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Successful administration of low-dose almonertinib in a patient with lung adenocarcinoma after osimertinib-induced interstitial lung disease: a case report and literature review

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Osimertinib, the third generation epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI), is the standard treatment for nonsmall cell lung cancer with EGFR mutation. However, osimertinib-induced interstitial lung disease (OsiILD) is considered to be a serious adverse event, so some patients will have to discontinue the use of osimertinib due to OsiILD. Almonertinib is a novel third-generation EGFR-TKI. We herein report a patient who developed OsiILD after the use of osimertinib and then switched to almonertinib for further treatment with success. This is the first report of a successfull rechallenge with low-dose almonertinib after OsiILD. We also reviewed the literature to explore the possible risk factors and the subsequent treatment of OsiILD, suggesting that low-dose almonertinib may be an option for follow-up treatment of OsiILD. *Anti-Cancer Drugs* 34:

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Introduction

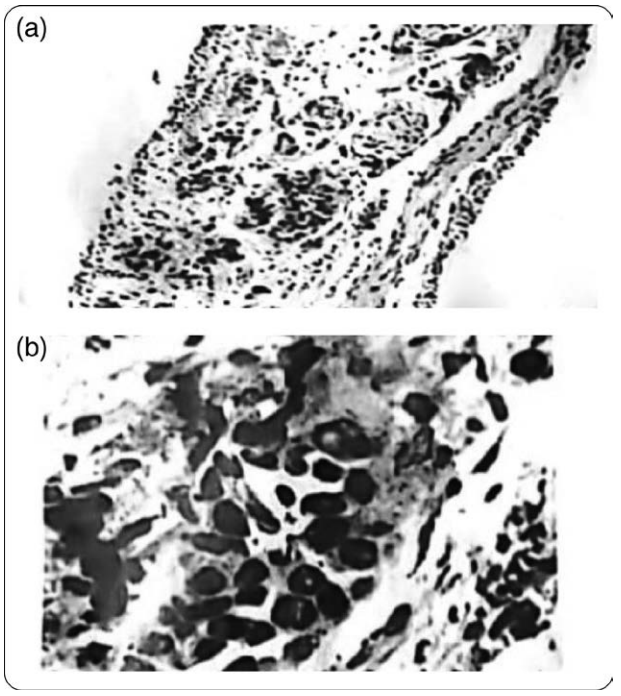
As the third-generation irreversible epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI), osimertinib has been approved for the treatment of nonsmall cell lung cancer (NSCLC) patients with EGFR mutation, especially in advanced T790M positive patients [1]. In first-line EGFR-TKI treatment, advanced NSCLC patients with T790M mutation had progression-free survival (PFS) of more than 10 months after the administration of osimertinib (80 mg per day) [2]. However, osimertinib-induced interstitial lung disease (OsiILD) can be fatal in severe cases [3,4]. In a recent case report, a patient with EGFR exon 19 deletion and T790M mutation received a standard dose of almonertinib (110 mg per day) to control the tumor progression following concurrent OsiILD [5].

We herein report a case of lung adenocarcinoma with EGFR exon 21 L858R mutation and T790M mutation that successfully switched to low-dose almonertinib (55 mg per day) after remission of OsiILD. In addition, we reviewed the literature to explore the possible risk factors and the subsequent treatment of OsiILD, as well as the efficacy and possible adverse reactions of almonertinib compared with osimertinib.

Case report

A 64-year-old woman with no history of smoking or allergy was diagnosed with right lung adenocarcinoma (Fig. 1) at Zhejiang Cancer Hospital in June 2018, and genetic analysis revealed the presence of the EGFR exon 21L858R mutation through her biopsy sample obtained by bronchoscopy. In addition, her PET-computed tomography (PET-CT) indicated the presence of L3 vertebral metastases as well as the Eastern Cooperative Group Performance Status (PS) of this patient was grade 1. According to the guideline of the Annual Congress of Chinese Thoracic Society (CTS), icotinib was administered 250 milligrams (mg) per day. During the period of taking icotinib, she has repeatedly reexamined for chest CT (Fig. 2a,b) and the results indicated that she had stable disease (SD). Unfortunately, the chest CT (Fig. 2c) showed multiple nodules increased in both lungs although the tumor size remained stable after the treatment of icotinib for 22 months. At the same time, the genetic testing in plasma indicated that the EGFR T790M mutation was present in addition to EGFR 21 L858R mutation and the PS of the patient was grade 2. Therefore, she switched to osimertinib (80 mg per day) according to the guideline of CTS and her chest CT showed that tumor size in the right lung and multiple

Fig. 1



A small number of poorly differentiated cancers in the middle lobe of the right lung invade the nerve (tend to adenocarcinoma) (a) Hematoxylin and eosin, ×100. (b) Hematoxylin and eosin, ×400.

nodules in both lungs remained stable after 2 months of treatment with osimertinib.

However, 3 months after taking osimertinib, she developed a fever as high as 38.6 °C, accompanied by cough, expectoration and a feeling of chest shortness of breath after exercise. Meanwhile, her chest CT (Figs. 2d, 3a) showed diffuse ground-glass opacities (GGOs) in both lungs and consolidation in the middle lobe of the right lung. In room air, her arterial partial pressure of oxygen was 45.7 mmHg (the oxygenation index was 218), and the partial pressure of carbon dioxide and pH value were in the normal range. Besides, the C reactive protein (CRP) was 15.4 $mg_* L^{-1}$. No pathogen was found through routine laboratory tests. According to the instructions of osimertinib and the relevant expert consensus [6], OsiILD usually occurs 3 months after the use of osimertinib. We immediately discontinued osimertinib because we believed that the patient was complicated with OsiILD based on the above clinical manifestations and examination results.

According to the patient's condition, we concluded that she has developed grade 3 interstitial lung disease (ILD) with severe acute lung injury. However, as the patient and her family refused to undergo bronchoscopy and endotracheal intubation, tissue specimens could not be obtained for further diagnosis. We used methylprednisolone pulse therapy (500 mg per day from the first day to the fifth day) to save the patient's life, and then regularly reduced the dose (120 mg per day from the sixth day to the twelfth day, 80 mg per day from the thirteenth day to the twenty-sixth day, 60 mg per day from the twenty-seventh day to the thirty-third day and 40 mg on the last day). After more than 1 month of treatment, the lung injury was relieved and the body temperature returned to normal. In addition, cough, expectoration, chest tightness and shortness of breath were also improved.

More than 2 months later, her chest CT (Fig. 3b) showed diffuse lesions in both lungs and consolidation shadow in the middle lobe of the right lung, and the cranial MRI suggested brain metastasis of lung cancer. So we considered that her lung adenocarcinoma had progressed, and the clinical stage was stage IV (cT4N2M1c). With the informed consent of the patient and her family, low-dose almonertinib (55 mg per day) was used to control the tumor progression, and oral prednisone (10 mg per day) was given to consolidate the therapy of ILD, as well as some calcium supplements and stomach-protecting drugs. One week after treatment, the chest CT (Fig. 3c) indicated that multiple nodules in both lungs were slightly absorbed than before (partially relieved), and then prednisone was changed to 5 mg per day. Prednisone was discontinued 3 weeks later. It remained stable about the diffuse lesions in both lungs and the consolidation shadow in the right middle lobe according to the subsequent reexamination of chest CTs (Fig. 2e, f). Also, her cranial MRI showed that the metastasis was slightly smaller than before.

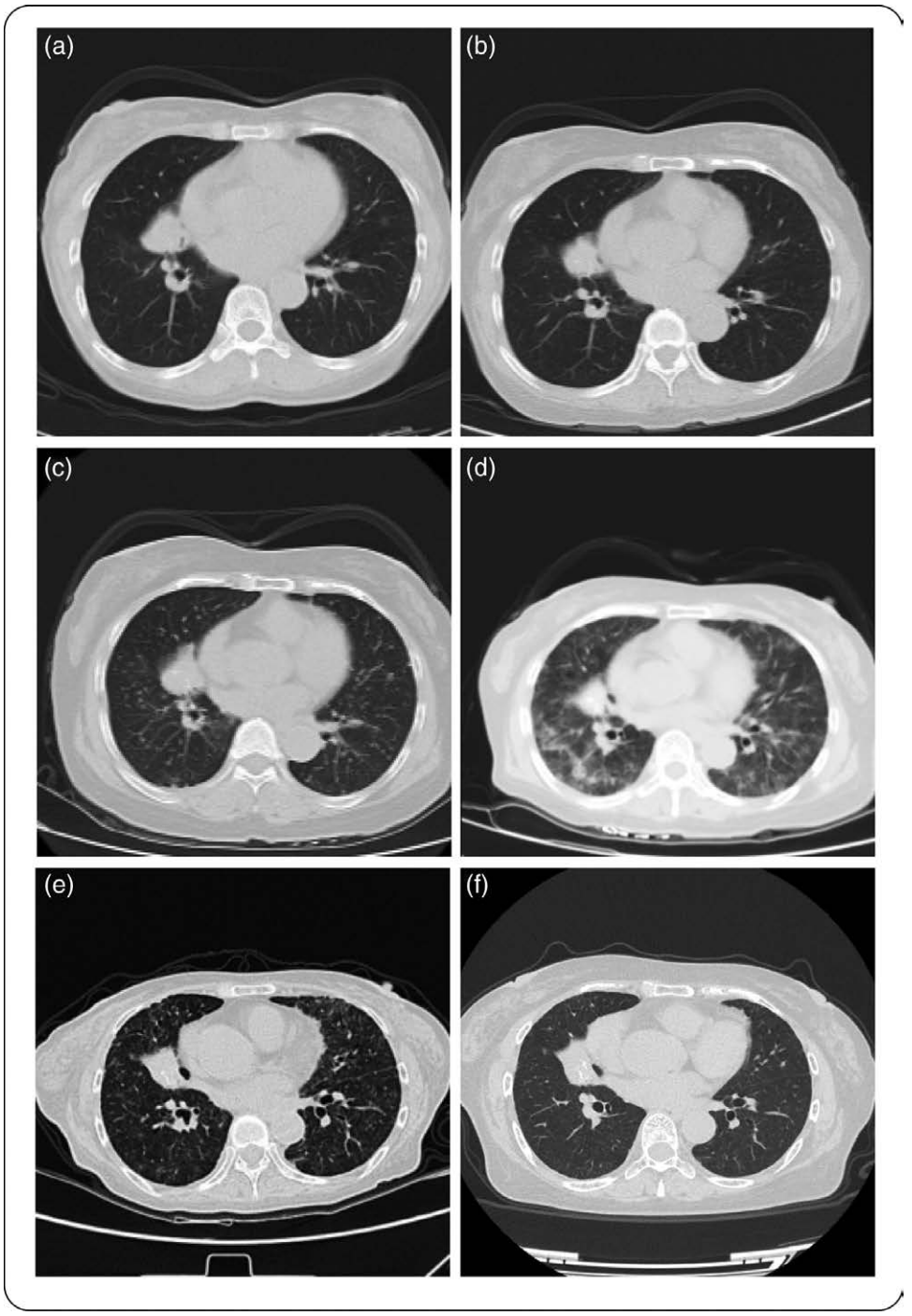
At the time of this writing, the patient has successfully used almonertinib to control tumor progression for more than 13 months without recurrence of ILD.

Discussion

Lung cancer was the leading cause of cancer deaths in the past 2020, accounting for 18% of all cancer deaths [7]. NSCLC accounts for about 80% of lung cancer, and traditional treatments include surgery, chemotherapy and radiotherapy [7,8]. With the development of the research on driver gene mutation, the application of targeted therapy is increasing drastically [9–11]. At present, it is recognized that EGFR mutation is an important carcinogenic factor of NSCLC, accounting for 49.1 and 12.8% of NSCLC patients in Asia and Europe, respectively [12].

Targeted therapy has become an important treatment method for NSCLC, and EGFR-TKIs have provided a good therapeutic effect for NSCLC patients with EGFR mutation [9]. However, after taking EGFR-TKI, patients may need to stop or change their medicine due to drug resistance [13,14], ILD [5,15], and so on, just like the patient we reported. The most common mechanism of acquired resistance is EGFR T790M mutation, which affects the use of first- and second-generation EGFR-TKIs [13], while third-generation EGFR-TKIs,

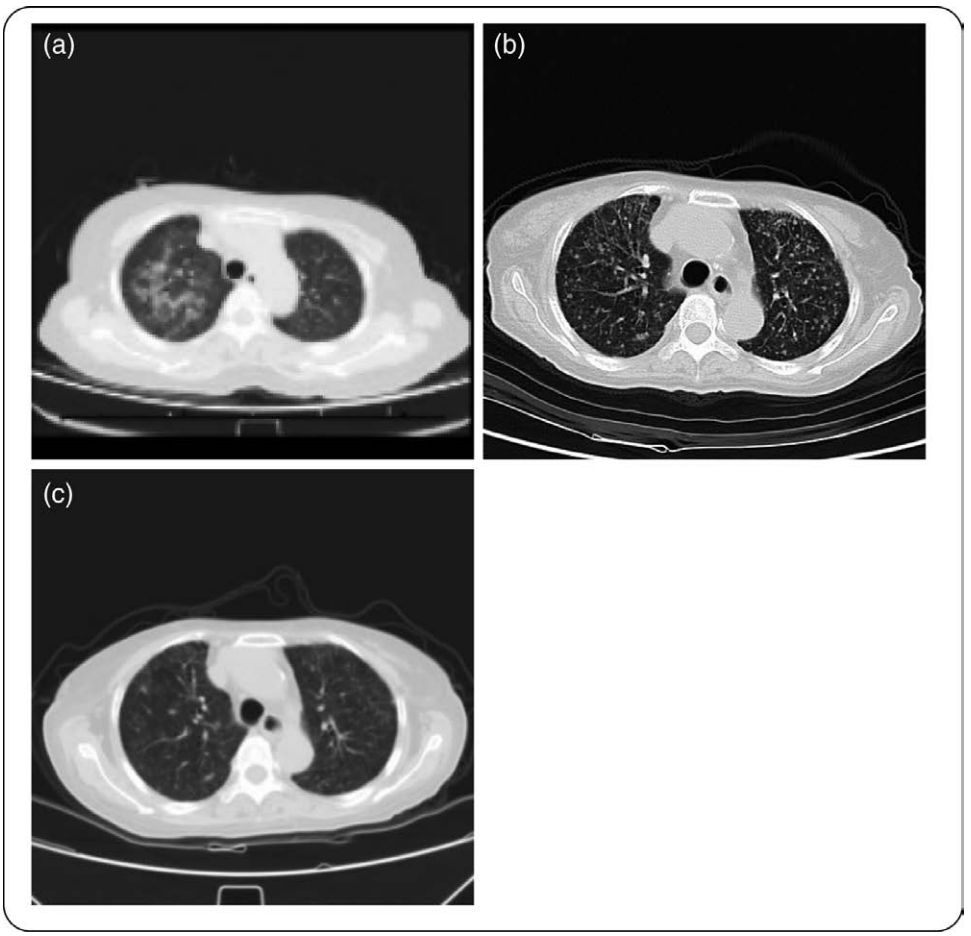
Fig. 2



Changes in the right lung adenocarcinoma. (a) Tumor size at the beginning of treatment with icotinib; (b) After 15 months of treatment with icotinib, the tumor size remained stable; (c) After treatment with icotinib for 22 months, the tumor size in the right lung remained stable, but multiple nodules in both lungs increased, so metastasis was considered; (d) After 3 months of treatment with osimertinib, the tumor size in the right lung and multiple nodules in both lungs remained stable, but multiple inflammation developed in both lungs; (e) After 1 month of treatment with almonertinib, the tumor size in the right lung and diffuse lesions in both lungs remained stable; (f) After 13 months of treatment with almonertinib, the tumor size in the right lung and diffuse lesions in both lungs remained stable.

such as osimertinib, have good efficacy in T790M positive patients [16,17]. In addition, third-generation EGFR-TKIs can exert better therapeutic effects on the central nervous system (CNS) [18–20], but the occurrence of EGFR-TKI-related ILD limits long-term use [13,20,21].

Fig. 3



Diffuse lesions in both lungs. (a) After 3 months of treatment with osimertinib, diffuse ground-glass opacities (GGOs) developed in both lungs. (b) After ILD improved, diffuse lesions in both lungs were considered to be lung metastases and lung adenocarcinoma progressed. (c) After treatment with almonertinib, diffuse lesions (multiple nodules) in both lungs were improved than before.

At present, the mechanism of EGFR-TKI-related ILD is not clear. It may be related to blocking the phosphorylation of EGFR, thus preventing the regeneration and proliferation of damaged epithelium. It may also disrupt the balance of cell survival under the condition rich in tumor necrosis factor (TNF) by inhibiting protein kinase B and extracellular signal-regulated kinase (ERK) 1/2 and activating p38 Mitogen-activated protein kinase (MAPK) [22]. In addition, EGFR-TKI may induce ILD by producing the cytokine interleukin-6 (IL-6) [23]. The occurrence of OsiILD may be related to the above mechanisms.

It is necessary to assess the risk of OsiILD for each patient using osimertinib. Previous studies have shown that the risk factors for ILD caused by EGFR-TKI include male, smoking, age 55 years and above, PS greater than or equal to 2, history of pulmonary fibrosis, presence of contralateral pulmonary metastasis, chronic obstructive pulmonary disease (COPD), history of interstitial pneumonia, history of radiotherapy within 1 year, combined heart disease, normal lung area less than 50%, pulmonary infectious diseases and inflammatory cytokine enrichment [22,24,25]. According to current research, OsiILD may be primarily associated with a history or complication of ILD and previous treatment with programmed cell death protein-1 (PD-1) inhibitors such as nivolumab [22,26]. In several cases about OsiILD reported so far, most of the patients had risk factors, such as advanced age, contralateral lung metastasis, use of nivolumab and so on [3,5,15,27–38]. The patient we reported was an elderly woman with contralateral lung metastasis, PS was grade 2, and she developed grade 3 ILD with acute lung injury after 3 months of treatment with osimertinib. In many cases, risk factors are unavoidable, but the progression of ILD can be controlled in time through early judgment and intervention.

Currently, OsiILD is mainly controlled by discontinuing osimertinib and using corticosteroids. Some cases have been reported that OsiILD has been alleviated by discontinuing osimertinib alone [29,31]. Of course, the lung

damage in these cases was relatively mild. It has been reported that a patient who developed OsiILD continued to use osimertinib without listening to the doctor's advice and died of ILD [3]. Therefore, timely intervention is very important. The majority of reported cases, including our case, successfully controlled OsiILD by discontinuing or reducing osimertinib and treating it with corticosteroids [5,15,27,28,30,32–35,37,38]. It has also been reported that OsiILD can be successfully controlled by nintedanib [36], so the use of nintedanib to control OsiILD can be considered in patients who are not suitable for corticosteroid therapy.

After the remission of OsiILD with acute lung injury, it is necessary to choose appropriate drugs to control tumor progression and prolong the survival time of patients. Most of the reported cases of rechallenge of EGFR-TKI after OsiILD were treated with osimertinib [27,30,33–35,38], and a few patients without T790M mutation used first- or second-generation EGFR-TKI, such as gefitinib [36] and afatinib [15,37], all of which successfully controlled the tumor progression. Moreover, in the cases of using osimertinib, one part used the regular dose (80 mg per day) [26,34,35], and the other part reduced the dose (40 mg per day or 80 mg every other day) [27,30,33,38], which all achieved good therapeutic effect. However, for the occurrence of OsiILD during the early use of osimertinib, it is obvious that there is a great risk of worsening the disease by choosing the routine or reduced dose of osimertinib to continue application.

As a novel, irreversible, third-generation EGFR-TKI, almonertinib, similar to osimertinib, is safe and well-tolerated in NSCLC patients with EGFR T790M mutation and brain metastasis [39–41]. Compared with osimertinib, almonertinib increases stability by introducing cyclopropyl [40,42,43]. It can flexibly bind to the small molecule sac of EGFR-T790M mutant protein and improve the affinity for T790M [40]. In addition, it improves the penetration of the blood-brain barrier and inhibits brain and spinal cord metastasis in patients with advanced NSCLC [39,40]. The latest phase II clinical trial found that the main adverse reactions of almonertinib were the increase of creatine phosphokinase (7%) and alanine aminotransferase (1.2%), while associated ILD and other serious adverse reactions were extremely rare [39]. Recently, one literature reported that almonertinib could induce ILD, and the dose used in that literature was 110 mg per day [44]. The reported patient [44] was a 70-year-old woman who developed chest tightness, shortness of breath and paroxysmal dry cough after using almonertinib for 3 months. Although the tumor was controlled, the partial pressure of oxygen and carbon dioxide were 53.4 and 38.2 mmHg, respectively. She discontinued almonertinib and used corticosteroids to control ILD. Eventually, her symptoms improved.

There has been a case report of successful control of tumor progression with a regular dose of almonertinib (110 mg per day) after OsiILD was relieved [5]. The reported patient, a 76-year-old woman with tumor progression after lobectomy, began taking gefitinib because of genetic tests on biopsy specimens showing deletion of EGFR 19 exon. Unfortunately, drug resistance (EGFR T790M mutation) developed after 7 months, and then osimertinib was used instead. Grade 3 ILD appeared after taking osimertinib for 3 months. Lung injury was improved after treatment with methylprednisolone, but a reexamination of CT indicated tumor progression. The tumor remained stable with pemetrexed and bevacizumab, but the gastrointestinal response was large, so the regular dose of almonertinib (110 mg per day) was switched. CT reexamination showed a reduction in pulmonary nodules without ILD or other adverse drug reactions 6 months after the use of almonertinib. At present, there is no report about reducing the dose of almonertinib to control the tumor progression after the remission of OsiILD.

The patient we reported was a 64-year-old woman who took icotinib because the genetic examination on her biopsy specimen revealed the presence of EGFR exon 21L858R mutation. Unfortunately, drug resistance (EGFR T790M mutation) developed after 22 months, and the tumor remained stable after switching to osimertinib. However, ILD occurred 3 months after taking osimertinib, which was eventually relieved by methylprednisolone. Due to tumor progression, low-dose almonertinib (55 mg per day) was administrated. The latest cranial MRI showed that the metastatic focus was reduced. Up to now, the tumor has been successfully controlled for more than 13 months, and there are no adverse drug reactions such as ILD.

In conclusion, it is important to assess ILD-related risk factors before using osimertinib. When risk factors cannot be avoided, timely intervention is needed to avoid greater harm when ILD occurs. Continued use of osimertinib to control tumor progression may be an option after ILD control, but other third-generation EGFR-TKIs can also be considered. Almonertinib is an effective and well-tolerated third-generation EGFR-TKI. In the case of high risk of ILD, low-dose almonertinib can be considered to control tumor progression, especially in NSCLC patients with EGFR T790M mutation and brain metastasis.

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All data generated or analyzed during this study are included in this published article.

Written informed consent was obtained from the patient for publication of identifying images or other personal or clinical details of this case report.

W.C. contributed to the data collection, manuscript drafting and literature research. Dr. LZ and Dr. HS contributed to the patient management. Dr. EC, Dr. BW, Dr. JL contributed to the clinical treatment and manuscript revision for important intellectual content. All authors read and approved the final manuscript.

Conflicts of interest

There are no conflicts of interests.

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