Official Case Reports Journal of the Asian Pacific Society of Respirology
Respirology Case Reports
OPEN ACCESS

Primary resistance to osimertinib despite acquired *T790M*

Ling-Kai Chang[1], Yih-Leong Chang[2,3] & Jin-Yuan Shih[1,2]

[1]Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan.
[2]National Taiwan University College of Medicine, Taipei, Taiwan.
[3]Department of Pathology, National Taiwan University Cancer Center and National Taiwan University Hospital, Taipei, Taiwan.

Keywords
Liquid biopsy, osimertinib, primary resistance, small cell transformation, *T790M*.

Correspondence
Jin-Yuan Shih, Department of Internal Medicine, National Taiwan University Hospital, No. 7, Chung Shan S. Rd, Taipei City 10002, Taiwan. E-mail: jyshih@ntu.edu.tw

Received: 8 December 2019; Revised: 19 January 2020; Accepted: 21 January 2020; Associate Editor: Stephen Lam.

***Respirology Case Reports*, 8 (2), 2020, e00532**

doi: 10.1002/rcr2.532

Abstract

Current National Comprehensive Cancer Network (NCCN) guidelines suggest plasma-based testing (liquid biopsy) for *T790M* in epidermal growth factor receptor (EGFR)-mutated non-small cell lung carcinoma (NSCLC) with acquired resistance to first-/second-generation EGFR tyrosine kinase inhibitors (TKIs). Positivity for resistant mutation on liquid biopsy may obviate the need for invasive tissue biopsy. We report a rare case of primary resistance to osimertinib, although liquid biopsy revealed *EGFR T790M* positivity. A 63-year-old male, never smoker, was diagnosed with stage IV lung adenocarcinoma with *EGFR* exon 19 deletion. Treatment started with erlotinib and was continued for 15 months until disease progression. Osimertinib was initiated when liquid biopsy showed *EGFR T790M* positivity. However, primary resistance to osimertinib was noted on follow-up imaging. Re-biopsy revealed small cell lung cancer. Detection of *T790M* via liquid biopsy among NSCLC patients with acquired resistance to EGFR-TKI might miss other possible resistant mechanisms. Tissue biopsy should be considered to exclude small cell lung carcinoma (SCLC) transformation.

Introduction

Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) represent the first-line treatment of advanced *EGFR*-mutated non-small cell lung carcinoma (NSCLC). However, most patients develop acquired resistance to EGFR-TKIs. One of the most well-known resistant mechanisms is the acquired *EGFR T790M* mutation, which accounts for 40–50% of all cases of resistance to first-generation EGFR-TKIs. Currently, T790M testing can be performed using liquid biopsy. Positive results for resistance mutation on liquid biopsy may obviate the need for an invasive tissue re-biopsy. However, the use of only liquid biopsy might lead to loss of information about other less frequent resistance mechanisms.

Case Report

A 63-year-old male, never smoker, was symptomatic for a non-productive cough. He was diagnosed with stage IV lung adenocarcinoma with *EGFR* exon 19 deletion (ex19del). Treatment was initiated with erlotinib (150 mg once daily) and bevacizumab (1000 mg every three weeks) in October 2017. The treatment was continued for 15 months, when a bone scan revealed disease progression in the sternum and a lesion in the ninth left rib. A test of resistance mutation via liquid biopsy revealed *EGFR* exon 19 deletion and *T790M* (mutant allele frequency: 0.21%). The T790M/activating mutation ratio in the blood prior to initiation of treatment with osimertinib was 0.126. Treatment with osimertinib (80 mg once daily) was started in February 2019. A follow-up computed tomography (CT) scan performed in April 2019 showed disease progression in the left lower lung, contralateral lung, and liver (Fig. 1). A bronchoscopy was performed and histological assessment of the left lower lung tumour was consistent with mixed small cell lung carcinoma (SCLC) and adenocarcinoma (Fig. 2). A liver tumour biopsy with concomitant radiofrequency ablation was performed. A liver tumour biopsy revealed small cell carcinoma, with positive synaptophysin staining (Fig. 2). The patient was treated with six cycles of chemotherapy, comprising etoposide

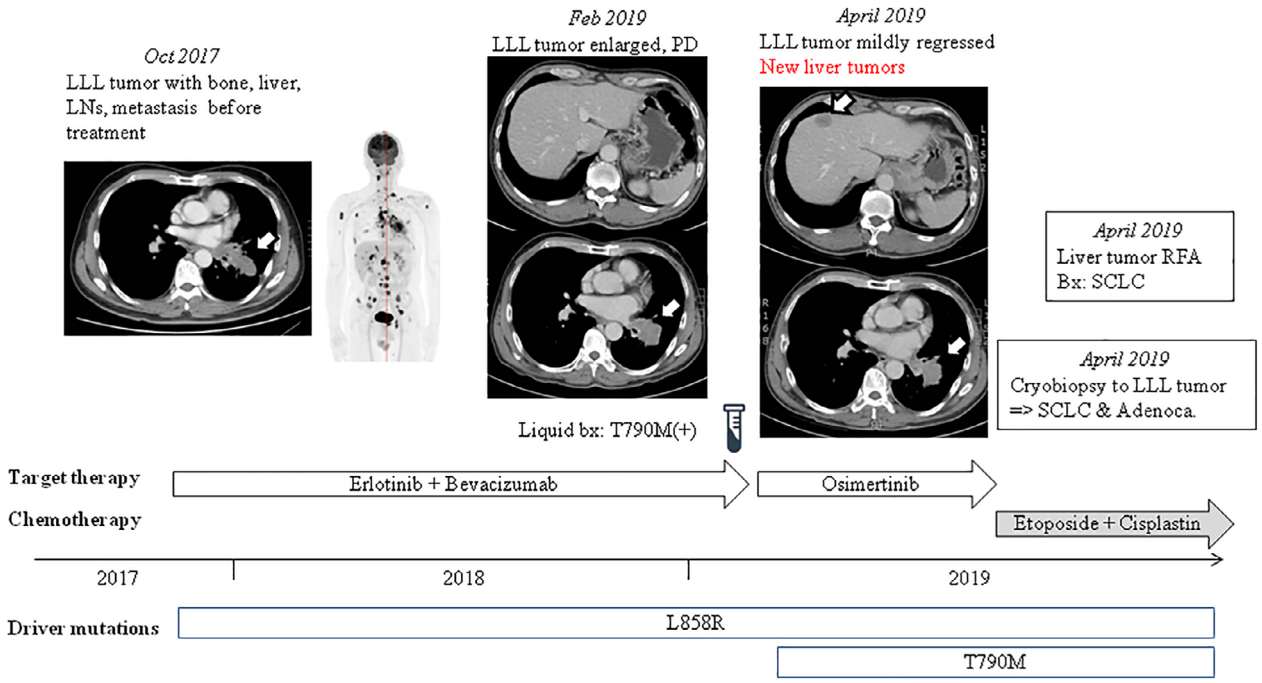

Figure 1. Summary of the treatment course in this case report. Hollow arrows indicate the target lesions in the image studies. LLL, left lower lung; LN, lymph node; PD, progressive disease; RFA, radiofrequency ablation; SCLC, small cell lung carcinoma.

(80 mg/m^2) and cisplatin (80 mg/m^2), and follow-up studies revealed stable disease.

Discussion

This report demonstrated the ineffectiveness of osimertinib in a case of lung cancer with liquid biopsy confirmed *EGFR ex19del* and *T790M* mutation and later shown to exhibit small cell transformation on biopsy. Further invasive tissue re-biopsy revealed SCLC transformation. Although liquid biopsy is a convenient and non-invasive method of assessing resistance to EGFR-TKIs, invasive tissue biopsy remains the standard to understanding the mechanisms of resistance, such as SCLC transformation. The AURA trials revealed that only 10% of patients were switched to osimertinib after *EGFR T790M* detection in liquid biopsy resulted in disease progression [1]. In our case, due to the primary resistance to osimertinib and the finding of SCLC at re-biopsy, we suspected that SCLC was present at the time of treatment with erlotinib.

Some previous studies have considered the pre-osimertinib plasma level of T790M and its ratio with respect to activating mutation. According to the cut-off level for mutation in liquid biopsy for clinical application proposed by Oxnard et al. (allelic fraction >0.06% for *T790M*) [2], our patient tested positive for *T790M* (allelic fraction: 0.21%). Two previous studies showed that higher ratio of T790M/activating mutation was strongly correlated with the level of tumour shrinkage [3,4]. The mechanism was explained by the underlying tumour heterogeneity; another possibility was SCLC transformation.

A recent case series reported by Minari et al. presented five patients treated with osimertinib after T790M detection on liquid biopsy, but presented a disease progression at first tumour assessment mediated by SCLC transformation, as evidenced at tissue re-biopsies. All the patients showed low T790M/activating mutation ratio in the blood before osimertinib treatment (lower than 0.03) [5]. Minari et al. suggested that for patients with a low T790M/activating mutation ratio, tissue biopsy should be considered to exclude the presence of SCLC transformation or other concomitant resistance mechanisms. However, our patient presented a higher T790M/activating mutation ratio of 0.126. Further studies may be required to decide the cut-off level using the T790M/activating mutation ratio to assess the need for invasive re-biopsy.

Although liquid biopsy is a promising method for the diagnosis of *T790M* mutation in *EGFR*-mutated NSCLC after resistance to first-/second-generation EGFR-TKIs, it may miss other possible resistance mechanisms. A low T790M/activating mutation ratio may assist clinicians to make decisions regarding tissue re-biopsy; however, the cut-off point of the ratio may need to be assessed in further studies.

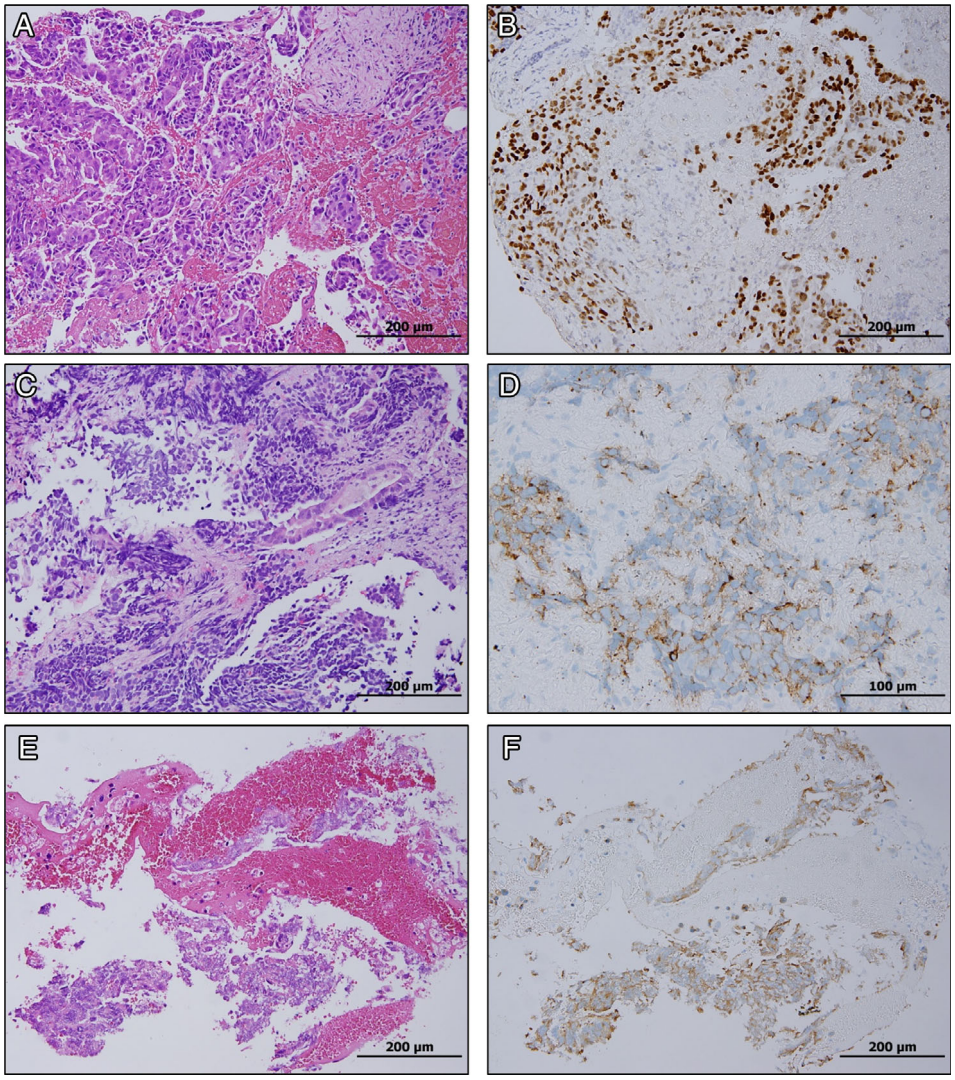

Figure 2. Tissue morphology and immunohistochemistry (IHC) of the pre-osimertinib left lower lung tumour biopsy (A, B), post-osimertinib left lower lung tumour biopsy (C, D), and liver lesions biopsy (E, F). Pathology of pre-osimertinib transbronchial biopsy of left lower lung tumour showed adenocarcinoma (A). IHC staining yielded positive results for thyroid transcription factor-1 (TTF-1) (B). Pathology of post-osimertinib transbronchial biopsy of left lower lung tumour was consistent with mixed small cell lung carcinoma (SCLC) and adenocarcinoma (C); IHC staining yielded positive results for synaptophysin in small cell carcinoma component but not in adenocarcinoma foci (D). Pathology of post-osimertinib liver tumour biopsy revealed small cell carcinoma (E); IHC staining yielded positive results for synaptophysin (F).

Disclosure Statement

Appropriate written informed consent was obtained for publication of this case report and accompanying images.

J.-Y. S. has served as an advisory board member for and has received speaker honoraria from AbbVie, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Chugai, Eli Lilly, Merck Sharp & Dohme, Novartis, Ono Pharmaceutical, and Roche, and has received allowances for expenses for travel and accommodation from Boehringer Ingelheim, Bristol-Myers Squibb, Merck Sharp & Dohme, Pfizer, and Roche.

References

1. Yang JC, Ahn MJ, Kim DW, et al. 2017. Osimertinib in pretreated T790M-positive advanced non-small-cell lung cancer: AURA study phase II extension component. J. Clin. Oncol. 35:1288–1296.
2. Oxnard GR, Thress KS, Alden RS, et al. 2016. Association between plasma genotyping and outcomes of treatment with osimertinib (AZD9291) in advanced non-small-cell lung cancer. J. Clin. Oncol. 34:3375–3382.
3. Piotrowska Z, Niederst MJ, Karlovich CA, et al. 2015. Heterogeneity underlies the emergence of EGFRT790 wild-type

clones following treatment of T790M-positive cancers with a third-generation EGFR inhibitor. Cancer Discov. 5: 713–722.
4. Chabon JJ, Simmons AD, Lovejoy AF, et al. 2016. Circulating tumour DNA profiling reveals heterogeneity of EGFR inhibitor resistance mechanisms in lung cancer patients. Nat. Commun. 7:11815.
5. Minari R, Bordi P, Del Re M, et al. 2018. Primary resistance to osimertinib due to SCLC transformation: issue of T790M determination on liquid re-biopsy. Lung Cancer 115:21–27.