A Lung Adenocarcinoma Patient With a Rare EGFR E709_T710delinsD Mutation Showed a Good Response to Afatinib Treatment: A Case Report and Literature Review

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For advanced lung adenocarcinoma patients with common epidermal growth factor receptor (EGFR) mutations (exon 19 deletions or the exon 21 L858R mutation), tyrosine kinase inhibitors (TKIs) are the standard therapies, and achieve favorable responses. However, for the rare EGFR deletion-insertion mutation of exon 18, there is no evidence of the efficacy of EGFR TKIs. Herein, we report a lung adenocarcinoma patient harboring a rare EGFR E709_T710delinsD mutation who was treated with afatinib as the first-line therapy and achieved a progression-free survival of 23 months. After the disease progressed, the patient received almonertinib treatment and exhibited a stable disease. This case indicated that non-small cell lung cancer patients harboring the EGFR E709_T710delinsD mutation could benefit from afatinib treatment, followed with almonertinib treatment, as a potential therapeutic strategy.

Keywords: NSCLC, EGFR mutation, exon 18, E709_T710insdelD, afatinib

HIGHLIGHTS

- A lung adenocarcinoma patient harbored a rare exon 18 deletion-insertion mutation of in EGFR (E709_T710delinsD) at with a mutant allele frequency of 74.8%.
- The patient was treated with afatinib as the first-line therapy and achieved a progression-free survival of 23 months.
After the disease progressed, almonertinib was administered as the second-line therapy for the NSCLC patient, and led to a stable disease.

INTRODUCTION

Lung cancer, of which 80% - 85% is classified as non-small-cell lung cancer (NSCLC), has the highest death rate of all cancers worldwide (1, 2). Somatic activating mutations in the epidermal growth factor receptor (EGFR) are the most common oncogenic driver mutations in Asian NSCLC patients, with a prevalence of 47% (3). Such mutations typically occur within exons 18 - 21. The most common EGFR mutations (nearly 85% - 90%) in NSCLC patients are deletions in exon 19 (19Del) and the L858R point mutation in exon 21, which are defined as classical mutations. The remaining 10% - 15% of EGFR mutations are non-classical mutations, including point mutations and deletions in exon 18, and point mutations and insertion mutations in exon 20 (4).

For NSCLC patients with EGFR mutations, it has been well documented that patients with EGFR 19Del and L858R mutations exhibit good clinical responses to EGFR tyrosine kinase inhibitors (TKIs). Clinically, first-line therapy with EGFR TKIs is recommended and significantly improves the survival of NSCLC patients with EGFR variations (5, 6). Although the T790M mutation in exon 20 is resistant to first- and second-generation EGFR TKIs, it is responsive to the third-generation EGFR TKI, osimertinib (7). However, there is insufficient clinical evidence to confirm the sensitivity of exon 18 mutations to EGFR TKIs. In this case, we report a lung adenocarcinoma patient with a rare EGFR exon 18 deletion-insertion mutation (E709_T710delinsD) that responded well to afatinib and achieved a progressive-free survival of 23 months. Following the development of afatinib resistance, the patient then benefited from almonertinib treatment.

CASE PRESENTATION

A 70-year-old Chinese female non-smoker with no family history of cancer suffered from repeated coughing for more than 10 days in October 2018. Computed tomography (CT) of the chest revealed a 5.1 × 3.6 cm density mass in the dorsal segment of the lower left lung (Figure 1A). Magnetic resonance imaging (MRI) scans showed that there were no metastases in the brain (Figure 1B). The level of the serum tumor biomarker, carcinoembryonic antigen (CEA), was 16.27 ng/mL, which was much higher than the normal range of < 5.0 ng/mL (Figure 1C). Immunohistochemical analyses revealed that the tumor cells of the left lung were positive for thyroid transcription factor-1 (TTF-1) and Napsin A, whereas focal staining was positive for CK5/6 (data not shown). Based on those data, the patient was diagnosed with stage II lung adenocarcinoma (cT3N0M0 of TNM staging system), and was recommended surgical...
Genetic alterations detected in lung cancers.

| Genes | Alternations                       | Coding change                      | MAF   | MAF   |
|-------|-----------------------------------|------------------------------------|-------|-------|
|       |                                    |                                    | 10/2018 | 09/2020 |
| EGFR  | p.E709_T710delInsD                 | c.2127_2129del                     | 74.8% | 87.4% |
| EGFR  | Amplification                     |                                    | 3.2 times | 3.4 times |
| TP53  | p.M246_T256del                    | c.735_767del                       | 26.5% | 49.5% |
| PIK3CA| p.E542K                           | c.1633G>A                          | 7.6%  | 1.0%  |
| CHD8  | p.N761Kfs*11                      | c.2282dup                          | 35.4% |       |
| RB1   | Splice-site mutation c.861+2T>A   | /                                  | 80.3% |       |
| SMAD4 | Single copy loss                  | /                                  |       | /     |
| NRG1  | p.T591M                           | c.1772G>T                          | 1.2%  |       |
| TERT  | p.T249M                           | c.1772G>T                          | 0.6%  |       |
| TERT  | p.T249M                           | c.1772G>T                          | 0.6%  |       |
| TERT  | p.T249M                           | c.1772G>T                          | 0.6%  |       |
| UGT1A1| p.L124F                           | c.372G>T                           | 7.5%  |       |

- not detected; /, not applicable; MAF, mutant allele frequency.
development of afatinib-resistance, almonertinib was then administered and the patient achieved SD.

Otherwise, Zeng et al. found that the E709_T710delinsD mutation was an acquired drug resistance mechanism and not sensitivity to afatinib in an advanced lung adenocarcinoma patient with an EGFR exon 18 E709H mutation (17). Thus, additional evidence of the clinical significance of the E709_T710delins mutation needs to be explored.

For uncommon EGFR mutations, although the data from prospective clinical trials are insufficient because of the low frequency and diversity of such mutations, some cases harboring uncommon EGFR mutations have been reported with effective treatment by EGFR TKIs. It has been reported that the major uncommon EGFR mutations, including G719X, S768I, and L861Q are more sensitive to afatinib and osimertinib, compared to first-generation EGFR TKIs (18). Therefore, afatinib or osimertinib have been suggested as possible first-line treatment options for major uncommon EGFR mutations (19). However, patients with uncommon mutations that co-occurred with common EGFR mutations exhibited responses to first-generation EGFR TKIs (20). Limited clinical data and our analyses suggest that other rare EGFR mutations, including E709X, L747P/S, Del18 mutations, and some exon 19 insertion-deletions are more sensitive to afatinib or osimertinib than gefitinib or erlotinib (Table 2). In particular, NSCLC patients with compound EGFR mutations involving T790M exhibit good responses to osimertinib compared to NSCLC patients with other mutations (19).

In summary, this study reported a lung adenocarcinoma patient who harbored an EGFR E709_T710delinsD mutation and received the second-generation EGFR TKI, afatinib, as the first-line therapy. Unexpectedly, lung lesion shrinkage lasted 7 months and the patient achieved a PFS of up to 23 months. Following the development of afatinib-resistance, almonertinib was administered and achieved a SD. Thus, this case detailed a reliable treatment option for NSCLC patients harboring a rare EGFR exon 18 deletion-insertion mutation.

**DATA AVAILABILITY STATEMENT**

The original contributions presented in the study are included in the article-supplementary files. Further inquiries can be directed to the corresponding author.

**ETHICS STATEMENT**

The studies involving human participants were reviewed and approved by Ethical committee of Jiangsu Province Hospital of Traditional Chinese Medicine. The patients/participants provided their written informed consent to participate in this study.

**AUTHOR CONTRIBUTIONS**

Conception and design: LZ, LL, and YW. Collection and assembly of data: YW, YG, and YC. Manuscript writing and revising: All authors. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: YC and YG are employees of Nanjing Geneseeq Technology Inc., China. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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