Case Report

*EGFR C797S as a Resistance Mechanism of Lazertinib in Non-small Cell Lung Cancer with EGFR T790M Mutation*

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**Running title:** EGFR C797S in Lazertinib Treated Patient

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as an 'Accepted Article', doi:10.4143/crt.2020.278

Korean Cancer Association
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Abstract

The non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) mutation eventually acquires resistant to either first or second-generation EGFR tyrosine kinase inhibitor (TKI). As the following option, targeting EGFR T790M with third-generation EGFR TKI is now established as a standard treatment option. In this study, we are reporting the first case of resistance mechanism to the novel third-generation EGFR TKI, lazertinib, which showed promising clinical efficacy in phase 1-2 study. The patients showed resistance to the treatment by acquiring the additional EGFR C797S mutation in cis which is also confirmed from the patient-derived cell lines.

Key words

Non-small cell lung cancer, Lazertinib, Third-generation EGFR tyrosine kinase inhibitor, EGFR
Introduction

Non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) mutation treated with either a first- or second-generation tyrosine kinase inhibitor (TKI) can experience treatment failure, most commonly by acquiring an additional genomic alteration in EGFR T790M [1]. Lazertinib (YH25448) is a potent irreversible third-generation EGFR TKI that targets both T790M and activating EGFR mutation with high penetration to the blood-brain barrier. Lazertinib showed promising anti-tumor efficacy with a 57% overall response rate and 9.7-month median progression-free survival in EGFR T790M-positive patients [2]. However, there is no previous report showing the mechanism of tumor resistance acquisition to lazertinib. In this case report, we conducted deep-targeted sequencing of resistant tumor samples and established patient-derived cell lines (PDC) from a patient treated with lazertinib to elucidate the underlying genomic alteration associated with resistance.

Case Report

A 38-year-old current male smoker presented with stage 4, cT1bN3M1b, NSCLC adenocarcinoma. Informed consent was received under supervision of institutional review board (SMC 2011-10-054-034). The patient was shown to harbor an EGFR exon 19 deletion using real-time polymerase chain reaction from the initial biopsy sample obtained from the mediastinal lymph node. Afatinib was administered as a first-line treatment and showed very good partial response with 7.1 months of progression-free survival. After first-line EGFR TKI failure, a second biopsy from the newly progressed metastatic lymph node showed acquired EGFR T790M mutation. As a subsequent treatment, the patient received lazertinib as a part of a clinical trial (NCT03046992; YH25448-201). However, after 6.2 months of partial response...
to lazertinib, the patient developed malignant ascites, suggesting peritoneal seeding due to resistance.

Deep-targeted sequencing (CancerSCAN [3]) of ascites samples demonstrated acquired \textit{EGFR C797S} mutation in cis, variant allele frequency (VAF) of 9.4%, \textit{EGFR T790M} (VAF of 3.5%), and \textit{EGFR} exon 19 deletion (VAF 9.2%) (Fig. 1A). PDCs established from the same ascites sample showed \textit{EGFR} exon 19 deletion (Fig. 1B). Cell viability of PDCs showed resistance to first- and third-generation \textit{EGFR} TKIs including erlotinib, gefitinib, lazertinib, and osimertinib or the c-met inhibitor savolitinib (Fig. 1C).

**Discussion**

Diverse resistance mechanisms to third-generation \textit{EGFR} TKI have been reported including loss of T790M, acquisition of \textit{EGFR C797S} mutation, c-met amplification, activation of other bypass tract, or small cell lung cancer transformation. Among them, \textit{EGFR C797S/T790M} mutation is the most frequently observed, accounting for 20%-30% of cases. It is of note that tumors acquiring an additional mutation of \textit{EGFR C797X} maintain the original \textit{EGFR T790M} mutation [4]. In this report, we present the first clinical case of new \textit{EGFR C797S/T790M} mutation in a patient who failed lazertinib. Further validation with a large number of patients and new treatment strategies to overcome this resistance mutation are warranted.

**Conflicts of Interest**

Conflict of interest relevant to this article was not reported.
References


**Fig. 1.** (A) Target sequencing in samples from lazertinib-resistant malignant ascites. Integrative genomic viewer of sample showing additional *EGFR C797S* cis mutation. (B) Western blot of patient-derived cell line (PDC) samples. (C) Cell viability analyses conducted in samples after exposure to tyrosine kinase inhibitor for 72 hours.