ORIGINAL ARTICLE

Clinical features, diagnosis, and outcome of anaplastic lymphoma kinase tyrosine kinase inhibitors associated interstitial lung disease

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ABSTRACT

Background and aim: To investigate the clinical features of anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitors (TKI)-associated interstitial lung disease (ILD), and to provide a reference for the rational use of ALK TKI.
Methods: Cases of ALK TKI-associated ILD before December 31, 2025 were collected by searching the database and clinical data were collected for retrospective analysis.
Result: Fifty patients were included, with a median age of 54.5 years (range 33, 86). The median time of ILD occurrence was 50 days (range 2, 630). Dyspnea (56.0%), hypoxemia (38.0%), cough (36.0%) and fever (26.0%) were the main clinical symptoms, and there may also be no symptoms. Computed tomography mainly showed ground-glass opacities (98.0%). After the patients discontinued ALK-TKI and received systemic steroid treatment, 90.0% of the patients had symptom relief and improved imaging, and 10.0% of the patients died.
Conclusion: ILD is a rare and fatal adverse event of ALK-TKI. The possibility of ILD should be considered if dyspnea, hypoxemia, and cough occur during ALK-TKI use. After ILD recovery, patients could switch to the same ALK-TKI or another ALK-TKI under the protection of glucocorticoid.

Key words: anaplastic lymphoma kinase tyrosine kinase inhibitors, brigatinib, alectinib, lorlatinib, interstitial lung disease

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Introduction

Lung cancer is the most common malignant tumor in the world, with an annual incidence of 2.09 million cases (1). Non-small cell lung cancer (NSCLC) accounts for about 85% of all lung cancers and is the leading cause of cancer death (2). The introduction of anaplastic lymphoma kinase-tyrosine kinase inhibitors (ALK-TKI) has changed the treatment pattern and has become the standard treatment method for advanced NSCLC with ALK rearrangement (3,4). ALK-TKI significantly improve the progression-free survival and better quality of life of patients (5). The relatively common adverse reactions related to ALK-TKI treatment in clinical practice mainly include gastrointestinal adverse reactions, visual impairment, rash, edema, hematological toxicity, etc (6,7). Interstitial lung disease (ILD) is a rare but life-threatening adverse event related to ALK-TKI. How to manage ALK-TKI-associated ILD and improve the quality of life and survival benefit has become an important topic in clinical use of ALK-TKI. The current understanding of ALKI-associated ILD comes mainly from case reports, and the specific clinical features are not clear. The aim of this study is to explore the clinical characteristics of ALK-TKI -associated ILD, and to provide a reference for the optimal treatment of ALK-TKI -associated ILD and the continued treatment of NSCLC after ILD remission.

Materials and Methods

Retrieval scheme

We collected clinical reports of ALK-TKI -associated ILD by searching the database. These databases include PubMed, Embase, Web of Science, Google Scholar, Cochrane Library databases, Wan-Fang Database, Chinese National Knowledge Infrastructure, China Biology Medicine disc and Chinese Science and Technology Periodical Database. We use Boolean operators ("OR" and "AND") to connect subject terms and keywords, including "crizotinib" OR "ceritinib" OR "alectinib" OR "brigatinib" OR "lorlatinib", "ensartinib", OR "iruplinalkib", OR "invonalkib" OR "anaplastic lymphoma kinase-tyrosine kinase inhibitors" AND "interstitial pneumonia" OR "pulmonary toxicity" OR "pneumonia" OR "interstitial lung disease" OR "organizing pneumonia" OR "organizational pneumonia" OR "lung toxicity" OR "pulmonary fibrosis". The search period is up to December 31, 2025, and the languages are Chinese and English.

Inclusion and exclusion

Case reports and case series of ALK-TKI -associated ILD were included. Review, duplicate patient and mechanism studies were excluded.

Data extraction

The author designed a table and extracted the clinical data of the patients, including gender, age, country, underlying diseases, smoking history, treatment history, concomitant medications, indications, dosage, onset time, type of ALK-TKI, gene mutation, clinical symptoms, computed tomography (CT), bronchoalveolar lavage fluid (BALF), transbronchial lung biopsy (TBLB), laboratory tests, treatment and prognosis.

Statistical analysis

The extracted data was analyzed statistically through SPSS 25.0. Measurement data were expressed as median values (range minimum, maximum), and count data were expressed as n (%).

Results

Epidemiological characteristics

After searching the database, a total of 42 articles involving 50 patients were included based on the inclusion and exclusion criteria. The epidemiological characteristics of the 50 patients are summarized in Table 1. The median age of the 50 patients was 54.5 (range 33, 86), including 27 (54.0%) females. These patients were mainly from Japan (18 cases, 36.0%) and China (14 cases, 28.0%). The median time to onset of ILD was 50 days (range 2, 630), and 68.0% of patients

Table 1. Epidemiological characteristics of 50 patients with ALK TKI-associated ILD

Parameters	Variable	Values
Age	year	54.5 (33, 86) [b]
Sex	female male	27 (54.0%) 23 (46.0%)
Country	Japan China France USA Spain India Australia Portugal Korea Brazil	18 (36.0%) 14 (28.0%) 8 (16.0%) 3 (6.0%) 2 (4.0%) 1 (2.0%) 1 (2.0%) 1 (2.0%) 1 (2.0%) 1 (2.0%)
Time to event onset (49)[a]	days 2-90 91-210 211-630 crizotinib (30) [a] alectinib (15) [a] brigatinib (2) [a] ceritinib (2)[a]	50 (2, 630) [b] 34 (68.0%) 10 (20.0%) 5 (10.0%) 48.5 (2, 630) [b] 90 (18, 360) [b] 13.5 (7, 20) [b] 132 (54, 210) [b]
ALK-TKI	crizotinib alectinib ceritinib brigatinib	30 (60.0%) 15 (30.0%) 3 (6.0%) 2 (4.0%)
Dosage (42)[a]	alectinib 300 mg twice daily 600 mg twice daily 150 mg twice daily crizotinib 250 mg twice daily 400mg daily 250 mg daily brigatinib 180 mg daily ceritinib 750 mg daily	15 (35.7%) 4 (26.7%) 9 (60.07%) 2 (13.3%) 24 (57.1%) 22 (91.7%) 1 (4.2%) 1 (4.2%) 2 (4.8%) 2 (100.0%) 1 (2.4%) 1 (100.0%)
Cancer	NSCLC	50 (100%)
Gene mutation (48)[a]	ALK mutation positive ROS1 cmet	43 (89.6%) 4 (8.3%) 1 (2.1%)
Stage at diagnosis (31)[a]	II III IV	1 (2.0%) 4 (8.0%) 26 (52.0%)
Smoking (37) [a]	nonsmoker current or former	26 (70.3%) 11 (29.7%)
Prior immunotherapy	crizotinib, alectinib, gefitinib, osimertinib, icotinib, pembrolizumab	5 (10.0%)
Line of ALK-TKI	1 2 3 4 5	23 (46.0%) 14 (28.0%) 8 (16.0%) 2 (4.0%) 3 (6.0%)
Medical history	allergic asthma, depression, dyslipidaemia, hypertension, chronic kidney disease, stroke, preexisting interstitial pneumonia,	6 (12.0%)
Concomitant medications	atenolol, amlodipine, irbesartan, zolpidem, morphine, alprazolam, carvedilol, divalproex, famotidine, simvastatin, furmonertinib, furosemide, levocetirizine, nadroparine calcique, tramadol-paracetamol, loperamide, tinzaparine, metoclopramine, omeprazole, domperidone, ondansetron, amitriptyline, tramadol, fondaparinux, prednisone, risedronate, rabeprazole, enoxaparin, venlafaxine, zoledronic acid	10 (20.0%)

Abbreviations: ALK-TKI, anaplastic lymphoma kinase-tyrosine kinase inhibitors; NSCLC, Non-small cell lung cancer. a Represents the number of patients out of 50 about whom information regarding this particular parameter was provided. b Median (range minimum, maximum).

had ILD within 3 months. The median occurrence time of brigatinib-associated ILD was the earliest, at 13.5 days (7, 20). The most reported ALK-TKI was crizotinib (30 patients, 60.0%), followed by alectinib (15 patients, 30.0%), ceritinib (3 patients, 6.0%), and brigatinib (2 patients, 4.0%). Gene mutations were described in 48 patients, including ALK mutation (43 cases, 89.6%), ROS1mutation (4 cases, 8.3%), and cMET mutation (1 case, 2.1%). Five (10.0%) patients received other immunosuppressant treatments, such as crizotinib, alectinib, gefittinib, osimertinib, icotinib, and pembrolizumab. Thirty-seven patients reported

smoking, 11 of whom were smokers. Six patients (12.0%) had a history of disease, including 1 patient with pre-existing interstitial pneumonia. Ten (20.0%) patients used other drugs simultaneously, such as amlodipine, rabeprazole and omeprazole.

Clinical symptoms

The clinical symptoms of 50 patients are summarized in Table 2. Nine patients (18.0%) had no symptoms. Dyspnea (28 cases, 56.0%), hypoxemia (19 cases, 38.0%), cough (18 cases, 36.0%) and fever (13 cases, 26.0%) were the main clinical symptoms. A few patients may present with short of breath (4 cases, 8.0%), chest distress (4 cases, 8.0%), short of breath (1 case, 2.0%), chest distress (1 case, 2.0%). Hemoptysis (1 case, 2.0%), chills (1 case, 2.0%), chest pain (1 case, 2.0%), fatigue (1 case, 2.0%) and myalgia (1 case, 2.0%). According to the CTCAE v5.0 standard, ALK-TKI-associated ILD was classified into grade 1 (9 cases, 18.0%), grade 2 (4 cases, 8.0%), grade 3 (25 cases, 50.0%), grade 4 (7 cases, 14.0%), and grade 5 (5 cases, 10.0%).

Computed tomography

The CT examinations of 50 patients are summarized in Table 2. CT mainly showed ground-glass opacities (47 cases, 98.0%), pleural effusion (9 cases, 18.0%), patchy (6 cases, 12.0%), consolidation (5 cases, 10.0%) and septal thickening (4 cases, 8.0%).

Table 2. Clinical symptoms, laboratory tests and imaging examinations of 50 patients with ALK TKI-associated ILD

Parameters	Variable	Values
Clinical symptoms	asymptomatic	9 (18.0%)
	dyspnea	28 (56.0%)
	hypoxemia	19 (38.0%)
	cough	18 (36.0%)
	fever	13 (26.0%)
	short of breath	4 (8.0%)
	chest distress	4 (8.0%)
	hemoptysis	1 (2.0%)
	chills	1 (2.0%)
	chest pain	1 (2.0%)
	fatigue	1 (2.0%)
	myalgia	1 (2.0%)
CT (50)[a]	ground-glass opacities	47 (98.0%)
	pleural effusion	9 (18.0%)
	patchy	6 (12.0%)
	consolidation	5 (10.0%)
	septal thickening	4 (8.0%)
	exudative lesion	1 (2.0%)
	mass-like lesions	1 (2.0%)
	organizing pneumonia	1 (2.0%)
	fibrosis	1 (2.0%)
BALF (24)[a]	predominantly lymphocytes	13 (54.2%)
	predominantly macrophages	3 (12.5%)
	negative culture	24 (100.0%)
	normal	1 (4.2%)
TBLB (12)[a]	organizing pneumonia	5 (41.7%)
	lymphocytic alveolitis	4 (33.3%)
	thickening of the septa	2 (16.7%)
	interstitial inflammation	2 (16.7%)
	macrophage alveolitis	1 (8.3%)
	alveolar oedema	1 (8.3%)
	fibrosis	1 (8.3%)
ILD grade	1	9 (18.0%)
	2	4 (8.0%)
	3	25 (50.0%)
	4	7 (14.0%)
	5	5 (10.0%)
KL-6 (6)[a]	U/mL	402 (211, 1439)[b]
Surfactant Protein-D (6)[a]	ng/mL	152 (19.3, 244)[b]
CRP (11)[a]	mg/dL	1.94 (0.02, 11.93)[b]
WBC (11)[a]	/μL	8750 (8200, 17050)[b]
	normal	6 (54.5%)
	elevated	5 (45.5%)
LDH (6)[a]	U/L	332.5 (202, 405)[b]
PCT (4)[a]	ng/ml	0.87 (0.09, 2.28)[b]

Abbreviations: BALF, Bronchoalveolar lavage fluid; CRP, C-reactive protein; CT, computed tomography; LDH, lactate dehydrogenase; KL-6, krebs von den Lungen-6; TBLB, transbronchial lung biopsy; WBC, white blood cell; ILD Interstitial lung disease, OP, organized pneumonia; a Represents the number of patients out of 50 about whom information regarding this particular parameter was provided. b Median (range minimum, maximum).

Laboratory tests

The laboratory tests of the 50 patients are summarized in Table 2. BALF was performed in 24 patients, mainly showing lymphocyte infiltration (13 cases, 54.2%) and macrophage infiltration (3 cases, 12.5%). The BALF culture of 24 patients were negative. TBLB was performed in 12 patients, mainly presenting as organizing pneumonia (5 cases, 41.7%) and lymphocytic alveolitis (4 cases, 33.3%). Krebs von den Lungen-6 (KL-6) was tested in 6 patients, with a median value of 402 U/mL (range 211, 1439). Surfactant Protein-D (SP-D) was detected in 6 patients, with a median value of 152 ng/mL (range 19.3, 244). Lactate dehydrogenase was detected in 6 patients, with a median value of 332.5 U/L (range 202, 405). C-reactive protein was reported in 11 patients, with a median value of 1.94 mg/dL (range 0.02, 11.93).

Treatment and outcomes

The treatment and outcomes of 50 patients are summarized in Table 3. Forty-six (92.0%) patients discontinued ALK-TKI, and 4 (8.0%) patients continued treatment. Thirty-seven (74.0%) patients received systemic steroid treatment, and one (2.0%) patient received systemic steroid combined with bevacizumab treatment. Fifteen (30.0%) patients received antibacterial drug treatment. After the above treatment, 45 (90.0%) patients had symptom relief and imaging improvement, and 5 (10.0%) patients died. After the improvement in symptoms and imaging findings, 17 patients (34.0%) received the same ALK-TKI treatment again, while 13 patients (26.0%) switched to another ALK-TKI. During the median follow-up of 5.5 months (range 1.5, 33), 2 (11.8%) of 17 patients receiving the same ALK-TKI relapsed, while after 13 patients switched to another ALK-TKI treatment, 3 patients (23.1%) had a recurrence.

Table 3. Treatment and prognosis of 50 patients with ALK TKI-associated ILD

Parameters	Variable	Values
ILD treatment	discontinued continued steroid steroid+ bevacizumab antibacterial drugs	46 (92.0%) 4 (8.0%) 37 (74.0%) 1 (2.0%) 15 (30.0%)
Outcomes	relief death	45 (90.0%) 5 (10.0%)
Subsequent treatment after recovery from ILD (30)[a]	re-challenge the same ALK-TKI switch to another ALK-TKI	17 (34.0%) 13 (26.0%)
ILD recurrence	re-challenge the same ALK-TKI no recurrence recurrence switch to another ALK-TKI no recurrence recurrence	17 (34.0%) 15 (88.2%) 2 (11.8%) 13 (26.0%) 10 (76.9%) 3 (23.1%)
Follow-up time (24)[a]	months	5.5 (1.5, 33) [b]

[a] Represents the number of patients out of 50 about whom information regarding this particular parameter was provided. [b] Median (range minimum, maximum).

Discussion

Drug-induced interstitial lung disease (DI-ILD) is a rare adverse event characterized by progressive respiratory symptoms and radiological pulmonary abnormalities after exposure to suspected drugs (8). The overall incidence of ALK TKI-associated ILD was 2.14% (9). Different types of ALK-TKI may all lead to ILD, but the incidence rates vary. The incidence rates of ILD in patients using crizotinib, ceritinib, alectinib, lorlatinib and brigatinib were 2%, 4.0%, 0.4%, 1.8% and 4.4%, respectively (10,11). When diagnosing ALK-TKI-associated ILD, it is necessary to carefully examine the other concomitant drugs in order to rule out other potential causes. In addition to ALK-TKI, other concomitant drugs can also cause ILD, such as venlafaxine and statins. First, it is based on the fact that the occurrence of ILD is reasonably temporally correlated with ALK-TKI. Secondly, ILD is a known adverse reaction of ALK-TKI. Thirdly, after the discontinuation of ALK-TKI, the patient's symptoms and radiological findings improved. Altogether, these findings indicate that ILD was associated with ALK-TKI exposure. Data analysis of the FDA's Adverse Event Reporting System (FAERS) revealed that female

gender and concomitant diseases (diabetes mellitus, hypertension, dyslipidemia) and constipation and concomitant drugs (proton pump inhibitors, amlodipine, and magnesium oxide) significantly increase the risk of ALK TKI-associated ILD (12). Hwang et al. 's retrospective analysis of non-small cell lung cancer patients exposed to ALK-TKI found that gender had no effect on pulmonary toxicity (13). Our study found a slight predominance of females in patients with ALK TKI-associated ILD. The influence of gender on ALK-TKI -associated ILD may be affected by multiple factors and further research is needed for confirmation. Kawamura et al. reported that patients who concurrently received proton pump inhibitors had a higher incidence and risk of acute exacerbation of ILD (14). Gemma et al. found that concurrent/previous ILD, emphysema or chronic obstructive pulmonary disease, pulmonary infection, smoking history, and a shorter interval from the initial cancer diagnosis to the start of treatment (<360 days) are important risk factors for the development of ILD in patients treated with erlotinib (15). Another study found that being over 55 years old, performance status (2-4), smoking history, previous or concomitant ILD and comorbidities of pleural effusion are risk factors for crizotinib-associated ILD (16). Oshima et al. found that the incidence of ILD was higher among patients who received PD-1/PD-L1 inhibitors before EGFR-targeted therapy (17). The risk of adverse events for patients is the greatest when they start within 3 months after the checkpoint suppression is stopped (18). One patient received two cycles of pembrolizumab treatment before using alectinib (19). Therefore, it should be noted that the sequential use of checkpoint inhibitors before ALK-TKI treatment may increase the risk of ALK-TKI-associated ILD. Increased blood concentration may be a risk factor for ALK TKI-associated ILD (20). Patients with kidney injury, liver injury or those using interacting drugs in combination should be aware of the possibility of ILD occurrence. Approximately 68% of ALK TKI -associated ILD cases occur within the first 3 months of initiating ALK-TKI treatment. However, the median time to ILD onset varied between ALK-TKI, with ceritinib having a significantly longer delay and brigatinib having the shortest onset. Like other DI-ILD, common symptoms of ILD associated to ALK-TKI include fever, dyspnea and cough, and it can also present as asymptomatic ILD. This indicates that it is necessary to monitor lung toxicity within three months before the use of ALK TKI. CT plays a core role in the diagnosis of ILD. The most common disease patterns of DI-ILD include nonspecific interstitial pneumonia (NSIP), organising pneumonia, and diffuse alveolar damage (DAD) hypersensitivity pneumonitis (HP) and simple pulmonary eosinophilia (8). The most common CT abnormality of ALK-TKI -associated ILD is GGO. Drugs can produce various histopathological patterns of ILD. The most common morphological patterns of DI-ILD include DAD and organising pneumonia, cellular and/or fibrotic NSIP, HP, granulomatous pneumonitis, eosinophilic pneumonia, pulmonary haemorrhage or oedema, constrictive bronchiolitis and vascular modifications (21). The histological morphology of ALK-TKI -associated ILD is manifested as organizational pneumonia and lymphocytic alveolitis. The mechanism of DI-ILD may involve direct damage to alveolar epithelial or capillary endothelial cells, dysregulation of the immune system, systemic cytokine release, cell-mediated lung damage and free radical generation (22). The mechanism of ALK-TKI -associated ILD remains unclear. Genetic factors are regarded as risk factors for the occurrence of DI-ILD. Compared with other populations, the allele frequency of HLA-DRB1*04:05 is higher in the Japanese population, which may be the high susceptibility of Japanese patients to DI-ILD (23). In this study, the Japanese were the main affected group. There is no clear treatment for DI-ILD. Similarly, the optimal treatment plan for ALK-TKI -associated ILD remains unclear. Once ILD occurs, discontinuing the suspected drug is the top priority. Data on the efficacy of systemic steroid treatment for DI-ILD are limited. Systemic steroid can be used for severe patients or those whose condition progresses after drug withdrawal. The dosage and duration of systemic steroid treatment vary greatly, mainly based on the radiological pattern of ILD (24). Given the definite efficacy of ALK-TKI in NSCLC, the reuse of ALK-TKI is worth considering. There are still no guidelines for the continued treatment of NSCLC after remission of ALK TKI-associated ILD. Although all ALK TKI carry the risk of ILD, ILD generally does not recur when switched

to another ALK TKI treatment, especially under the protection of glucocorticoids. It might be due to the different inhibitory pathways of different ALK-TKI that further research is needed to explain the underlying mechanism (25). The treatment of non-small cell lung cancer with the same ALK TKI under the protection of glucocorticoids is also an option. For patients who have recovered from ILD, whether to switch to another ALK-TKI or use the same ALK-TKI needs to take into account the patient's condition to formulate a plan. Despite receiving timely treatment, 10% of the patients still died. This is lower than the previously reported 50% mortality rate (26). However, it is unclear whether ALK-TKI-associated ILD progresses to pulmonary fibrosis. More studies and longer follow-up are needed to investigate the prognosis of ALK-TKI -associated ILD.

Conclusion

ILD is a rare and fatal adverse event of ALK-TKI. The possibility of ILD should be monitored during the use of ALK-TKI, especially within the first three months. ILD mainly presents with dyspnea, hypoxemia and cough, but may also have no symptoms. CT is an important tool for diagnosing ILD and often presents as ground-glass opacities. After ILD recovery, patients could switch to the same ALK-TKI or another ALK-TKI under the protection of glucocorticoid.

Abbreviations

ALK-TKI: Anaplastic lymphoma kinase-tyrosine kinase inhibitors
BALF: Bronchoalveolar lavage fluid
CT: Computed tomography
DI-ILD: Drug-induced interstitial lung disease
FAERS: FDA's Adverse Event Reporting System
ILD: Lnterstitial lung disease
NSCLC: Non-small cell lung cancer
TBLB: Transbronchial lung biopsy
KL-6: Krebs von den Lungen-6
SP-D: Surfactant Protein-D

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Data Availability Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

Ethical Approval: This study did not require ethical approval in accordance with local/national guidelines. The published case report includes evidence that medical treatment was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

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