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After Sequential Therapy with First and Third Generation EGFR-Tkis, A Patient Acquired EGFR G719A Mutation and Responded to Afatinib, and Then, Acquired EGFR T790M Mutation When Developed Resistance to Afatinib: A Case Report

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1. Abstract

NSCLC patients who had sensitive EGFR mutation had great possibility to get benefit from EGFR-TKIs. But this efficacy was relied on related EGFR mutation, if related EGFR mutation changed, resistance would happened. In our report, we did next generation sequencing(NGS) each time the patient had progression. We observed the patient acquired rare mutation after the resistance to third-generation EGFR-TKIs and this mutation was sensitive to second-generation EGFR-TKIs. And after the resistance to second-generation EGFR-TKIs, the patient had T790M EGFR mutation again and third-generation EGFR-TKIs could be continue taken.

2. Introduction

In Asia, about 50% of NSCLC patients will achieved EGFR mutation which is exquisitely responsive to EGFR-TKIs therapy [1-3]. Of all EGFR mutations, the EGFR exon 19 Del and EGFR L858R are accounted for about 84.6% [1-6]. However, despite the primary beneficial response, its always occurs resistance to the EGFR TKIs, most frequently by reason of the T790M mutation [7,8]. After patients acquired T790M mutation, third-generation TKIs like osimertinib can be used [9]. But the resistance to third-generation EGFR-TKIs always occurs, with a median time to progression of 10.1 months [10,11]. Thereafter, strategies for the administration of this condition have largely been limited to chemotherapy [12]. Besides, immune checkpoint inhibitor therapy and best supportive care are also recommended by standard guidelines [13]. With this background, we report an NSCLC patient who received sequential therapy with first, third, second generation EGFR-TKIs and finally returned to third generation EGFR-TKIs (Figure 1). Everytime we changed the patient's treatment, the accurate genetic test was utilized.

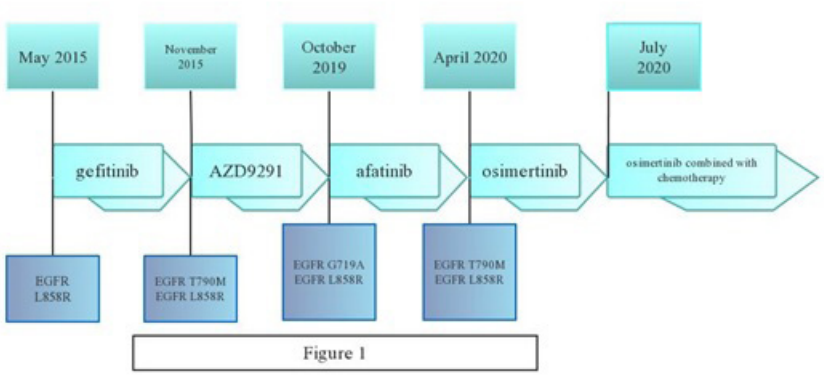

Figure 1: Diagram showing the treatment history of the patient.

3. Case Report

An 81-year-old male underwent computed tomography (CT) scans which showed a right lung upper lobe mass with intrapulmonary metastasis, multiple mediastinal lymph nodes enlarged and low density shadow of the left adrenal nodule in April 2015. Pathologic examination on CT-guided tissue biopsy (lung tissue) confirmed adenocarcinoma and molecular pathology of biopsy identified EGFR L858R mutation. The patient began taking gefitinib as first-line treatment. The computed tomography (CT) scans showed obvious shrinkage in the lesion, contributing to partial response. The partial response last about six months. Six months later, in November 2015, computed tomography (CT) scans emerged that the lesion was progressed and AZD9291 was be taken as second-line treatment when EGFR T790M was been detected by next generation sequencing(NGS). After the application of AZD9291, computed tomography (CT) scans showed the lesion consistent disease control. And the patient continued on AZD9291 treatment last about three years. Then, in September 2019, the computed tomography (CT) scans revealed enlarged lesion. One month later, in October 2019, the patient required hospitalization for encephalalgia, dizziness and unsteady walking. The patient also complained that his right extremities were numb and weak. Subsequent next generation sequencing(NGS) of tissue biopsy at the time of relapse confirmed an acquired EGFR G719A mutation in addition to the original EGFR L858R mutation. According to the result of next generation sequencing(NGS), the patient commenced on afatinib as the third-line treatment. Then, his clinical symptoms were notably relieved and radiograph revealed with reduced lesion. However, on May 31, 2020, the patient got worsen cough and coughed up a lot of white sputum. The Computed tomography (CT) scans in April 2020 demonstrated worsening of the lesion. Repeated next generation sequencing(NGS) detected the emergence of EGFR T790M mutation, in conjunction with EGFR L858R mutation (Table 1). Therefor the patient achieved osimertinib as the forth line treatment. Finally, in August 2020, the patient got worsen cough and suffered from headache. the computed tomography (CT) scans revealed enlarged lesion (Figure 2). He went to another hospital and was treated with osimertinib combined with chemotherapy. Until now the cut off day, the patient still alive.

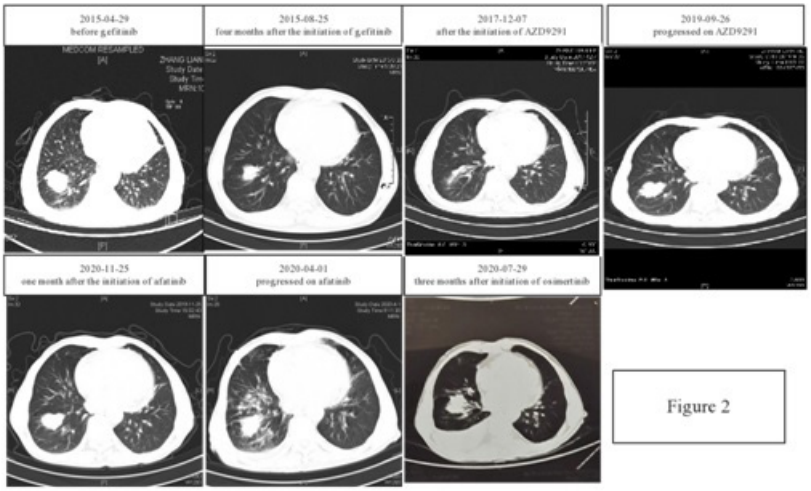

Figure 2: Computed tomography (CT) scans are ordered according to the time point relative to the treatment.

Table 1: Next generation sequencing(NGS) screenshot in different times.

Gene	Exon	Amino acid change
EGFR	21	L858R

2015-05

Gene	Exon	Amino acid change	Enrichment
EGFR	21	L858R	3.27%
	18	G719A	8.61%

2019-10

Gene	Exon	Amino acid change
EGFR	21	L858R
	20	T790M

2015-11

Gene	Exon	Amino acid change	Enrichment
EGFR	21	L858R	0.49%
	20	T790M	0.35%

2020-04

Table 1: Next generation sequencing(NGS) screenshot in 2015-05 revealed EGFR L858R mutation. Next generation sequencing(NGS) screenshot in 2015-11 revealed the original EGFRL858R mutation in addition to an acquired EGFR T790M mutation. Next generation sequencing(NGS) screenshot in 2019-10 revealed the original EGFRL858R mutation in addition to an acquired EGFR G719A mutation. Next generation sequencing(NGS) screenshot in 2020-04 revealed EGFR L858R mutation and EGFR T790M mutation.

4. Discussion

Resistance mutation would been acquired in patients with EGFR-TKIs resistance in some percentage [14] But some of these mutation were rare to seen. The occurrence of EGFR G719X mutation after third generation EGFR-TKIs resistance ranged between 2% and 5% [15]. Here we describe an unreported cases. Each time the disease progressed, the patient acquired resistance mutation and got clinical benefit from the sequential therapy with first, third, second and third generation EGFR-TKIs. The patient was treated by first generation EGFR-TKIs after the detection of the EGFR 21 exon L858R mutation. And he changed the treatment to the third generation EGFR-TKIs when he was detected with EGFR L858R mutation and EGFR T790M mutation after resistance. After the resistance to third generation EGFR-TKIs, repeated next generation sequencing(NGS) revealed he acquired EGFR G719A mutation, besides the original EGFR L858R mutation and treated with the second generation EGFR-TKIs. Finally, the patient received next generation sequencing(NGS) again, after the resistance to second generation EGFR-TKIs, he was detected with EGFR L858R mutation and EGFR T790M mutation and treated with third generation EGFR-TKIs continued.

During the treatment, accurate genetic tests had been utilized. Every time, when the patient developed the resistance to the EGFR-TKIs, he achieved next generation sequencing(NGS). And according to the outcomes, we adjusted his treatment. Based on the accurate genetic tests, our selections of therapeutic schedule will have more scientific evidence and will be more targeted. As we reported, the patient had durable clinical response. The patient was diagnosed with a stage IV adenocarcinoma of the lung in May 2015 and treated with EGFR-TKIs. His treatment was adjusted under the guidance of next generation sequencing(NGS) and now, in the end of 2020, the patient still alive.

5. Conclusion

Our report provides an rare case of sequential therapy with EGFR-TKIs. An rare mutation (EGFR G719A) occurred after osimertinib resistance and the second generation EGFR-TKIs can be used. By coincidence, EGFR T790M mutation acquired again and osimertinib can be used again. These mutation Prolonged sequential therapy. In similar condition, our treatment therapy can be an option. Furthermore, our report also highlights the significant of accurate genetic tests in the treatment progress and confirmed the accurate genetic tests can guide our options of treatment.

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