is 35 years, although it has been described in the young and the old, including a 12 year old girl (37) and in an 86 year old woman (38). A clinical diagnosis of LAM can be based on the European Respiratory Society Guidelines (39), without the need for tissue confirmation in some cases. In a patient with typical cystic changes on HRCT, the presence of any one of the following additional features are diagnostic by ERS Criteria; tuberous sclerosis, chylothorax, lymphangiomyoma or an angiomyolipoma. We maintain that a serum VEGF-D >800 pg/ml is also diagnostic when the CT is characteristic (40) (*Fig. 6*). When tissue is required, transbronchial biopsy has a yield of >50% and appears to be safe in several small series (41,42). Video-assisted thoracoscopic biopsy remains the gold standard, but is required for diagnosis in only about 15-20% of cases when all of the above modalities are employed, and should be reserved for cases where less invasive approaches fail. Cystic lung diseases that are often considered in the differential of LAM include emphysema, alpha-1 antitrypsin deficiency, pulmonary Langerhans cell histiocytosis, Birt-Hogg-Dubé syndrome, or cystic lung disease due to follicular bronchiolitis, lymphocytic interstitial pneumonitis (as occurs in Sjögren's syndrome), hypersensitivity pneumonitis or desquamative interstitial pneumonitis. Serum VEGF-D testing can be useful for making the diagnosis of LAM when positive (>800 pg/ml) (*Fig. 6*), but is not informative when negative. It is often helpful to obtain an alpha 1-antitrypsin protein level, SS-A, SS-B, ANA, RA, and WESR to help with differential diagnosis. Cytological analysis of cells obtained from pleural effusion or ascitic fluid can be diagnostic (29). Pathological examination of tissue obtained by transbronchial or VATSs biopsy includes staining for HMB-45,

an antibody that recognizes the gp-100 protein in the melanogenesis pathway. HMB-45 staining is specific for LAM but it can be sparse and may be even absent. Other markers that stain positive in LAM tissue include alpha-smooth muscle actin, desmin, vimentin, hormone receptors (ER,PR), VEGF-R3, podoplanin, among many others (19).

Involvement of Lymphatics

Approximately 30% of patients with LAM have axial abdominal or thoracic lymphadenopathy, compared to about 9% of patients TSC-LAM. LAM can occasionally be restricted to the retroperitoneum, abdomen, or pelvis, with a normal HRCT or only scattered rare lung cysts, consistent with regional spread from a pelvic or low abdominal source. More often, abdominal LAM manifestations occur in patients who have diffuse cystic change on CT.

Clusters of LAM cells in the chylous pleural fluid of patients with LAM were first described by Valensi in 1973 (43). Later, Itami and coworkers demonstrated that the clusters were also present within the dilated lymphatic circulation and were composed of alpha smooth muscle actin-positive spindle cells enveloped by a single layer of endothelial cells (44). They suggested that LAM cell clusters could be used diagnostically to obviate the need for biopsy in patients with chylous manifestations of LAM. More recent data from Japan provided additional evidence that a likely source and mechanism of spread of LAM may be through the lymphatic circulation. In a small autopsy series, Kumasaka and colleagues described the infiltration of the thoracic duct wall and surrounding fat by LAM cells (30). They also noted the presence of LAM cell clusters enveloped by lymphatic endothelial cells budding from the walls of lymphatic vessels and in the lumen of lymphatic channels and the thoracic duct. LAM cell clusters were found in chylous pleural and peritoneal effusions and within lymphatic vessels.

Lymphangioleiomyomas in LAM most commonly affect the retroperitoneal and pelvic regions (30,36,45-48). On CT screening, lymphangioleiomyomas appear as well circumscribed, lobulated, low density cystic to solid masses of various sizes (31). Diurnal variation in size and echotexture of lymphangioleiomyomas occurs, suggesting gravitational and dietary influences on the retention of lymphatic fluid in these lesions (31), with increase in size between morning and afternoon.

Chyle leakage into body cavities occurs in a subset of LAM patients, due to direct invasion or proximal obstruction of the lymphatic system, particularly the thoracic duct and its tributaries (30,49). Chylothorax (36,50), chylous ascites, chyle leak in pericardial space (51), chyluria (52,53), chyle loss in intestinal lumen (54-55) and also chyle loss in vagina has been described in various studies and case reports (33,49). Chyloptysis can occur with development of a bronchopleural fistula (56). Chylous bronchial casts have been described in case reports (57). About 10-15% of LAM patients have chylothorax at presentation, eventually affecting 20-40% of patients at some point in the disease course (45,48,58,59). In most cases, fluid accumulation is likely the result of chylous reflux, increased pressures in the lymphatic vessels of the lung and retrograde weeping of chyle from visceral and diaphragmatic pleural surfaces (60). Transdiaphragmatic flow of chylous ascites through porous defects in the diaphragm may also result in chylothorax, most commonly on the right. Chyle loss in intestine or protein-losing enteropathy may occur (55) due to retroperitoneal involvement by LAM and associated intestinal lymphangiectasia. Patients may present with diarrhea, peripheral edema, and hypoalbuminemia (34,59). Lymphedema with chyluria was first described in 1968 (61,62). Lymphedema has been described in a case report with LAM without evidence of pulmonary involvement (63).

Lymphatic Biomarkers in LAM

Lymphatic growth factors have shown to have diagnostic, prognostic and predictive utility in patients with LAM. Serum VEGF-D, but not VEGF-C or VEGF-A, is elevated in serum of patients with LAM. There is a negative correlation between serum VEGF-D and markers of disease severity such as FEV1/FVC and diffusion capacity of lung for carbon monoxide (DLCO) (3). A statistically significant correlation between greater lymphatic involvement and higher VEGF-C expression by immunohistochemistry has been demonstrated, and both VEGF-C and -D (by IHC) were associated with worse prognosis and more rapid progression, based on the LAM histology score (LHS) and time to death or transplantation (20). Young et al demonstrated that VEGF-D levels are significantly elevated in patients with LAM compared to those with other cystic lung diseases, such as those due to PLCH, Sjögren's cystic lung disease, and emphysema, and can obviate the need for lung biopsy in patients with typical cystic change on HRCT (40,64,65). Furthermore, VEGF-D levels were much higher in women with TSC and LAM than in women with TSC and normal HRCT (40,65). Glasgow et al also showed that VEGF-D levels appear to reflect lymphatic involvement. Patients with LAM and lymphatic involvement have significantly decreased pulmonary function (3). VEGF-D has also recently been shown to correlate with disease progression and treatment response, in that patients with higher levels are more likely to progress and more likely to respond to therapy with sirolimus (66).

Treatment

Sirolimus, also called rapamycin, blocks mTOR activation (*Fig. 1*) and partially restores homeostasis in cells with defective TSC gene function (67). The double blind, randomized Multicenter International LAM Efficacy of Sirolimus (MILES) trial, demonstrated that treatment with sirolimus for one year stabilized FEV1, reduced serum VEGF-D, and improved FVC, quality of life and functional performance. Sirolimus therapy has also been shown to be highly effective for the treatment of chylous effusions and lymphangioleiomyomas (68) (*Figs. 4d,5B*).

The management of chylous complications in patients with LAM is often challenging. Thoracentesis or paracentesis is indicated for relief of shortness of breath, but repeated chyle drainage can result in malnutrition and immunodeficiencies (69,70). Institution of a fat restricted diet enriched in medium chain triglycerides has been met with variable success in small studies (71). Peritoneovenous shunts have been used for management of refractory chylous ascites (69). Mechanical abrasion and chemical pleurodesis are generally effective therapies for chylothorax (50), but can result in diversion of flow and appearance of chylous fluid collection or drainage in other sites. Octreotide and other somatostatin analogues reduce lymphatic flow and have shown promise for the treatment of chylous effusions in other conditions (72-75) and use in LAM has been trialed (ClinicalTrials.gov Identifier: NCT00005906) and reported (76). Older studies of hormonal treatment with the progesterones or gonadotropin-releasing hormone (GnRH) suggested a salutary effect on chylous effusions in LAM (58). However, many conflicting reports regarding the effects of antiestrogen therapies in LAM have been published. Lymphedema can be managed with leg elevation, compressive hose, physiotherapy, and/or exercise (77).

Future Prospects

Anti-lymphangiogenic strategies are promising in LAM. mTOR inhibitors such as sirolimus and everolimus are anti-angiogenic and anti-lymphangiogenic, and effective in the treatment of chylous complications in LAM. Other candidates include tyrosine

kinase inhibitors such as axitinib, and pazopanib, anti-VEGF-D and anti-VEGF-C antibodies, and anti-VEGFR3 and soluble VEGFR3 have all been mentioned in the context of future trials. Stratification by VEGF-D status and menopausal state may greatly reduce the number of patients required for trials.

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INTERNAL MEDICINE

□ CASE REPORT □

An Intractable Case of Hermansky-Pudlak Syndrome

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Abstract

A 52-year-old Japanese man with congenital amblyopia and oculocutaneous albinism was admitted to our hospital. Chest CT showed reticular opacities and traction bronchiectasis without honeycombing. Specimens obtained by a video-assisted thoracoscopic surgery showed patchy chronic fibrotic lesions. We diagnosed him with Hermansky-Pudlak syndrome (HPS). A mutation in the *HPS1* gene was detected, and the diagnosis was confirmed. The patient was treated with prednisolone, pirfenidone, and azathioprine, but he nevertheless died within four months. Autopsy lung specimens showed diffuse alveolar damage suggesting comparatively rapid deterioration, although this presentation was not typical of an acute exacerbation. These pathological changes may be a possible progression pattern in HPS patients.

Key words: Hermansky-Pudlak syndrome, usual interstitial pneumonia, diffuse alveolar damage, pirfenidone

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Introduction

Hermansky-Pudlak syndrome (HPS) is a rare autosomal recessive disease with the triad of albinism, a hemorrhagic tendency due to a platelet storage pool defect, and systemic accumulation of ceroid pigments (1). HPS consists of 9 genetically distinct subtypes, and patients with *HPS1*, *HPS2*, or *HPS4* mutations develop pulmonary fibrosis (2, 3). Among these subtypes, patients with the *HPS1* mutation have the highest incidence of pulmonary fibrosis (4), histologically characterized by usual interstitial pneumonia (UIP) (5). Treatment for pulmonary fibrosis caused by HPS with pirfenidone, an antifibrotic agent recently used to treat idiopathic pulmonary fibrosis (IPF), is controversial (6, 7). We herein describe a case of HPS that rapidly deteriorated despite treatment with prednisolone, pirfenidone, and azathioprine. We compared the pathological findings between surgical lung biopsy specimens and autopsy specimens to understand the mechanism of fatal pulmonary fibrosis in HPS. We detected diffuse alveolar damage (DAD), which was not observed in specimens from the video-assisted thoracoscopic surgery (VATS). These pathological changes may be an avenue to understand the mechanism of disease progression in HPS patients.

Case Report

A 52-year-old Japanese, non-smoking man who had congenital amblyopia and oculocutaneous albinism was referred to our hospital with an exacerbation of exertional dyspnea [grade 2 by the modified British Medical Research Council Scale (MRC)]. His brother and uncle had congenital albinism and died during childhood. In addition, his maternal grandfather was his paternal grandmother's sibling (Fig. 1). A physical examination revealed fine crackles at the basal lesions of both lungs. The patient's skin and hair were white and brown-colored, respectively. The laboratory data on admission revealed impaired clot retraction and platelet adhesiveness without thrombocytopenia or delayed coagulation time. The patient had increased serum levels of Krebs von den Lungen-6 (KL-6), surfactant protein (SP)-D and SP-A. A pulmonary function test revealed a restrictive pattern with impaired diffusion capacity (Table). During the six minute

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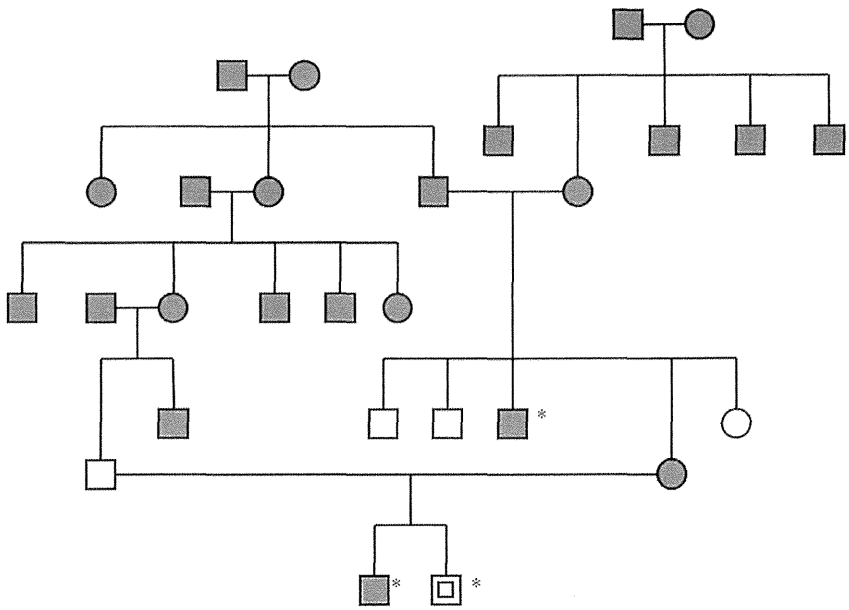

Figure 1. The pedigree of our HPS patient. The case (proband) is indicated by a doubled square. His maternal grandfather was his paternal grandmother's sibling. Asterisks (*) indicate relatives with oculocutaneous albinism. The patient died at 53 years of age, while his brother and his uncle died during childhood.

Table. Laboratory Data on Admission

Peripheral blood		
WBC	11,100	/μL
RBC	553×10^4	/μL
Hb	15.6	g/dL
Hct	38.7	%
Plt	39.7×10^4	/μL
ESR	53	mm/h
Blood chemistry		
LDH	367	IU/L
CRP	1.05	mg/dL
Glucose	185	mg/dL
HbA1c	10.0	%
Serology		
ANA	x80	
Homogeneous	x80	
Speckled	x80	
Other autoantibodies*	(-)	
KL-6	2,820	U/mL
SP-D	315	ng/mL
SP-A	210	ng/mL
Hemostasis and coagulation		
PT-INR	0.94	
APTT	24.2	seconds
Bleedind time	90	seconds
Fibrinogen	432.5	mg/dL
D-dimer	1.3	μg/mL
ATIII activity	110	%
Blood clot retraction	24.7	%
Platelet adhensiveness	21.5	%
ADP	48.0	%
Colloagen	45.0	%
PRP	36.1×10^4	/μL

Arterial blood gas analysis (room air)	
pH	7.418
PaO_2	91.5 Torr
$PaCO_2$	36.6 Torr
HCO_3	23.2 mEq/L
SaO_2	97.1 %
Pulmonary function test	
VC (%VC)	1.54 L (43.0%)
FVC (%FVC)	1.31 L (36.6%)
$FEV_{1.0}$ ($FEV_{1.0}$%)	1.31 L (100%)
RV (%RV)	0.90 L (45.5%)
RV/TLC	36.9 %
DLco (%DLco)	5.58 mL/min/mmHg (27.5%)
BALF analysis (rt. B^5b) 64/150 mL	
Total cell count	0.78×10^5 /μL
Macrophage	76.0 %
Lymphocyte	3.4 %
Neutrophil	15.0 %
Eosinophil	5.6 %
CD4/8	1.30

* Other autoantibodies include antibodies for anti-DNA. Double-stranded DNA IgG, CCP, RNP, Jo-1, Scl-70, Sm, SS-A, SS-B, PR-ANCA and MPO-ANCA

walk test, the patient's oxygen levels fell below 85% at 95 seconds (103 meters). The chest X-ray showed bilateral diffuse reticular shadows. The high-resolution computed tomography (HRCT) showed reticular opacities and traction bronchiectasis mainly in the lower lung zone, but not honeycombing (Fig. 2). The lung specimens from the upper and

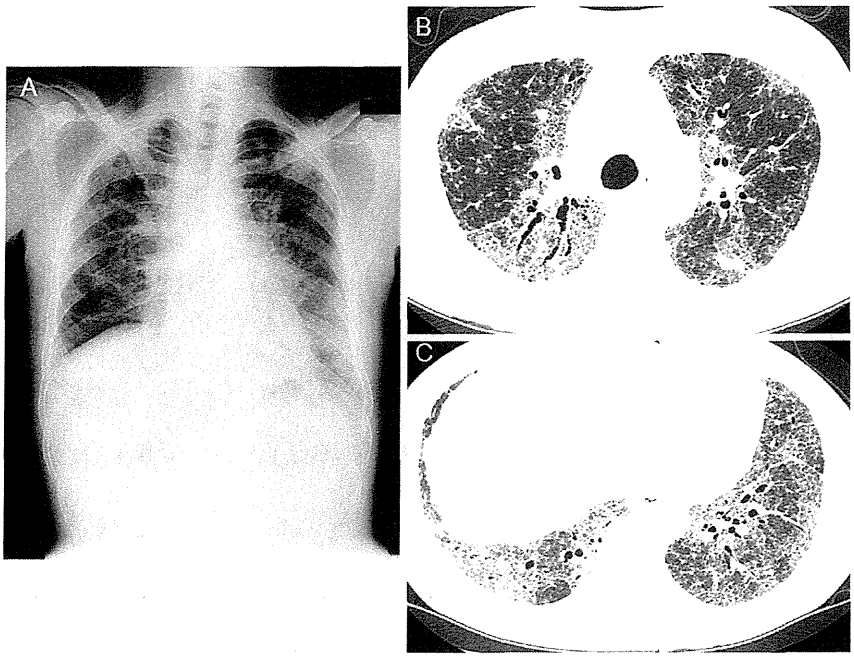

Figure 2. **(A) The chest X-ray at the first visit to our hospital in February 2009 showed diffuse bilateral pulmonary infiltrates in all of the lung fields. (B, C) Computed tomography of the chest during the same visit showed bilateral reticular opacities predominantly in the subpleural and lower lung zones and traction bronchiectasis.**

lower lobes of the left lung via VATS showed patchy chronic fibrotic lesions consistent with UIP. In the less fibrotic areas, there was a proliferation of pneumocytes with foamy cytoplasm (Fig. 3).

The patient demonstrated a progressive shortness of breath (grade 5 by the modified MRC at six weeks after VATS). We diagnosed him as having HPS and started treatment with prednisolone (30 mg daily). However, the patient's lung disease progressively deteriorated. We added pirfenidone to the treatment (initially 600 mg daily; thereafter increased to 1,800 mg daily). Simultaneously, azathioprine (50 mg daily) was administered to the patient. However, his respiratory failure progressed in proportion to the gradual deterioration of the bilateral diffuse reticular shadows on the chest X-ray, and he died four months after the start of treatment.

An autopsy was performed with permission from his family. Tissue sections of the skin did not contain melanin pigment in the epidermis. Ceroid pigments (brown pigments), negatively stained with the Berlin blue iron stain, were observed in the renal tubular epithelial cells and the bone marrow. The lung tissue from all lobes showed chronic fibrosing interstitial pneumonia (Fig. 4). We also observed alveolar lining cells with foamy cytoplasm in the less fibrotic regions (Fig. 4D), similarly observed in the biopsied lung tissues, characteristic of pulmonary fibrosis associated with HPS (5). Furthermore, we detected lesions of DAD and ring-like cystic lesions (Fig. 4C), which were formed in the process of DAD. A mutation of the *HPS1* gene, c.2003T>C, p.L668P homozygote or hemizygote, was detected after the patient expired, and the diagnosis of HPS was thus confirmed.

Discussion

Among Japanese HPS patients with the *HPS1* gene mutation, eight different types of genetic mutations have been reported (8). Functional analysis of the L668P variant, one of *HPS1* mutations, showed that this missense substitution is pathologic and leads to the inability of *HPS1* to assemble into a protein complex, namely the biogenesis of the lysosome-related organelles complex. As a result, it is supposed that cellular degeneration occurs with an overaccumulation of surfactant. In a recent report, the intracellular accumulation of surfactant was shown to lead to increased apoptosis of alveolar epithelial type II cells in a murine model of HPS, which represents a prominent reason for the development of lung fibrosis (2).

In HPS patients, pulmonary fibrosis, hemorrhage or colitis typically lead to death at an age of 40 to 50 years (9). In some patients with HPS, the interstitial lung disease worsens several years after the onset of pulmonary symptoms. To monitor disease status and progression, HRCT may be a useful tool (10, 11). The HRCT scores were shown to correlate with patient age and the extent of pulmonary dysfunction. Brantly et al. reported that the HRCT scores were also associated with the mortality of HPS patients (mean age: 37 years old); all patients with an HRCT score of 3 with severe disease (i.e., accompanying parenchymal consolidation, diffuse peribronchovascular thickening, traction bronchiectasis and reticulation) died of pulmonary fibrosis within four

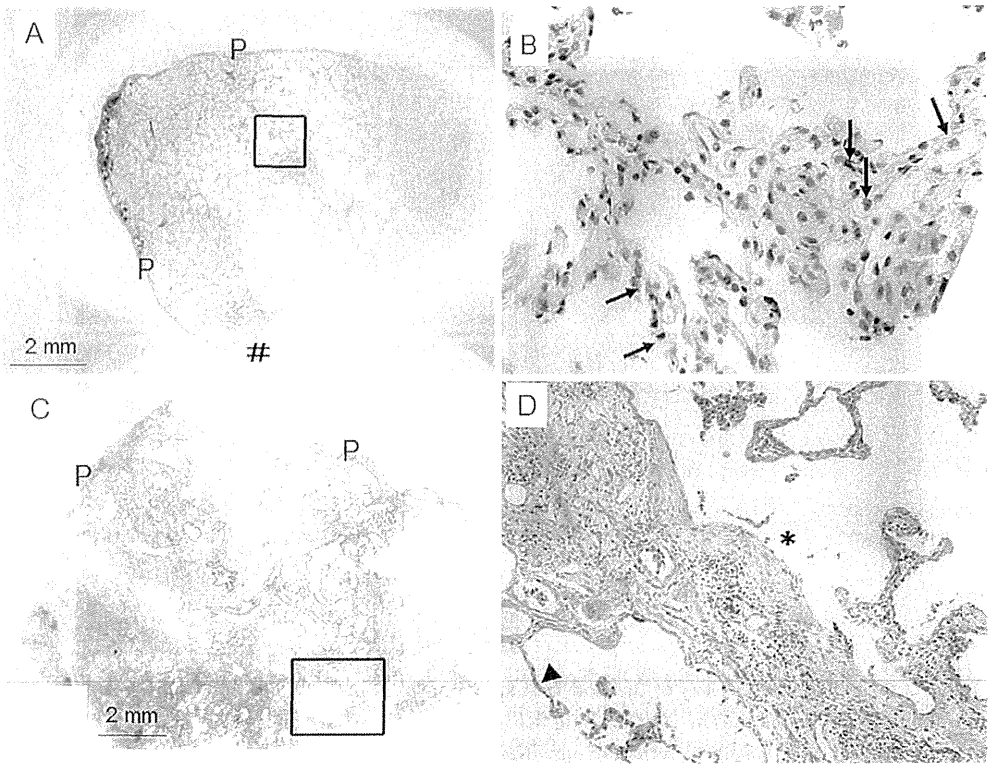

Figure 3. **Histopathological findings of the surgical biopsy specimens of the left lung in April 2009. (A) The lung tissue from the upper lobe (lt. S^{1+2}) showed mildly patchy fibrotic lesions consistent with usual interstitial pneumonia (#) [Hematoxylin and Eosin (H&E) staining, 1×]. P, visceral pleura. Bar=2mm. (B) A high magnification of the square frame in (A) showed cuboidal epithelial cells with foamy cytoplasm lining the alveolar walls (arrows) (H&E staining, 40×). (C) The lung tissue from the lower lobe (lt. S^{10}) showed extensive, periacinar dominant fibrotic lesions (H&E staining, 1×). P: visceral pleura. Bar=2mm. (D) A high magnification image of the square frame in (C) showed fibrotic lesions with loss of normal alveolar structure and a fibroblast focus (*). Adjacent alveolar walls were almost normal (arrowhead) (H&E staining, 10×).**

months after examination, while all patients with an HRCT score under 2 with non-diffuse interstitial shadows survived within one year after examination (11). Our patient was over 50 years, and his HRCT findings already showed diffuse reticular opacities and traction bronchiectasis in the bilateral lung fields, consistent with a Brantly's score of 3 on the initial HRCT. From these clinical findings, we may have recognized rapid progression and poor prognosis in this patient at the time of diagnosis.

The postmortem examination showed DAD and ring-like cystic lesions formed in the process of DAD. These pathological findings were not observed in the tissues from the VATS lung biopsy. After the diagnosis, rapid deterioration of the patient's clinical symptoms and HRCT findings, including reticular opacities and traction bronchiectasis, occurred; however, we believe the progression was not an acute exacerbation of interstitial pneumonia for two reasons. In this case, new ground-glass opacity or consolidation did not occur abruptly, and we did not observe a rapid increase in the patient's serum levels of KL-6, SP-D and SP-A [previously reported in the acute exacerbation of IPF (12)] (data not shown). Alveolar epithelial apoptosis is hypothesized to be intimately related to pulmonary fibrosis in IPF (13) and HPS (2, 3). Bleomycin-induced apoptosis of alveolar epithelial type II cells is promoted in the murine model of HPS (compared to wild-type mice) (14). We speculate that some weak stimuli may have led to the occurrence of rapid deterioration with DAD pattern in our patient, although this presentation was not typical of an acute exacerbation. Although supplementation of high concentrations of oxygen may cause pulmonary injury, we speculate that the progression of pulmonary fibrosis is due to a gradual deterioration with DAD pattern. These pathological changes between the specimens from VATS and autopsy may explain the mechanism of progression in HPS patients.

Current treatment strategies, such as corticosteroids or other immunosuppressive agents, generally fail to curtail this pulmonary disease progression in Japanese HPS patients (15-17). Pirfenidone is approved for the treatment of IPF, inhibits both inflammatory and fibrotic cytokines, and has antioxidant effects (18-21). The inhibitory effects of pirfenidone on alveolar macrophage cytokine secretion have

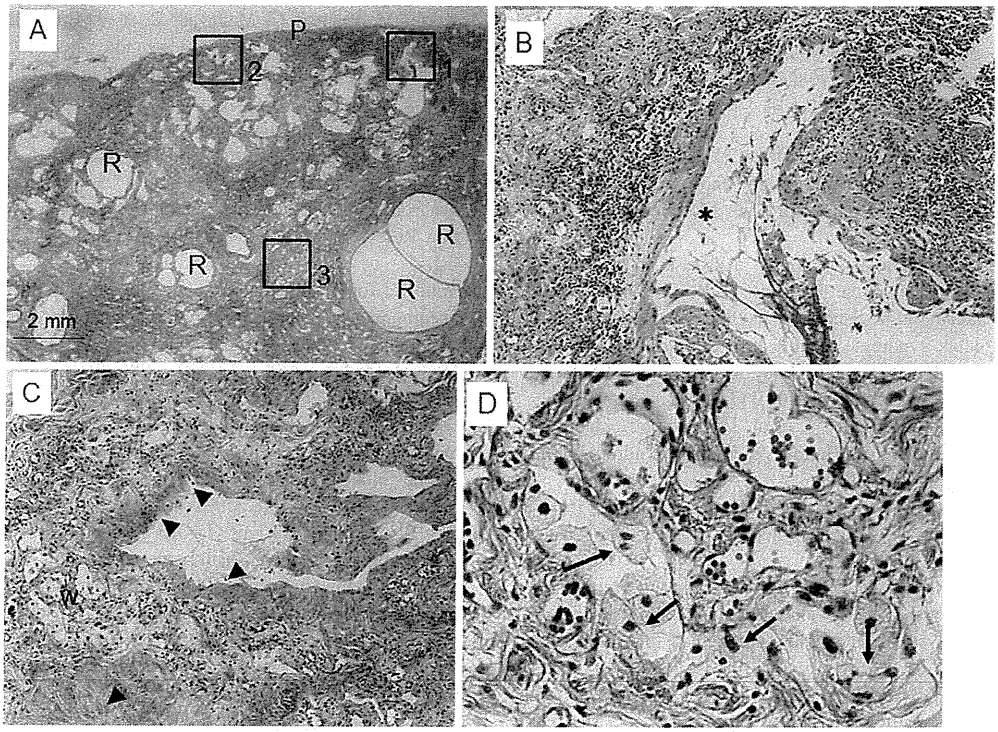

Figure 4. **Autopsy findings of the patient in September 2009. (A) The upper lobe tissue of the left lung (lt. S^{1+2}) showed extensive fibrosis with numerous ring-like lesions (R) [Hematoxylin and Eosin (H&E) staining, 1×]. P, visceral pleura. Bar=2mm. (B) A high magnification image of the square frame 1 in (A) showed a fibroblast focus covered with flattened epithelial cells (*) and a fibrotic lesion with moderate infiltration of lymphoid cells and mucin stasis in the dilated air space at the level of a respiratory bronchiole (H&E staining, 10×). (C) A high magnification image of the square frame 2 in (A) showed hyalinous materials without epithelial lining (arrowheads) that covered the wall of the alveolar ducts. In between, there were a few alveolar walls with mild, fibrous thickening (W) (H&E staining, 10×). (D) A high magnification image of the square frame 3 in (A) showed some cuboidal epithelial cells with foamy cytoplasm (arrows) (H&E staining, 40×).**

also been reported in patients with HPS1 (22). In a previous double-blind, randomized, placebo-controlled trial of 21 adult HPS patients, pirfenidone was shown to slow the progression of pulmonary fibrosis associated with HPS, especially in patients with an initial forced vital capacity (FVC) >50% of the predicted (6). This result is similar to the study conducted by Azuma et al. who showed that pirfenidone exerted more pronounced effects in IPF patients with mild impairments (23). Our patient may have shown poor response to pirfenidone because his FVC at pirfenidone initiation was 36.6% of the predicted value. Recently, O'Brien et al. reported that pirfenidone showed no inhibitory effects on the decline of FVC in HPS patients with an FVC >50% (7). A limited number of patients were enrolled in this trial, and large-scale trials are necessary to conclude that pirfenidone is not effective. Pirfenidone may not be an epoch-making drug, and the development of other drugs is suggested for HPS patients.

We herein detected DAD pattern lesions and ring-like cystic lesions in the autopsy specimens; these lesions were not observed in the specimens from VATS. We suspect that a rapid deterioration with DAD pattern may be one of the progression patterns observed in HPS patients. Further investigation of the HPS pathogenesis is necessary for improving the prognosis in HPS patients, which may be a therapeutic avenue to this intractable disease.

The authors state that they have no Conflict of Interest (COI).

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Final safety and efficacy of erlotinib in the phase 4 POLARSTAR surveillance study of 10 708 Japanese patients with non-small-cell lung cancer

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Key words

Erlotinib, interstitial lung disease, Japanese, non-small-cell lung cancer, surveillance

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Interstitial lung disease (ILD) occurrence and risk factors were investigated in the Japanese non-small-cell lung cancer, post-marketing, large-scale surveillance study, POLARSTAR. All patients with unresectable, recurrent/advanced non-small-cell lung cancer who were treated with erlotinib in Japan between December 2007 and October 2009 were enrolled. Primary endpoints were patterns of ILD and risk factors for onset of ILD and ILD-related death. Overall survival, progression-free survival, and occurrence of adverse drug reactions were secondary endpoints. Interstitial lung disease was confirmed in 429 (4.3%) patients. Concurrent/previous ILD (hazard ratio, 3.19), emphysema or chronic obstructive pulmonary disease (hazard ratio, 1.86), lung infection (hazard ratio, 1.55), smoking history (hazard ratio, 2.23), and period from initial cancer diagnosis to the start of treatment (<360 days; hazard ratio, 0.58) were identified as significant risk factors for developing ILD by Cox multivariate analysis. Logistic regression analysis identified Eastern Cooperative Oncology Group performance status 2–4 (odds ratio, 2.45 [95% confidence interval, 1.41–4.27]; $P = 0.0016$), ≤50% remaining normal lung area (odds ratio, 3.12 [1.48–6.58]; $P = 0.0029$), and concomitant honeycombing with interstitial pneumonia (odds ratio, 6.67 [1.35–32.94]; $P = 0.02$) as poor prognostic factors for ILD death. Median overall survival was 277 days; median progression-free survival was 67 days. These data confirm the well-characterized safety profile of erlotinib. Interstitial lung disease is still an adverse drug reaction of interest in this population, and these results, including ILD risk factors, give helpful information for treatment selection and monitoring. Erlotinib efficacy was additionally confirmed in this population. (POLARSTAR trial ML21590.)

Erlotinib is an orally administered EGFR TKI that has demonstrated survival benefits over placebo (median OS 6.7 *vs* 4.7 months, respectively; $P = 0.002$) with acceptable tolerability in previously treated patients with NSCLC.[1] Promising survival data were also reported in two Japanese phase 2 trials of erlotinib in patients with advanced NSCLC (median OS 13.5–14.7 months).[2,3] This led to the approval of erlotinib in Japan for the treatment of patients with recurrent/advanced NSCLC after failure on at least one prior chemotherapy regimen.

Interstitial lung disease has been reported as an AE of special interest in erlotinib-treated Japanese patients with NSCLC in 4.9% (6/123) of patients with a mortality rate of 2.4% (3/123 patients).[2–4] Similar incidences of ILD have been reported in Japanese patients with NSCLC treated with the EGFR TKI gefitinib, suggesting this may be a class-related AE.[5,6]

Risk factors for developing ILD have been previously reported primarily in gefitinib-treated patients. Kudoh *et al.*[6] reported old age, smoking history, pre-existing ILD, poor ECOG PS, short duration since NSCLC diagnosis, and ≤50% normal lung area as ILD risk factors, with all of the factors, except ECOG PS and short duration since NSCLC diagnosis, also being associated with poor ILD prognosis (fatal ILD).

Hotta *et al.*[7] reported existing pulmonary fibrosis, poor ECOG PS, and prior irradiation as risk factors for ILD. Pre-existing pulmonary fibrosis and poor ECOG PS have also been shown to be associated risk factors for ILD in patients treated with either gefitinib or erlotinib.[8]

POLARSTAR was a large-scale surveillance study including all Japanese patients with NSCLC treated with erlotinib,[9] undertaken as a post-approval commitment in Japan to monitor safety and efficacy. The objectives were to obtain decisive information on the incidence of ILD, risk factors for developing ILD, and the efficacy of erlotinib. Here, we report the final analysis of the POLARSTAR surveillance study investigating the safety and efficacy of erlotinib treatment in Japanese patients with NSCLC.

Methods

Study design. All patients with unresectable, recurrent /advanced NSCLC who were treated with erlotinib in Japan between December 2007 and October 2009 were enrolled. Eligible patients receiving erlotinib (150 mg orally, once daily), from the 1027 institutions that could prescribe erlotinib, were monitored until erlotinib therapy termination or completion of 12 months of treatment. The study was approved by the relevant ethics committees and patients gave informed consent to participate in the analysis.

Assessments. Demographic and baseline data were collected for each patient, including age, gender, body mass index, tumor histology, ECOG PS, smoking history, and medical history (including hepatic dysfunction, renal dysfunction, cardiovascular disease, and lung disorders). Safety data were collected at 1, 6, and 12 months after the start of erlotinib therapy. All AE reports were collected and graded using the National Cancer Institute Common Terminology Criteria for AEs version 3.0 and coded using the Medical Dictionary for Regulatory Activities version 14.1 thesaurus terms.

Outcome measures. Primary endpoints were patterns of occurrence of ILD and risk factors for onset of ILD. Overall survival and PFS were secondary endpoints and were assessed according to the treating physician's standard clinical practice. The pattern of ADRs, excluding ILD, was an additional secondary endpoint.

Statistical analyses. The sample size determination is previously described.[9] Briefly, 3000 patients were to be enrolled to detect an AE in one case out of 3000 patients with at least a power of 95%; however, during enrolment, target accrual was increased to 10 000 patients by the Japanese Health Authority to further evaluate the safety and efficacy of erlotinib. The increased patient number allows high sensitivity regarding low-frequency ADRs. The safety population comprised all patients who received erlotinib and had case report form data available. The efficacy population comprised all patients included in the safety population, except those where erlotinib therapy was prescribed off-label (i.e. in the first-line setting) at the time of this study, or where a patient's therapeutic history was unknown.

Median PFS and OS were estimated using Kaplan–Meier methodology. Patients without data for the duration of the observation period or from the time of treatment initiation were excluded from the PFS analyses.

Statistical analyses were carried out using Statistical Analysis Software version 9.1 and 9.2 (SAS Institute, Cary, NC). Multivariate Cox regression analysis using a stepwise model was carried out to determine risk factors for ILD; occurrence of ILD was used as the dependent variable. Exploratory variables with $P > 0.05$ were not included in the final model. In the final step, additional multivariate analyses were carried out to investigate two-factor interactions; statistical significance was set at $P < 0.05$. This method is described in more detail in the interim analysis publication.[9]

To examine factors affecting poor prognosis in ILD, a stepwise, 5% significance level, multivariate logistic regression analysis was carried out with an analysis set of 310 patients in whom an ILD diagnosis was confirmed by the ILD Review Committee. The target variable was fatal ILD; exploratory variables included gender, age, primary lesion, histological type, smoking history, ECOG PS, honeycomb lung, non-metastatic lesions, and remaining normal lung. The exploratory variables were chosen by the results of a univariate analysis using ILD death as the target variable, with baseline characteristics and characteristics previously reported to affect poor ILD prognosis as the univariate exploratory variables.

Results

A total of 10 708 patients were enrolled in this study. Of these, 9909 patients were evaluated for the final safety analysis and 9663 patients were evaluated for the final efficacy analysis (Fig. 1). Baseline characteristics are shown in Table 1. Of note, more males than females were enrolled; the majority of patients had adenocarcinoma histology (80.9%) and most had ECOG PS 0–1 (74.0%).

Safety analysis. Adverse drug reactions were reported in 79.1% (7835/9909) of patients, the most common being skin disorders (67.4%), including rash (60.9%), diarrhea (21.5%), hepatitis, hepatic failure and hepatic function disorder (9.8%), eye disorders (3.3%) and hemorrhage (1.6%; Table 2). Median time to onset of ADRs was 9 days for rash, 8 days for diarrhea, 13 days for hepatitis, hepatic failure, and hepatic function

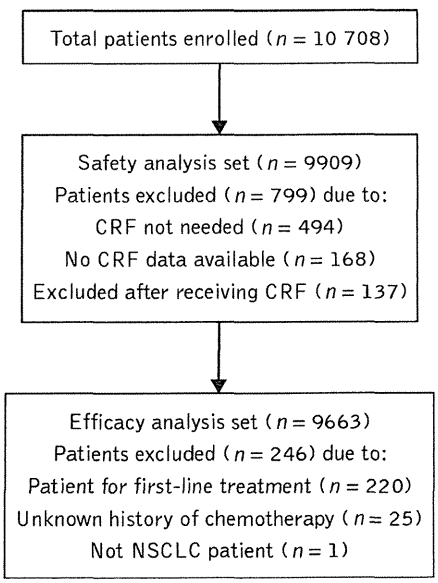

Fig. 1. Disposition of patients with unresectable, recurrent/advanced non-small-cell lung cancer who were treated with erlotinib in Japan between December 2007 and October 2009 and who were included in the final analysis. CRF, case report form; NSCLC, non-small-cell lung cancer.

Table 1. Baseline characteristics of patients with unresectable, recurrent/advanced non-small-cell lung cancer who were treated with erlotinib in Japan between December 2007 and October 2009

Characteristic	Patients, *n* (%) (*n* = 9909)
Gender	
Male	5300 (53.5)
Female	4609 (46.5)
Age	
<65 years	4466 (45.1)
65–74 years	3382 (34.1)
≥75 years	2059 (20.8)
Histology	
Adenocarcinoma	7950 (80.9)
Squamous cell	1285 (13.1)
Large cell	155 (1.6)
Other	438 (4.5)
ECOG PS	
0–1	7315 (74.0)
2–4	2576 (26.0)
Smoking history	
No	4366 (44.9)
Yes	5367 (55.1)
Number of previous treatment lines	
0	220 (2.2)
1	2481 (25.1)
2	2646 (26.8)
3	1993 (20.2)
4	1546 (15.6)
≥5	998 (10.1)
Previous gefitinib treatment	
Yes	4396 (44.7)
No	5446 (55.3)

ECOG PS, Eastern Cooperative Oncology Group performance status.

Table 2. Incidence of the most common adverse drug reactions (ADRs) in patients with unresectable, recurrent/advanced non-small-cell lung cancer who were treated with erlotinib in Japan between December 2007 and October 2009

ADR	All grades		Grade ≥3	
	Patients		Patients	
	n	%	*n*	%
ILD	429	4.3	257	2.6
Skin disorder				
Rash	6032	60.9	673	6.8
Dry skin	738	7.4	30	0.3
Pruritus	351	3.5	13	0.1
Paronychia	654	6.6	77	0.8
Hepatitis, hepatic failure, hepatic function disorder	976	9.8	183	1.8
Diarrhea	2133	21.5	137	1.4
Eye disorders	331	3.3	19	0.2
Corneal disorders	186	1.9	11	0.1
Hemorrhage	158	1.6	46	0.5
Gastrointestinal hemorrhage	39	0.4	20	0.2

ILD, interstitial lung disease.

disorder, 15 days for eye disorders, and 16 days for hemorrhage.

Interstitial lung disease. *Incidence.* Of the patients analyzed, 491 patients had 497 ILD-like events, of which 62 events were deemed non-ILD by the independent ILD Review Committee. In total, 429 (4.3%) patients were classified as having ILD (310 confirmed and reported by the ILD Review Committee, 119 patients not confirmed by the ILD Review Committee due to not having an evaluated image [*n* = 93], too difficult to distinguish from tumor progression [*n* = 4], and too difficult to distinguish from pneumonia due to insufficient evaluable images or clinical findings [*n* = 22] were still classified as ILD), with an overall mortality rate of 1.5% and a mortality rate of 35.7% in patients with ILD.

The majority of ILD cases (58.5%) were reported within 4 weeks of receiving erlotinib. The incidence of ILD (per 100 patient-weeks) was 0.63–0.81 within 4 weeks of the start of erlotinib treatment and 0.09–0.27 from 6 weeks after the start of erlotinib treatment (Fig. 2). Univariate analysis identified patients who were female, patients with non-adenocarcinoma histology, those with a period of treatment from initial NSCLC diagnosis to the start of treatment <360 days, concomitant or previous emphysema or COPD, concomitant or previous ILD, concomitant or previous lung infections, concomitant hepatic disorders, concomitant renal disorders, history of allergies, smoking history, ECOG PS 2–4, prior chest radiotherapy, pretreatment lactate dehydrogenase, and no previous treatment with gefitinib as risk factors for ILD development (Table 3). Age at start of treatment, body mass index, concurrent cardiovascular disorders, number of chemotherapy regimens and previous treatment with gemcitabine were variables that were not identified as risk factors from the univariate analysis. Multivariate analysis showed that concurrent/previous ILD (HR, 3.19), concurrent/previous emphysema or COPD (HR, 1.86), concurrent/previous lung infection (HR, 1.55), smoking history (HR, 2.25), and period from initial NSCLC diagnosis to the start of treatment (<360 days; HR, 0.58) were identified as significant risk factors for developing ILD by multivariate analysis (Table 3).

Outcomes of ILD. Of the confirmed cases of ILD, 75 (17.5%) patients fully recovered, 154 (35.9%) patients improved their condition, 32 (7.5%) patients did not recover, five (1.2%) patients had sequelae, 153 (35.7%) patients died, and 10 (2.3%) patients had unknown outcomes.

The outcome of ILD by CT image pattern was investigated in 283 patients out of the 310 patients deemed as having confirmed ILD by the independent ILD Review Committee. Diffuse alveolar damage-like pattern on CT was defined as abnormalities that showed non-segmental ground-glass attenuation or airspace consolidation with traction bronchiectasis and loss of volume. In the 63 patients with CT-DAD-like pattern, six (9.5%) patients recovered, 12 (19.1%) patients improved, three (4.8%) patients did not recover, one (1.6%) patient had residual ILD sequelae, and 41 (65.1%) patients died. In the 220 patients with a CT-non-DAD-like pattern, 37 (16.8%) patients recovered, 95 (43.2%) patients improved, 13 (5.9%) patients did not recover, one (0.5%) patient had residual ILD sequelae, 71 (32.3%) patients died, and three (1.4%) patients had unknown outcomes.

Fatal outcome of ILD. The multivariate logistic analysis identified ECOG PS 2–4 (OR, 2.45), ≤50% remaining normal lung area (OR, 3.12), and concomitant honeycombing with

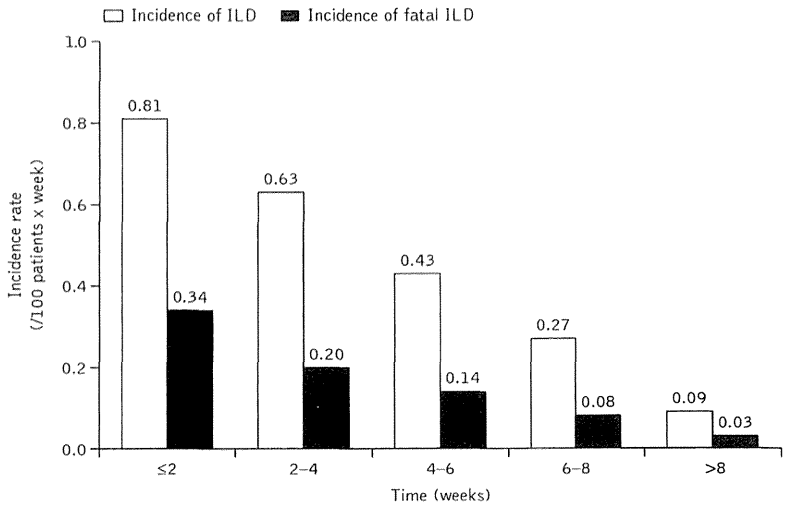

Fig. 2. Incidence rate of interstitial lung disease (ILD) stratified by time from start of erlotinib treatment to onset of ILD. The 34 patients without data for either the duration of observation or the time from the start of erlotinib treatment to the onset of ILD were excluded from the analysis. Value determined by dividing the number of patients developing ILD during the specified duration of observation by the patient-days during the observation period (total duration [number of days] of observation of all patients receiving erlotinib during the specified duration of observation).

Table 3. Cox regression univariate and multivariate analysis of factors affecting the incidence of interstitial lung disease (ILD) in patients with unresectable, recurrent/advanced non-small-cell lung cancer (NSCLC) who were treated with erlotinib in Japan between December 2007 and October 2009

Variables	Criterion variable	Evaluation variable	X^2 value	*P*-value	HR	95% CI
Univariate analysis						
Gender	Male	Female	76.3424	<0.0001	0.390	0.315–0.481
Age (years)	<55	≥55	2.257	0.133	1.256	0.933–1.692
Body mass index (kg/m^2)	<25	≥25	2.4468	0.1178	0.788	0.585–1.062
Histology	Adenocarcinoma	Non-adenocarcinoma	32.0958	<0.0001	1.847	1.494–2.283
Period from initial NSCLC diagnosis to the start of treatment	<360 days	≥360 days	20.1885	<0.0001	0.638	0.525–0.776
Concurrent/previous emphysema or COPD	No	Yes	85.1118	<0.0001	3.071	2.420–3.898
Concurrent/previous ILD	No	Yes	88.7072	<0.0001	3.862	2.915–5.116
Concurrent/previous lung infection	No	Yes	18.7152	<0.0001	1.979	1.453–2.697
Concurrent hepatic disorder	No	Yes	4.9716	0.0258	1.426	1.044–1.949
Concurrent renal disorder	No	Yes	9.1417	0.0025	1.611	1.183–2.195
Concurrent cardiovascular disorder	No	Yes	2.8576	0.0909	1.191	0.973–1.459
History of allergies	No	Yes	5.2846	0.0215	1.358	1.046–1.764
Smoking history	No	Yes	87.4412	<0.0001	2.896	2.318–3.620
ECOG PS	0–1	2–4	20.0203	<0.0001	1.620	1.311–2.001
Prior chest radiation therapy	No	Yes	11.9016	0.0006	1.431	1.167–1.753
Baseline lactate dehydrogenase†	–	–†	7.0077	0.0081	1	1–1
Number of chemotheraphy regimens for the primary diseases		–†	1.2809	0.2577	1.033	0.977–1.092
History of gemcitabine treatment	No	Yes	0.1141	0.7355	0.967	0.797–1.174
History of gefitinib treatment	No	Yes	38.7111	<0.0001	0.517	0.420–0.636
Multivariate analysis						
Concurrent/previous ILD	No	Yes	55.3796	<0.0001	3.187	2.349–4.325
Smoking history	No	Yes	34.1327	<0.0001	2.246	1.712–2.946
Concurrent/previous emphysema or COPD	No	Yes	20.704	<0.0001	1.860	1.424–2.431
Period from initial NSCLC diagnosis to the start of treatment	<360 days	≥360 days	19.3818	<0.0001	0.581	0.456–0.740
Concurrent/previous lung infection	No	Yes	6.5905	0.0103	1.550	1.109–2.165
ECOG PS	0–1	2–4	8.9467	0.0028	1.431	1.131–1.809
History of gefitinib treatment	No	Yes	5.3133	0.0212	0.729	0.557–0.954
Number of chemotherapy regimens†	–	–†	10.4136	0.0013	1.121	1.046–1.201

Objective variable: occurrence or non-occurrence of ILD. Explanatory variables: gender, age, body mass index, histological type, concurrent/previous emphysema or chronic obstructive pulmonary disease (COPD), concurrent/previous ILD, concurrent/previous lung infection, concomitant hepatic disorder, concomitant renal disorder, period from initial NSCLC diagnosis to the start of treatment, concomitant cardiovascular disease, history of allergies, smoking history, Eastern Cooperative Oncology Group performance status (ECOG PS), radiotherapy (chest), pretreatment lactate dehydrogenase, number of chemotherapy regimens for the primary disease, history of gemcitabine treatment, history of gefitinib treatment. †Analyzed as a continuous quantity. NSCLC, non-small-cell lung cancer; ILD, interstitial lung disease.; CI, confidence interval; HR, hazard ratio.

Table 4. Interstitial lung disease (ILD) poor prognosis risk factors from the final analysis results for Post-Launch All-patient-Registration Surveillance in Tarceva®-treated non-small-cell lung cancer patients (POLARSTAR)

Risk factors for ILD-related death	Criterion variable	Evaluation variable	X^2 value	*P*-value	OR	95% CI
ECOG PS 2–4	0–1	2–4	9.974	0.0016	2.45	1.41–4.27
≤50% normal lung area	>50	≤50	8.896	0.0029	3.12	1.48–6.58
Concomitant honeycombing	No	Yes	5.414	0.02	6.67	1.35–32.94

CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; OR, odds ratio.

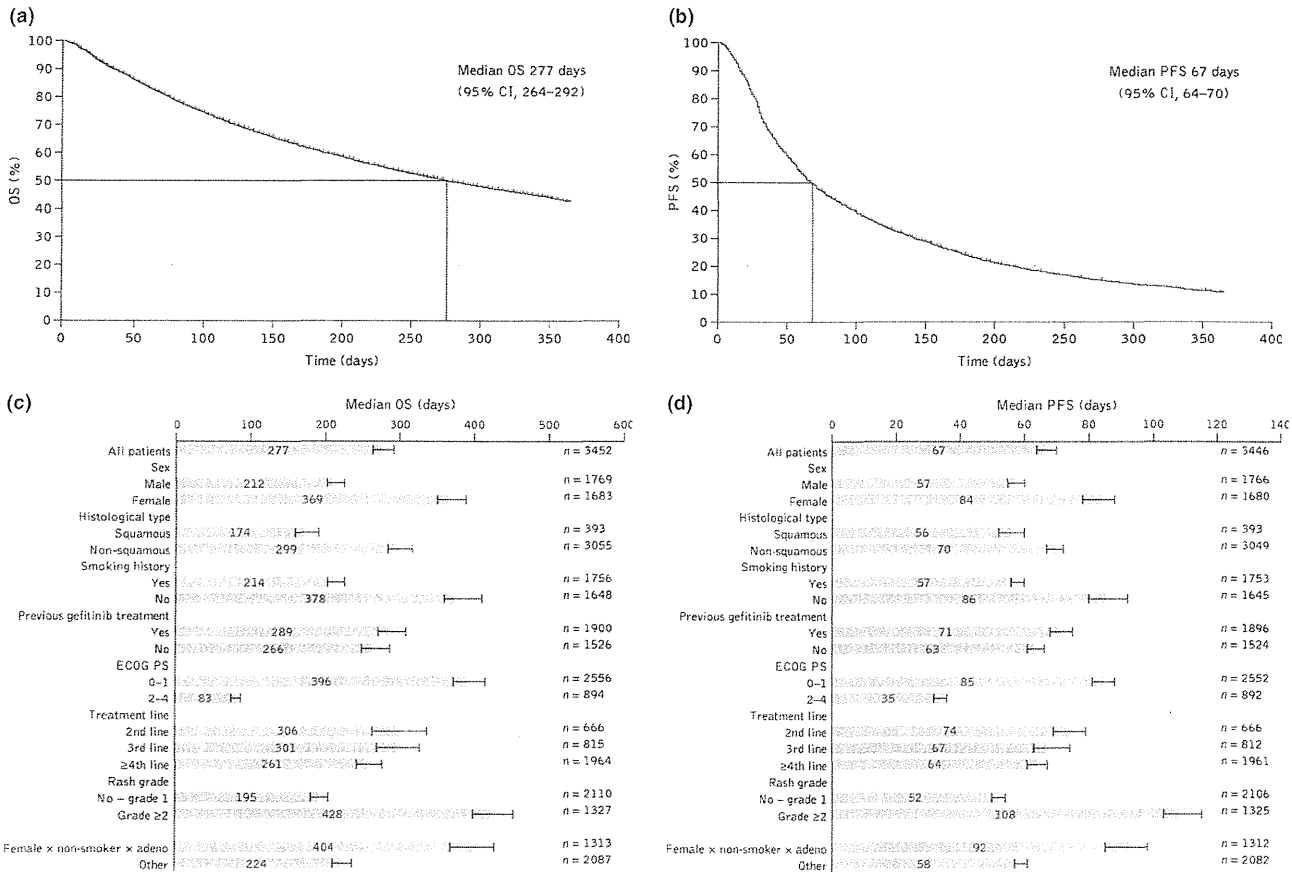

Fig. 3. (a) Overall survival (OS) and (b) progression-free survival (PFS) assessed by Kaplan–Meier methodology in the overall population of patients with unresectable, recurrent/advanced non-small-cell lung cancer who were treated with erlotinib in Japan between December 2007 and October 2009; (c) median OS and (d) PFS in patient subpopulations. CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status.

interstitial pneumonia (OR, 6.67) as poor prognostic factors for ILD death (Table 4).

A total of 12 patients reported concomitant honeycombing and interstitial pneumonia; of these patients, nine patients died of ILD, two patients improved their condition, and one patient did not recover. Of those who died, eight were determined as having CT-non-DAD-like pattern on CT scan and the remaining patient was determined as having CT-DAD-like pattern.

Efficacy. Median OS was 277 days (95% CI, 264–292), with a 6-month survival rate of 62.6% and a 12-month survival rate of 42.8% (Fig. 3a). Median PFS was 67 days (95% CI, 64–70), with a 6-month progression-free rate of 25.8% and a 12-month progression-free rate of 10.6% (Fig. 3b). Compared with the overall population, median OS and PFS appeared to be longer in female patients, non-smokers, patients with ECOG PS 0–1, and patients with grade ≥2 rash (Fig. 3c,d).

Discussion

The development of drug-induced acute pulmonary disorders or interstitial pneumonia caused by EGFR TKIs is a common problem; this has particular importance in Japan, because a variety of evidence has suggested that Japanese populations are more vulnerable to these disorders. This large-scale POLARSTAR study provides further decisive information on this issue. Final data from the POLARSTAR study confirm that erlotinib has a well-characterized safety profile with proven efficacy in Japanese patients in routine clinical practice.

In the final analysis from POLARSTAR, the rates of ILD development and mortality in patients with ILD (4.3% and 35.7%, respectively) were comparable with the ILD-associated incidence rates of 3–5% and mortality rates of 27.9–50.0% previously reported among Japanese patients with NSCLC and ILD treated with gefitinib or erlotinib.[2,3,5,6,9] In the POLARSTAR analysis, it was shown that ILD onset was typically soon after initiation of erlotinib, with the highest incidence occurring during the first 4 weeks. Physicians should therefore monitor patients for the symptoms of ILD, which usually occur within 8 weeks of treatment initiation. These findings are further supported by those reported in Japanese NSCLC studies with gefitinib.[5,6]

The risk factors identified as significant primary risk factors (HR, ≥1.5) for ILD occurrence or exacerbation using a Cox proportional hazards multivariate analysis were concurrent/previous ILD, concurrent/previous lung infection, concurrent/previous emphysema or COPD, and smoking history. Cox proportional hazards multivariate analysis was selected for this assessment as the authors considered that a time-dependent analysis was needed, as there was no information regarding the ILD development point in the initial analysis. Concurrent /previous emphysema or COPD was newly identified as a significant primary risk factor for ILD occurrence when analyzed in 9909 patients compared with the result of the interim analysis of 3488 patients (Table 5).[9,10] As ILD is a collective term for a variety of different lung conditions, it is important to be careful not to misdiagnose conditions as ILD, as this will affect the risk factor analysis.

The period from initial NSCLC diagnosis to the start of treatment (<360 days) was not considered as a risk factor for ILD that needed to be highlighted at this time (HR, 0.58), as the clinical grounds for this factor were not clear. Stage of progression of primary disease or bias of observational period from initial NSCLC diagnosis to termination of treatment were speculated to be the reason; however, details of these reasons are uncertain. In contrast to this analysis, risk factors for ILD associated with gefitinib have been reported as ECOG PS ≥2, smoking history, concomitant interstitial pneumonia, and prior chemotherapy.[5,7,8]

The multivariate analysis identified ECOG PS 2–4, ≤50% remaining normal lung area and concomitant honeycombing with interstitial pneumonia as poor prognostic factors for ILD death in POLARSTAR. Many patients with idiopathic interstitial pneumonias have idiopathic pulmonary fibrosis or non-specific interstitial pneumonia, which have a heterogeneous natural progression, with some patients remaining stable for extended periods, while others show steady worsening of the condition.[11] Some patients with chronic idiopathic interstitial pneumonias, such as idiopathic pulmonary fibrosis and non-specific interstitial pneumonia, experience acute exacerbations characterized by suddenly progressive and severe respiratory failure, with new lung opacities and pathological lesions of DAD.[12] It should be noted that there are racial differences between Mongolians (including the Japanese) and Caucasians in the frequency of acute exacerbations.[13] In the POLARSTAR study, the outcome of ILD by CT image pattern was investigated in 283 patients out of the 310 patients deemed as having confirmed ILD by the independent ILD Review Committee. The mortality rate for ILD among patients who were deemed to have CT-DAD-like pattern was higher than that seen among patients who were deemed as having CT-non-DAD-like pattern (65.1% *vs* 32.2%, respectively). Those patients with honeycombing and interstitial pneumonia ($n = 12$) had a high risk of poor prognosis, regardless of their CT pattern. Therefore, physicians should be actively aware of the symptoms of ILD and it is suggested to carefully monitor for these symptoms by CT image or X-ray throughout the disease course. Once physicians recognize ILD, they should immediately discontinue the EGFR TKI and should take the necessary steps to manage the ILD.

The final efficacy results from POLARSTAR are in line with the results of our interim analysis of the study (Table 6).[9] The final efficacy results (median OS, 277 days; median PFS, 67 days) were also comparable with efficacy reported in previous clinical trials of erlotinib treatment. The BR.21 study reported median PFS of 2.2 months (67 days) versus 1.8 months (55 days) and OS of 6.7 months (203 days) versus 4.7 months (143 days) for erlotinib and placebo, respectively, in the second- or third-line setting.[1] Kubota *et al.* investigated second-line erlotinib in Japanese patients, resulting in a median PFS of 77 days and OS of 14.7 months (447 days).[2] In a sec-

Table 5. Comparison of the interstitial lung disease (ILD) analysis from the interim and final analysis results for Post-Launch All-patient-Registration Surveillance in Tarceva®-treated non-small-cell lung cancer patients (POLARSTAR)

Endpoint	Interim analysis (safety, $n = 3488$) (efficacy, $n = 3453$)	Final analysis (safety, $n = 9909$) (efficacy, $n = 9663$)
ILD analysis		
Patients with confirmed ILD, *n* (%)	158 (4.5)	429 (4.3)
ILD-related mortality rate, %	1.6	1.5
ILD-related mortality rate in ILD patients	34.8	35.7
Risk factors for ILD development, HR		
Previous/concurrent ILD	4.1	3.2
Previous/concurrent Emphysema or COPD	–	1.9
Previous/concurrent lung infection	2.0	1.6
Smoking history	3.0	2.2
ECOG PS 2–4	1.6	1.4
<360 days from diagnosis to treatment	–	0.58

COPD, chronic obstructive pulmonary disease; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio.

Table 6. Comparison of the efficacy endpoints from the interim and final analysis results for Post-Launch All-patient-Registration Surveillance in Tarceva®-treated non-small-cell lung cancer patients (POLARSTAR)

Endpoint	Interim analysis (safety, $n = 3488$) (efficacy, $n = 3453$)	Final analysis (safety, $n = 9909$) (efficacy, $n = 9663$)
Efficacy endpoints		
Median OS, days	260	277
6-month OS rate, %	62.2	62.6
12-month OS rate, %	40.9	42.8
Median PFS, days	64	67
6-month PFS rate, %	23.7	25.8
12-month PFS rate, %	9.6	10.6

OS, overall survival; PFS, progression-free survival.

ond phase 2 study in Japanese patients with NSCLC, second-line erlotinib treatment resulted in median OS of 13.5 months (410 days).[3]

We acknowledge that there are several limitations of this study, including the fact that this was a single-arm observational study with no control group, and the lack of a strict observation period, unlike a clinical trial. The lack of information on *EGFR* mutation status is also considered a limitation as this is known to strongly affect the efficacy of erlotinib. The lack of patient selection criteria may also be seen as a limitation; however, this may mean that our study population was more representative of the actual Japanese population than would be the case in a clinical trial, especially because of the large patient population in this study. The information on EGFR TKI-associated ILD in this study is thought to be decisive; it provides valuable information for treatment considerations and monitoring in Japanese patients with *EGFR* mutant or wild-type lung cancer.

Healthcare providers should carefully observe patients during treatment with erlotinib to ascertain whether the patient has any of the risk factors detailed in this analysis. After suspicion of the onset of ILD and diagnosis by CT, it is important to follow the patient's status continuously and carefully monitor their risk level. The final safety and efficacy data from the large-scale POLARSTAR surveillance study confirm that erlotinib has a well-characterized safety profile with proven efficacy in Japanese patients; however, the risk of ILD should still be monitored.

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Disclosure Statement

KN, SK, YO, TJ, MA, NY, and MF have all participated as independent advisory board members for erlotinib, reimbursed by Chugai Pharmaceutical Co. Ltd. YO also has an immediate family member who is an employee of Chugai Pharmaceutical Co. Ltd. HA, YI, ME, TJ, MK, KK, FS, HT, AG, and YF have all participated as independent ILD Review Committee members for erlotinib, reimbursed by Chugai Pharmaceutical Co. Ltd. AS and TI are full-time employees of Chugai Pharmaceutical Co. Ltd. This trial was designed, funded, and monitored by Chugai Pharmaceutical Co. Ltd. Data were gathered, analyzed, and interpreted by Chugai with input from all authors. The corresponding author had full access to the relevant data and took full responsibility for the final decision to submit the report for publication. Although technically classed as a clinical trial, the POLARSTAR study was a non-interventional surveillance study analyzing all NSCLC patients receiving erlotinib in Japan, therefore it was not registered as a phase II/III clinical trial would be.

Abbreviations

ADR	adverse drug reaction
AE	adverse event
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CT	computed tomography
DAD	diffuse alveolar damage
ECOG	PS Eastern Cooperative Oncology Group performance status
EGFR	epidermal growth factor receptor
HR	hazard ratio
ILD	interstitial lung disease
NSCLC	non-small-cell lung cancer
OR	odds ratio
OS	overall survival
PFS	progression-free survival
POLARSTAR	Post-Launch All-patient-Registration Surveillance in Tarceva®-treated NSCLC patients
TKI	tyrosine-kinase inhibitor

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