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 management 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 drugs 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).

### Table 1: Frequency and Mortality Rate of Drug-induced ILD

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

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The incidence of ILD related to afatinib was reported as 1.3% (3/229 patients) in a phase II study 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 multigenerated 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 (RC). 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 multigenerated 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 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. Bronchoalveolar 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 management 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 pulmonary 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 (≥ 2 mg/kg/day methylprednisolone) should be used [6,47]. In patients with impending respiratory failure or respiratory failure requiring mechanical ventilation, administrain 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 responsiveness 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 expections exist. 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 management 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.


