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Interstitial Lung Disease Induced by Targeted Therapy for Non-Small Cell Lung Cancer: A Review of Diagnosis, Workup, and Management

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Abstract

Targeted therapies are being increasingly used for cancer treatments and had been proven to improve clinical outcomes. Although targeted therapies demonstrate survival benefit in particular patient populations, they may also increase the frequency of treatment-related toxicities and morbidity. The pulmonary toxicities, especially drug induced-interstitial lung disease (ILD), have emerged as critical adverse drug reactions which are potentially fatal. The main managment of targeted therapy-induced ILD includes drug discontinuation and corticosteroid therapy, but no standard guideline for the treatment of targeted therapy-induced ILD was established. Clinical physicians must cautiously weigh the benefits and risks of targeted therapies causing ILD in order to provide optimal treatments and favorable outcomes. Relevant clinical information regarding management of targeted therapy-induced ILD was reviewed in this article.

Keywords: Targeted therapy; Interstitial lung disease; Non-small cell lung cancer

Introduction

Over the past decade, a large number of antineoplastic targeted therapies had demonstrated remarkable advances, and many of these durgs had been proven to improve patients' survival time, either progression-free survival or overall survival. More and more targeted therapies were used according to the specific molecular features of various tumors. Although targeted therapies provide survival benefit in specific patient populations, they may also increase the frequency of treatment-related toxicities and morbidity [1,2]. The pulmonary toxicities, especially drug induced- interstitial lung disease (ILD), have emerged as critical adverse drug reactions. Therefore, not only pulmonologists may confront ILD, but clinical oncologists of various subspecialties also have chances to deal with drug-induced ILD. In this article, we have reviewed relevant clinical information regarding the management of targeted therapy-induced ILD.

Clinical symptoms of targeted therapy-induced ILD are nonspecific, including cough, shortness of breath, low-grade fever, and hypoxemia [3]. The disease course may range from asymptomatic radiographic findings of pulmonary infiltrates to fulminant disease. Many targeted therapies for the treatment of non-small cell lung cancer (NSCLC) and the other malignancies are associated with ILD, including epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKI), anaplastic lymphoma kinase (ALK) inhibitors, angiogenesis inhibitors, Bcr-Abl tyrosine kinase inhibitors, human epidermal growth factor receptor 2 (HER2) inhibitors, mammalian target of rapamycin (mTOR) inhibitors, various monoclonal antibodies, etc [1,4]. The succinct introduction of targeted agents which induce ILD is described below (Table 1).

Drug class	Drugs	Frequency	Mortality rate
EGFR-TKI	Gefitinib	0.3%-5.3%	0.3%-1.6%
	Erlotinib	0.8%-4.5%	0.6%-1.58%
	Afatinib	1.3%	1%
	AZD9291	2.5%	NA
	Lapatinib	0.5%	0.05%
Anti-EGFR monoclonal antibodies	Cetuximab	1.2%	0.5%
	Panitumumab	1.1%	0.4%
ALK inhibitors	Crizotinib	1.6%	0.5%
	Ceritinib	4%	0.3%
Angiogenesis inhibitors	Bevacizumab	0.37%	0.07%
	Sorafenib	0.33%-0.62%	0.16%-0.31%
	Sunitinib	0.65%	0.14%
Bcr-Abl tyrosine kinase inhibitors	Imatinib	1.3%	NA
	Dasatinib	2.9%	NA
	Nilotinib	1.4%	0.32%
HER2 inhibitors	Trastuzumab	<1%	NA
Anti-CD20 monoclonal antibody	Rituximab	8%	NA
mTOR inhibitors	Temsirolimus	0.5%-5%	Rare

	Everolimus	8%-14%	3.8%

Table 1: Reported frequency, and mortality rate of targeted therapy-induced interstitial lung disease; ALK: Anaplastic lymphoma kinase; EGFR: epidermal growth factor receptor; HER: human epidermal growth factor receptor; mTOR: mammalian target of rapamycin ; NA: not available; TKI: tyrosine kinase inhibitor

EGFR-TKI

First-generation EGFR-TKIs include gefitinib and erlotinib. Both are orally administered small molecules that reversibly inhibit the EGFR tyrosine kinase for the treatment of advanced non-small cell lung cancer (NSCLC). They provide better response rate, improved progression free survival (PFS), and less toxicity when compared with platinum-based doublet chemotherapy for advanced NSCLC with activating EGFR mutation [5]. Their side effects such as dose-dependent skin rash and diarrhea are usually mild to moderate. Pulmonary toxicity was also reported, and drug-induced ILD may be lethal. The mechanism of drug-induced ILD remains unclear. Previous reports suggested that the EGFR on type II pneumocytes was associated with alveolar wall repair. Thus, EGFR inhibition due to EGFR-TKIs may interfere with alveolar repair ability, and interrupt recovery from lung injury [6-8].

The worldwide incidence of ILD related to gefitinib was reported as approximately 1% [higher in Japan (2%) than in USA (0.3%)], and about one-third of these cases were fatal in a postmarketing analysis of 50,005 patients [9,10]. In several clinical trials, the reported incidence of ILD ranged from 1.3 to 5.3 % [11-14]. The reported risk factors for ILD related to gefitinib were older age (more than 55 years old), poor performance status (ECOG≥2), smoking history, short period since diagnosis of lung cancer (less than 6 months), preexisting ILD, and concurrent heart disease [4,15].

The frequency of Erlotinib-induced ILD has been reported by US FDA (Food and Drug Administration) to be about 0.8% [16]. In the independent review of TRIBUTE (Tarceva Responses in Conjunction with Paclitaxel and Carboplatin) study, fatal ILD related to erlotinib was identified in 0.6% of patients (3/526 cases) [17]. A post-marketing surveillance study in Japan revealed that 158 of 3488 patients (4.5%) had erlotinib-induced ILD, and 55 of 158 cases (34.8%) with ILD were fatal [4,18]. Patients receiving erlotinib usually developed ILD within the first 2 weeks, and the frequency of ILD following initiation of erlotinib therapy gradually decreased over time. The reported risk factors for erlotinib-induced ILD included preexisting ILD, smoking history, poor performance status, and prior pulmonary infection [18].

Afatinib, a second-generation EGFR-TKI, was developed as irreversible pan-HER (human epidermal growth factor receptor) inhibitors for the treatment of NSCLC with activating EGFR mutation. The incidence of ILD related to afatinib was reported as 1.3% (3/229 cases), and resulted in fatal outcome in 1% of patients receiving afatinib [19]. AZD9291, a third-generation EGFR-TKI, is an irreversible EGFR inhibitor that target T790M and classic EGFR mutations while sparing wild-type EGFR for the treatment of NSCLC. In a multicenter phase I trial, ILD-like events were identified in 2.5% of patients receiving AZD9291 (5/199 cases), and all of them were resolved without fatality [20]. Lapatinib is a dual EGFR/HER2 TKI for the treatment of HER2-overexpressing breast cancer. The reported frequency of ILD related to lapatinib was 0.5% (11 of 2201 patients), and 1 of 11 cases with ILD was fatal [4].

Anti-EGFR Monoclonal Antibodies

Cetuximab and panitumumab are monoclonal antibodies that target the ligand-binding domain of the epidermal growth factor receptor (EGFR), and both are approved for advanced colorectal cancer. The frequency of ILD related to cetuximab was 1.2% (24 of 2006 cases), and the rate of fatality was 41.7% (10 of 24 cases) in patients with ILD [21]. Panitumumab-induced ILD was reported to occur in 1.1% of treated patients (19 of 1767 cases), and 7 of 19 cases with ILD died. The ILD related to cetuximab and panitumumab appears to be uncommon [4].

Anaplastic Lymphoma Kinase (ALK) Inhibitors

Crizotinib and ceritinib are orally anaplastic lymphoma kinase (ALK) inhibitors for the treatment of advanced NSCLC. In a phase II studies of crizotinib, 1.6% of patients (4/255 cases) had pneumonitis [22]. The frequency of ceritinib-induced ILD/pneumonitis was reported in 4% of treated patients (n=255), and one patient with pneumonitis died [23].

Angiogenesis Inhibitors

Bevacizumab was a monoclonal antibody that targets vascular endothelial growth factor (VEGF) for the treatment of nonsquamous NSCLC and metastatic colorectal cancer. In an analysis with 2698 colorectal cancer patients, 10 patients had ILD (0.37%), and 2 of 10 patients (20%) with ILD died [4].

Sorafenib is a multitargeted tyrosine kinase inhibitor against Raf kinase, VEGF receptor, and platelet-derived growth factor receptor (PDGFR). It was used to treat hepatocellular carcinoma (HCC), and renal cell carcinoma (RCC). The reported frequencies of ILD related to sorafenib were 0.62% (4 of 647 cases) in HCC patients, and 0.33% (8 of 2407 cases) in RCC patients, and 50% of ILD cases was fatal [24].

Sunitinib is also a multitargeted tyrosine kinase inhibitor against PDGFR, VEGF receptor, FMS-like tyrosine kinase-3 (FLT3), colony-stimulating factor type 1 (CSF-1R), and glial cell-line-derived neurotrophic factor receptor (RET). It was used to treat gastrointestinal stromal tumors (GIST) with resistance to imatinib, pancreatic neuroendocrine tumors (PNET), and RCC. In an analysis with 2141 patients with GIST and RCC, 14 patients had ILD (0.65%), and 3 of 14 patients (21.4%) with ILD was fatal [4].

Bcr-Abl Tyrosine Kinase Inhibitors

Imatinib is a tyrosine kinase inhibitor against Bcr-Abl, KIT, PDGFR tyrosine kinases for the treatment of GIST, and Philadelphia chromosome-positive chronic myelogenous leukemia. Imatinib-induced ILD is rare [25]. In an analysis of 3023 adverse events during imatinib treatment, 39 patients with ILD were reported. Among them, 27 patients were analyzed, and 24 cases were treated with corticosteroids. ILD was improved in 23 patients, and no fatality was reported in this study [26].

The second generation Bcr-Abl tyrosine kinase inhibitors include dasatinib and nilotinib. ILD related to dasatinib was reported in 24 of 838 treated patients (2.9%) [4]. The frequency of ILD related to nilotinib was 1.4% (9 of 629 cases), and the rate of fatality was 22.2% (2 of 9 cases) in patients with ILD [4].

HER2 Inhibitors

Trastuzumab is a monoclonal antibody binding to the extracellular domain of the HER2 protein for the treatment of breast cancer. The incidence of trastuzumab-induced interstitial pneumonitis, organizing pneumonia, and acute respiratory distress syndrome (ARDS) was less than one percent in the previous reports [27-30].

Anti-CD20 Monoclonal Antibody

Rituximab is an anti-CD20 monoclonal antibody for the treatment of non-Hodgkin lymphoma, and rheumatoid arthritis. The frequency of ILD had been reported in 9 of 107 lymphoma patients (8%) receiving rituximab and one patient with ILD died of secondary infection [31].

Mammalian Target of Rapamycin (mTOR) Inhibitors

The mTOR inhibitors include temsirolimus and everolimus. Temsirolimus was used for the treatment of advanced RCC. Temsirolimus-associated ILD had been reported in 0.5 to 5 % of cancer patients in several studies, and the fatalities were rare [32-36]. Everolimus was used for the treatment of advanced RCC, and PNET. The frequencies of ILD related to everolimus ranged from 8 to 14% of treated patients [36-42]. The mortality rate due to ILD was reported to be 3.8% (4 of 105 patients) in a previous study [4].

Diagnosis and Management of Targeted Therapy-Induced ILD

Patients with drug-induced ILD (DILD) usually present with non-specific symptoms and signs, and no specific laboratory test, radiographic features, or pathologic findings are available to establish the diagnosis. Therefore, DILD usually remains a diagnosis of exclusion. The diagnostic criteria has been suggested as follows [4,43-45] : (1) A drug exposure history; (2) clinical, radiographic, and histopathological characteristics which are compatible with previous findings of the the identical drug; (3) other pulmonary diseases should be excluded; (4) improvement after cessation of the suspected drug; and (5) Recurrence of ILD after rechallenge.

Exclusion of other pulmonary disease is very important, and the differential diagnosis includes pulmonary infection, cardiogenic or non-cardiogenic pulmonary edema, pulmonary metastasis, lymphangitic carcinomatosis, pulmonary embolism, radiation-induced lung injury, preexisting ILD, etc.

The laboratory tests (such as blood examinations, bacterial cultures, viral serology, etc.) are utilized to determine the disease processes. Radiographic studies are useful to evaluate the disease severity and properties, but the radiographic findings are usually insufficient to establish the diagnosis. Pulmonary function tests are used to measure the severity of pulmonary impairment rather than to provide a specific diagnosis. Bronchoscopic examinations, such as bronchoalveolar lavage and transbronchial lung biopsy, are helpful to distinguish other processes, including infectious causes, lymphangitic carcinomatosis, diffuse alveolar hemorrhage, etc [1,46,47]. Proper evaluations of these examinations and clinical manifestations to establish the diagnosis is very important, because DILD may have significant influence on the treatment. Cessation of a drug merely by clinical suspicion of DILD may deprive the patient of a potent treatment with survival benefit.

No standard guideline for the treatment of targeted therapy-induced ILD was established and the treatment tends to be empirical rather than evidence-based. The main managment of targeted therapy-induced ILD includes drug discontinuation, corticosteroid therapy, and supportive care [4,48,49]. Diagnosis of significant ILD justifies discontinuation of the culprit causing pulmonayr toxicities. Nevertheless, the decision of drug discontinuation must be made carefully, because patients may be deprived of a life-prolonging drug. When affected patients have persistent symptoms or severe pulmonary impairment (such as dyspnea at rest, a decreased arterial oxygen saturation < 90%, or deterioration of symptoms, etc.), the initiation of systemic corticosteroid therapy is recommended. Oral prednisolone or methylprednisolone (0.5-1 mg/kg/day) is generally used according to the previous reports [4,6,44,47]. Once patients suffered from rapidly progressive symptoms or more severe symptoms, high-dose steroid therapy ($\geq$ 2 mg/kg/day methylprednisolone) should be used [6,47]. In patients with impending respiratory failure or respiratory failure requiring mechanical ventilation, administratoin of intravenous methylprednisolone up to 500-1000 mg/day for 3 days had been demonstrated in the anecdotal reports [44,47,49]. If clinical symptoms are improved, the dose of corticosteroid should be tapered gradually. Previous reports revealed that corticosteroid responsivenss was observed in several pathological patterns of DILD, such as nonspecific interstitial pneumonia, organizing pneumonia, eosinophilic pneumonia, and hypersensitivity pneumonia [4,47,50]. Nevertheless, patients with DILD are often unable to receive lung biopsy due to severe illness, and high-resolution computed tomography may be useful to evaluate the patterns of DILD.

The rechallenge of targeted therapies causing ILD is generally avoided, but a number of exeptions exsist. For instance, previous studies have demonstrated successful rechallenge with dasatinib, temsirolimus, and everolimus [4,38,51]. The decision of rechallenge should be individualized according to different drugs, severity of illness, and available treatments.

Conclusion

More and more targeted therapies have been used for cancer treatments and had been proven to improve clinical outcomes. However, a number of targeted agents are associated with DILD leading to morbidity and mortality. Clinical physicians should be aware of this potentially lethal adverse drug reaction and pursue early diagnosis to prevent fatal outcomes. No standard guideline for the treatment of targeted therapy-induced ILD was established and the treatment tends to be empirical rather than evidence-based. The major managment of targeted therapy-induced ILD includes drug discontinuation, and corticosteroid therapy. The decision of rechallenge should be individualized depending on the various drugs, severity of illness, and available treatments. Clinicians should cautiously weigh the benefits and risks of targeted therapies causing ILD in order to provide optimal treatments and favorable outcomes.

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