Editorial Commentary

Tyrosine kinase inhibitors interstitial pneumonitis: diagnosis and management

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Submitted Apr 18, 2019. Accepted for publication May 06, 2019.
doi: 10.21037/tlcr.2019.05.02
View this article at: http://dx.doi.org/doi: 10.21037/tlcr.2019.05.02

Lung cancer is the most common cancer in the world (1-3). In the past 10 years, studies have shown that tyrosine kinase inhibitors (TKIs), such as gefitinib, afatinib, and crizotinib, provide significant benefits to advanced non-small cell lung cancer (NSCLC) patients (4,5). NSCLC with positive epidermal growth factor receptor (*EGFR*) or anaplastic lymphoma kinase (*ALK*) mutations can achieve longer progression-free survival (PFS) and a higher life quality through treatment with TKIs (4,5).

It should be noted that there are some side effects of TKIs, such as increased alanine aminotransferase concentrations, hepatic dysfunction, skin rash, diarrhea, etc. (5-9). Although it is uncommon, drug-induced interstitial lung disease (ILD) is one of the most serious complications of TKIs (10-12), and is thus a major concern during *EGFR*-TKI treatment (11,12). The incidence of ILD is about 1% in TKI-treated NSCLC patients worldwide; it was reported that ILD occurred in about 3.5% of NSCLC patients treated with gefitinib in Japan (13). Meanwhile, the frequency of ILD induced by *ALK* has been reported to be <1% (14-17).

There are some high-risk factors for ILD in patients with TKIs: male sex, smoking, and a history of pulmonary fibrosis (18). Interstitial shadow on chest CT has been correlated with TKI-related ILD (19), and it was reported that prior radiotherapy was also a risk factor for ILD (11,12,19,20). Another potential risk factor of TKI-induced ILD is Anti-PD-1 monoclonal antibodies (21).

The incidence, histopathology, pathophysiology, and prognosis of TKI-induced ILD remain poorly understood. The pathogenesis of ILD was reported to be related to different types of cytotoxicity. In this process, TKIs directly injure the endothelium of alveolar capillaries and/or the pneumocytes. Cytokines are released and the inflammatory cells are recruited. These cytokines releasing induce the dysfunction of endothelial and lung edema (22). It was reported that increasing IL-6 played an important role in *EGFR*-TKI-related ILD, and blocking of IL-6 pathway could reduce the incidence of ILD during TKI treatment (23). For gefitinib-induced ILD, metformin demonstrated an inhibitory effect, while *EGFR*-TKI combined with metformin in treating NSCLC patients was shown to reduce drug-related adverse reactions (24).

Clinical manifestations of ILD are cough, fever, and acute or subacute dyspnea, and patients with ILD usually need to be hospitalized. Respiratory failure is common, and its occurrence in one third of cases is fatal. Chest computed tomography (CT) is similar to interstitial pneumonitis, while radiographic findings are nonspecific. The histopathology of ILD induced by TKIs is diffuse alveolar damage. As it is rare that tissues can be acquired from these patients, diagnosis is often based on clinical and radiographic findings (18).

The following points can assist in the diagnosis of ILD induced by TKIs (18):

(I) Acute or subacute, progressive dyspnea with or without cough and/or fever;
(II) Exclusion of pulmonary infection;
(III) Radiographic findings showing bilateral, diffuse, or patchy interstitial and/or alveolar opacifications without evidence of marked progression of lung

cancer;

(IV) Pathologic findings consistent with ILD (if available).

If TKI-induced ILD is diagnosed, it is important to give patients symptomatic supportive treatment. As immune disorder may be one of the mechanisms of TKI-induced ILD, it is often treated with steroids. Discontinuation of TKIs is another critical option, but can pose a clinical dilemma: some patients may receive the benefits of TKIs before ILD occurs, some patients may have no suitable alternative, and some patients may suffer severe side effects if they switch to other treatments. It was reported that TKI could continue to be used with steroids (25). Doctors need to judge the benefits and risks and closely monitor their patients (26). Some patients can recover from TKI-induced ILD through a reduction of its dosage. This might be another potential therapeutic option for treating TKI-induced ILD. Doctors need to pay attention to the recurrence of ILD during the time patients are being treated with a reduced TKI dose. Overall, the understanding of the underlying mechanisms of ILD and strategies to overcome TKI-induced ILD is immature, and further investigation is required in these areas (27).

In summary, TKIs have heralded a new era in the treatment of cancers, but ILD still remains its most serious side effects. Male sex, smoking, history of pulmonary fibrosis, history of radiotherapy, and combination with immune therapy, are the risk factors of TKI-induced ILD. TKI-induced ILD presents with cough, fever, dyspnea, and hypoxemia. Should TKI-induced ILD be diagnosed, symptomatic supportive treatment is important, and patients should be treated with steroids which can be used simultaneously with TKIs. The discontinuation of TKIs can be clinically problematic as other treatment options may not be viable, and doctors should pay close attention to these patients. The above facts notwithstanding, the mechanisms of ILD and strategies to overcome TKI-induced ILD are limited, and need continued study focus.

Acknowledgments

Funding: This study was supported in part by a grant from National Natural Science Foundation of China (81802255), Shanghai Pujiang Program (17PJD036) and a grant from Shanghai Municipal Commission of Health and Family Planning Program (20174Y0131). National Key Research & Development Project (2016YFC0902300), Major Disease Clinical Skills Enhancement Program of Three-year Action Plan for Promoting Clinical Skills and Clinical Innovation in Municipal Hospitals, and Shanghai Shen Kang Hospital Development Center Clinical Research Plan of SHDC (16CR1001A). The fundamental research funds for the central universities.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: He Y, Zhou C. Tyrosine kinase inhibitors interstitial pneumonitis: diagnosis and management. Transl Lung Cancer Res 2019;8(Suppl 3):S318-S320. doi: 10.21037/tlcr.2019.05.02

