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Case Series
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Advanced Lung Adenocarcinoma with EGFR Exon 20 Insertional Mutation Treated with Furmonertinib: A Report of 2 Cases

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Abstract

Epidermal Growth Factor Receptor (EGFR) exon 20 insertion (ex20ins) mutations account for approximately 0.1% to 4% of all Non-Small Cell Lung Cancers (NSCLC) and 4% to 12% of all EGFR mutations. Since patients with EGFR ex20ins usually respond poorly to 1st- and 2nd-generation EGFR Tyrosine Kinase Inhibitors (EGFR-TKIs), treatment options for this group of patients remain a headache. Here, we report two cases of lung adenocarcinoma patients with EGFR ex20ins mutation treated with furmonertinib (160 mg daily), both achieved Partial Response (PR) at the initial efficacy assessment with no specific adverse effects. One of them had Progression-Free Survival (PFS) of more than 12 months. Unfortunately, the other had a PFS of only 5.2 months with the same regimen, which may be related to the high heterogeneity of EGFR ex20ins or the coexistence of TP53 co-mutations. In any case, this case report presents a new and possible option for NSCLC patients with EGFR ex20ins mutations.

Keywords: Furmonertinib; Exon-20 insertion mutation; Epidermal growth factor receptor; Non-small cell lung cancer; Next-generation sequencing

Introduction

With the widespread use of Next-Generation Sequencing (NGS) technology, the incidence of rare EGFR gene mutations, including ex20ins mutations, is increasing. EGFR ex20ins mutations account for approximately 0.1% to 4% of all NSCLC, and the most common EGFR ex20ins mutation is A767_V769dup [1-3]. No history of smoking, female and adenocarcinoma are common features of NSCLC with EGFR ex20ins [4-6]. The first-line treatment of choice for EGFR mutation-positive NSCLC patients is EGFR-TKIs, but patients with EGFR ex20ins usually respond poorly to 1st and 2nd generation EGFR-TKIs, which may be related to their primary drug resistance [7-9].

Furmonertinib is a third-generation EGFR-TKI developed independently in China. Its structure has been further innovated compared to Osimertinib by introducing a unique trifluoroethoxy pyridine structure, which is strongly hydrophobic and has a high affinity for the depressed hydrophobic pocket consisting of hydrophobic amino acids L792 and M793 in the EGFR ATP binding region, thus making the drug itself much more active [10]. Preclinical studies have found that furmonertinib has an IC50 value of 11.0 nM against EGFR ex20ins and shows a very strong inhibitory activity against them. Here, we present two patients with advanced NSCLC carrying EGFR ex20ins who responded well to furmonertinib, with one having a PFS of more than 12 months, aiming to provide a new option for the targeted treatment of such rare mutations.

Case Series

Case 1

The patient was a 41-year-old female with no history of smoking or family history of tumor, who came to our hospital on January 26th, 2022 with "cough for six months and back pain for more than two months". Physical examination did not show any abnormality. Computed Tomography (CT) scan showed an occupying lesion in the upper lobe of the left lung, measuring about 4.0 cm × 4.0 cm (Figure 1A, 1B), with multiple lymph node enlargement in the left hilum, bilateral subclavian fossa and mediastinum, as well as metastases in both lungs, liver and multiple vertebrae. Cranial Magnetic Resonance Imaging (MRI) suggested an intensifying focus in the right insula with possible metastasis. After systemic evaluation, the patient underwent CT-guided lung puncture biopsy on January 28th, 2022. The pathology suggested: lung adenocarcinoma (Figure 1C). Ventana detected a

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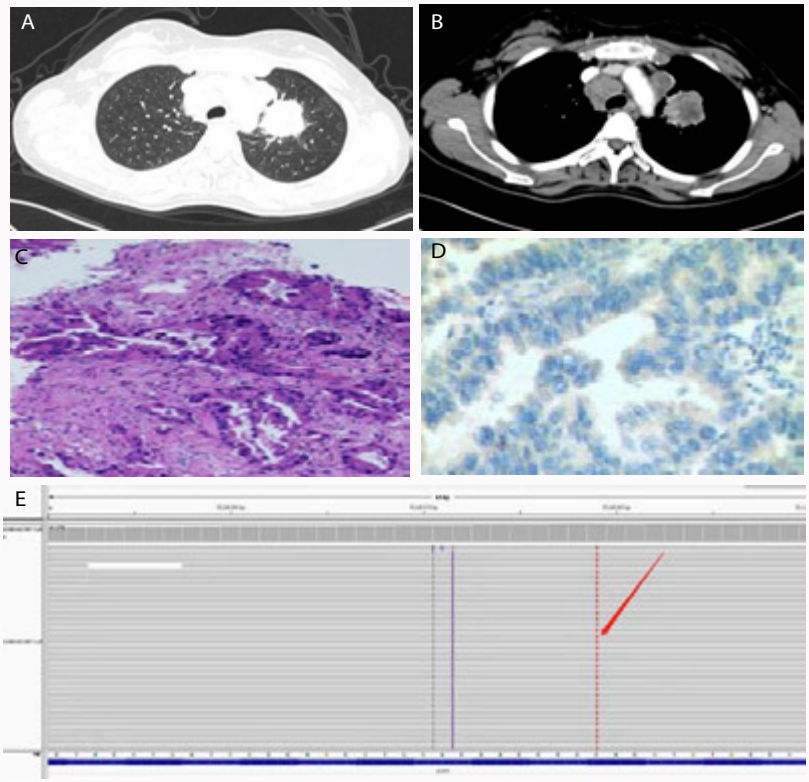

Figure 1: (A,B): Chest CT on January 26th, 2022 (pre-treatment); (C): Hematoxylin-eosin staining; (D): Immunohistochemistry indicated negative for ALK fusion protein; (E): NGS found that the patient had EGFR ex20ins mutation.

Table 1: The details of patient's genetic mutation.

Gene name	Mutation	Tissue abundance	Blood abundance
EGFR	Exon20 c.2317delinsAACCCCT p.H773delinsNPY	58.01%	80.32%
DNMT3A	Exon3 c.101G>C p.G34A	6.43%	0.80%

Table 2: The status and quantity of ctDNA.

Number of plasma tests	1st time	2nd time	3rd time	4th time	5th time
Time of plasma sample	27-01-2022	2022-04-19	2022-08-02	2022-11-03	2023-02-15
ctDNA status	positive	negative	negative	positive	positive
ctDNA quantity	3/4	0/4	0/4	1/4	1/4
ctDNA content (hGE/ml)	2118.29	0.00	0.00	5.43	4.58

negative Anaplastic Lymphoma Kinase (ALK) fusion protein (Figure 1D). Combined with the immunological results, the final diagnosis was: Primary left lung adenocarcinoma with multiple distant metastases (cT2N3M1, stage IVC). Detected by NGS: EGFR exon20 p.H773delinsNPY mutation, tissue abundance: 58.01%; Tumor Mutation Burden (TMB): 8.58 Muts/Mb. Circulating tumor DNA (ctDNA): Positive at 2118.29 (hGE/ml) (Figure 1E and Table 1). With the patient's fully informed consent, platinum-based chemotherapy combined with furmonertinib (160 mg daily) was started on 2022-02-07. Two months later, chest CT showed a significant reduction in the size and number of intrapulmonary and hepatic lesions compared with the previous one, and the efficacy was assessed as PR and the ctDNA content turned negative (Table 2). However, Measurable Residual Disease (MRD) dynamic monitoring results on November 03rd, 2022 showed that ctDNA turned positive with one increase (from 0.00 hGE/ml to 5.43 hGE/ml) from the previous (August 02nd, 2022), but CT on November 03rd, 2022 showed that the lesions were similar to before, and Stable Disease (SD) was evaluated. Consideration of ctDNA positivity suggests possible resistance to current regimen. After thorough discussion, anlotinib (12 mg daily, d1-d21) was added for 3 cycles therapy. On March 14th, 2023, chest CT showed larger lesions than before (Figure 2), and a new lesion was found in the brain, which meant the progression of the disease with PFS of 13.3 months. The patient is still being actively followed up and treated.

Case 2

The patient was a 39-year-old female with no history of smoking or family history of tumor. Chest CT on May 12th, 2022 for physical examination suggested a lobulated soft tissue shadow (3.2 cm × 2.6 cm) in the dorsal segment of the left lower lung lobe with multiple lymph nodes enlargement in the mediastinum (Figure 3C). Cranial MRI and Positron Emission Tomography (PET-CT) confirmed metastases in the brain, both lungs, lumbar spine, and kidneys (Figure 3F). Combined with pathology and immunohistochemistry

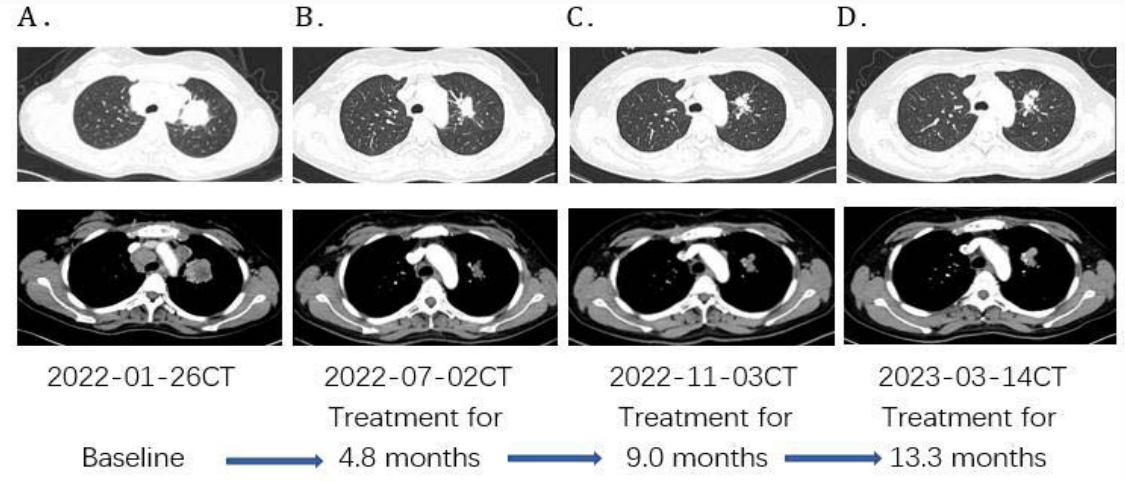

Figure 2: (A) Pre-treatment chest CT showed a mass lesion in the upper lobe of the left lung, about 4.0 cm × 4.0 cm in size, platinum-based chemotherapy combined with furmonertinib (160 mg daily) was started on 2022-02-07; (B) On July 02nd, 2022, CT showed that the lesion shrank to 2.7 cm × 1.8 cm; (C) CT on November 02nd, 2022 showed that the lesion size was similar to before; (D) Chest CT showed larger lesions than before on March 14th, 2023.

Table 3: The details of patient's genetic mutation.

Gene name	Mutation	Tissue abundance
EGFR	Exon20 p.A767_V769dup (c.2300_2308dupCCAGCGTGG)	27.58%
TP53	Exon6 p. I195F (c.583A>T)	21%
TP53	Exon6 p. V216L (c.646G>T)	2.61%
FGFR2	Exon7 p. P253R (c.758C>G)	0.72%

results, the diagnosis was: Left lung adenocarcinoma, cT2N3M1, stage IV (Figure 3A). NGS testing suggested: EGFR ex20ins mutation (p. A767_V769dup, 27.58% abundance), along with TP53 mutation (p.I195F, 21% abundance; p.V216L, 2.61% abundance), FGFR2 mutation (p.P253R, 0.72% abundance). TMB: 15.05 Muts/Mb (Figure 3B and Table 3). Since 2022-05-05, patients have been started with platinum-double-agent chemotherapy combined with furmonertinib (160 mg per day), during which the efficacy is evaluated for PR, during which the efficacy was assessed PR (Figure 3D). However, after 5.2 months of treatment (2022-10-07), the chest CT and cranial MRI revealed a progressive lesion (Figure 3E, 3H), and the regimen was adjusted to chemotherapy combined with furmonertinib and anlotinib targeted therapy. Unfortunately, the patient's brain lesions continue to progress and on March 10th, 2023, she started cranial radiotherapy on the basis of the existing protocol. As seen above, the patient's PFS with furmonertinib treatment was 5.2 months.

Discussion

EGFR ex20ins mutations have a wide range of subtypes and heterogeneity due to the location and length of the insertion fragment. Up to 100 mutant subtypes have been identified worldwide, most of which are insensitive to EGFR-TKIs, except for A763_Y764insFQEA [11-14]. EGFR ex20ins mutations are mostly located at the C-terminus of the C-helix or in the loop immediately following the C-helix, thus causing permanent activation of EGFR proteins [1,9]. However, unlike EGFR-sensitive mutants, the C-helix and phosphate binding loop active conformations occupy both the binding pocket of EGFR-TKIs, this spatial site blocking effect results in the inability of EGFR-TKIs to enter this active conformational domain for therapeutic effect, reducing the affinity for EGFR-TKIs [15]. On the other hand, EGFR ex20ins mutants are conformationally similar to wild-type EGFR proteins and have a very close binding pattern and apparent affinity to ATP, resulting in a narrow therapeutic window of safety for the drugs. Drug candidates, even if they can inhibit EGFR ex20ins mutants, are prone to accidentally injure wild-type EGFR proteins, causing serious adverse effects (e.g., diarrhea, rash, etc.) [16]. Therefore, it is very difficult to develop a drug that is safe and effective against multiple EGFR exon20ins mutant subtypes.

Although the FDA has approved Mobocertinib and Amivantamab for marketing, chemotherapy is still the standard of care in clinical practice [17,18]. Our real-world study published in lung cancer in 2020 found that the proportion of patients with advanced EGFR ex20ins receiving platinum-based chemotherapy in the first line was as high as 80%, and the proportion treated with EGFR-TKIs was also 18%, with less than 5% receiving immunotherapy (single agent or combination). The most effective chemotherapy regimen had an ORR of 19.2% and a median PFS of 6.4 months, compared with 8.7% for EGFR-TKIs and 2.9 months for PFS (of which the first generation of EGFR-TKI patients had an ORR of 0% and PFS for 2 months). Efficacy of immunotherapy was even less satisfactory, with a PFS of only 1.5 months [12]. It was found that the domestic furmonertinib has better safety and efficacy in treating EGFR ex20ins mutation advanced NSCLC. In the phase I dose creep trial, furmonertinib dose escalation to 240 mg/d still did not reach the maximum tolerated dose. The results of the FAVOUR study showed an ORR of 60% with three times the standard recommended dose (240 mg/d) of furmonertinib for EGFR ex20ins mutation advanced NSCLC. The median PFS (mPFS) data are not yet available and the mechanism of action of the drug mechanism of action of this drug needs to be further investigated. Notably, at three times the standard recommended dose, none of the 10 patients experienced ≥ grade 3 adverse events, including treatment-related interstitial pneumonia

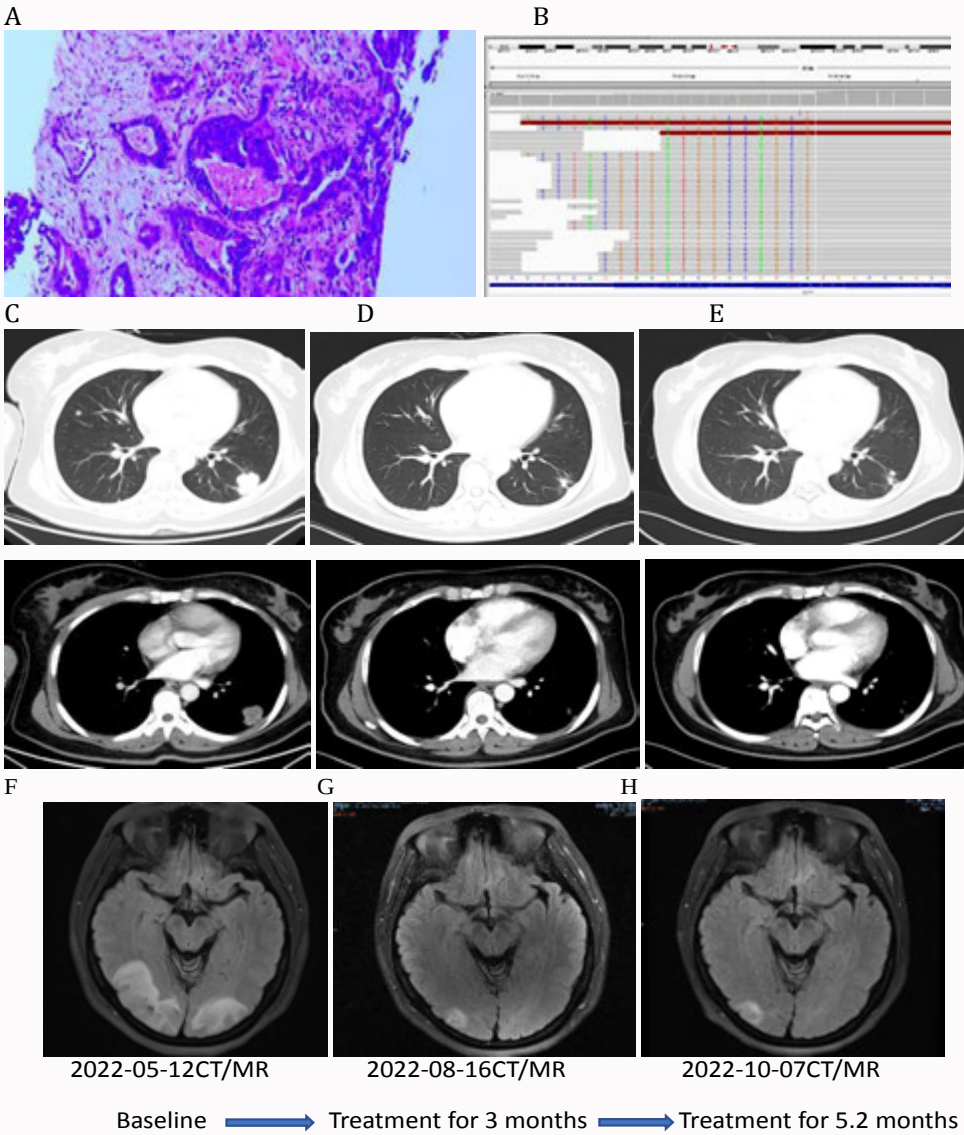

Figure 3: (A): HE staining suggests lung adenocarcinoma; (B): The NGS detected a non-frameshift insertion mutation in exon 20 of the EGFR gene (c.2300_2308dupCCAGCGTGG) with the amino acid sequence mutation p. Ala767_Val769dup(20ins); (C, F): Chest CT and brain MRI before furmonertinib treatment; (D, G): After 3 months of treatment with furmonertinib, CT and brain MRI suggested a significant shrinkage of the lesion compared with the previous. (E, H): Chest CT on 2022-10-07 showed that some lesions in lung were larger than before, and brain MRI also indicated the progression of lesions.

or enterocolitis. Thus, the use of furmonertinib is a potentially viable targeted treatment option for NSCLC patients with EGFR ex20ins mutations.

In this present case report, 2 patients received furmonertinib (160 mg daily) for financial reasons. With similar clinicopathological features, the PFS of the two were very different. Both achieved PR at the initial efficacy assessment with no specific adverse effects. This implies the efficacy and safety of furmonertinib against EGFR ex20ins mutation. Unfortunately, the second patient was found to have tumor lesion progression at the end of the sixth cycle of treatment, and we speculate that there may be two reasons for this: 1. EGFR ex20ins mutations are highly heterogeneous and different insertion locations may affect the kinetics of drug and ATP binding, thus affecting the patient's sensitivity to EGFR-TKIs and prognosis [2]. 2. By comparing the two patients' genetic test results, we found that this patient had a high abundance of TP53 concomitant mutations. Results from a clinical trial on Osimertinib showed that deletion of the TP53 gene reduced PFS and OS. In TP53 mutations and wild-type patients, the main mechanism of drug resistance was EGFR T790M mutation, and TP53 mutations accelerated the progression of drug resistance but did not affect the initial efficacy of Osimertinib. Moreover, patients with TP53 deletion mutations had a significantly increased TMB after treatment compared to those before treatment (median 9.68 *vs.* 7.60, p=5.228e-05), thus increasing genomic instability and consequently the potential for tumor cell mutations, making drug-resistant mutations more likely to occur [19]. By analysis, this patient's left lower lung lesion shrank from 4.0 cm × 3.3 cm × 2.8 cm to 1.6 cm × 1.2 cm × 0.8 cm during the initial furmonertinib treatment, and the brain lesion was also significantly smaller than before, which confirmed that TP53 did not affect the sensitivity of EGFR exon20 p.A767_V769dup mutation to furmonertinib. However, resistance developed at the end of cycle 6, we suspect that TP53 mutations are associated with faster resistance progression in the EGFR ex20ins mutation NSCLC and may co-mutate with other genes to mediate the

acquisition of resistance to EGFR-TKIs. Unfortunately, this patient did not undergo genetic testing again due to financial reasons, and we were unable to determine whether the patient had genomic changes and the cause of drug resistance.

Overall, due to the low incidence and strong heterogeneity of EGFR ex20ins mutations, there is a lack of sufficient clinical trial evidence for targeted therapies. The optimal treatment plan for patients with EGFR ex20ins still needs to be further explored, and more prospective clinical studies are needed to further validate whether the appropriate drugs can be selected according to different mutation subtypes or combined with different pathway inhibitors, chemotherapy or anti-angiogenic drugs to produce a "1+1>2" effect. This article presents two cases of patients with EGFR ex20ins mutations showing that effective treatment with furmonertinib may provide a new treatment option for such mutations. However, the mechanism of subsequent resistance is not yet clear and needs to be further investigated.

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