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Case Report

CASE REPORT

T790M mutation in stage IV EGFR-mutated NSCLC patient with acquired resistance reverted to original 19Del mutation after administration of a series of precision treatments: a case report

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Abstract

Existing studies have yet to elucidate clearly the mechanisms of secondary resistance to third generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs), neither is there any established standard therapy for patients resistant to third generation EGFR-TKIs. This case report demonstrates a rare mutation pattern in a male patient with a pathologic diagnosis of non-small cell lung cancer (NSCLC) harboring an EGFR exon 19 deletion (19Del) mutation, who then acquired an EGFR-T790M mutation after developing resistance to the first generation EGFR-TKI (gefitinib). The mutation reverted to the original EGFR-19Del mutation after the patient developed secondary resistance against the third generation TKI (osimertinib). This patient eventually achieved partial response (PR) with second generation TKI (afatinib) as a fourth-line treatment.

Key words: NSCLC; EGFR mutation; acquired resistance; driver gene

Introduction

Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are promising in treatment of patients with non-small-cell lung cancer (NSCLC) harboring sensitive EGFR mutations. Response rate to first generation EGFR-TKIs gefitinib and erlotinib has been reported as 71% and 58%, respectively, in some "sensitive" patients who were previously confirmed to harbor EGFR mutations.[1,2]

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Despite an initial treatment response to EGFR-TKI, most of these patients inevitably acquire resistance after a progression-free period of about 10 months.[3,4] Development of the EGFR-T790M mutation is the main mechanism of resistance against the first and second generation EGFR-TKIs,[5] and Matsuo *et al.* demonstrate that T790M mutation frequency is linked to duration of first/second-line treatment in patients with exon 19 deletion.[6] After approval by the Food and Drug Administration (FDA) for patients with EGFR-T790M mutation suffering disease progression during or after EGFR-TKI treatment,[7,8] osimertinib (Tagrisso™) showed an overall response rate of about 73%, and a longer progression-free survival (PFS) of 13.8 months. Nonetheless, relapse occurred 9-13 months after osimertinib, with resistance acquired because of EGFR-dependent resistance mechanisms, such as EGFR mutation, amplification, and loss, and EGFR-independent resistance mechanisms, such as alternative kinase activation, histological transformation, and phenotypic change.[8–12] Strategies to combat osimertinib-resistance have been suggested in some studies according to the subsequently acquired mutations such as the C797S mutation or the MET activation[9–11,13]; however, observations of exon 19 deletion (19Del) mutation after the secondary resistance have not been commonly reported. There are no clinical guidelines nor has any large-scale study been put forward to advise the management of such cases.

Case presentation

Informed consent was obtained from the patient for publication of this case report.

The patient was a 38-year-old man with a smoking history of 10 years, who presented with a complaint of dry cough in February 2016. No other remarkable symptoms or signs were found at that time and he was diagnosed with lung adenocarcinoma in March 2016. From tissue immunohistochemistry analysis, tumor cells were presented as positive for TTF and Napsin A, but negative for CK5/6, CgA, Syn, ROS-1, and ALK-V. A baseline positron emission tomography/computed tomography (PET/CT) scan showed a tumor (3.2×2.0 cm) in the dorsal segment of the lower lobe of the right lung, with metastases in ipsilateral hilum and mediastinum lymph nodes, bilateral pleura, and lung. After the EGFR-19Del (NM-00522.3 (EGFR):c.2236-2250del(p.Glu746-Ala750del)) mutation was confirmed on 1 April 2016, the patient was treated with the first generation TKI, gefitinib (Iressa™) from 4 April 2016 to 10 January 2017, during which the patient had no complaints of characteristic symptoms. A PET/CT follow-up review on 30 November 2016 showed a tumor (1.3×1.0 cm) in the dorsal segment of the lower lobe of the right lung, with a significant decrease in the glycometabolism of the interlobular pleura. Reduction of the lesion size by about 59.4% was a significant improvement and was classified as a partial response (PR) according to RECIST 1.1.

The patient then complained of cough again in January 2017; a follow-up chest CT scan showed further growth of tumor, which referred to an increase in the size of the primary lesion (dorsal segment of the lower lobe of the right lung). A genetic test using plasma was conducted on 22 February 2017 confirming a EGFR-T790M (NM-005228.3 (EGFR):c.2369C>T(p.Thr790Met)) mutation, after which a third generation TKI, osimertinib, was given to the patient on 26 February 2017.

On 30 June 2017, a CT review scan confirmed the growth of the lesions. A biopsy was conveyed and pathologically resulted in adenocarcinoma and gene detection confirmed EGFR-19Del (NM-00522.3(EGFR): c.2236-2250del(p.Glu746-Ala750del)) mutation on 10 July 2017. A PET/CT follow-up review on 14 July 2017 also confirmed growth of the lesion in the dorsal segment of the lower lobe of the right lung, ipsilateral hilum and mediastinum lymph nodes, and the ipsilatera pleura (no new symptoms were reported).

As the disease continued to progress despite administration of osimertinib, the patient accepted further treatment consisting of four cycles of chemotherapy of pemetrexed combined with cisplatin plus bevacizumab (Avastin™), specifically pemetrexed 930 mg d1; cisplatin 50 mg d1; 40 mg d2-3, bevacizumab 500 mg d1, 21 days repeated from 24 June 2017 to 30 September 2017, and two cycles of maintenance therapy with pemetrexed plus bevacizumab (pemetrexed 930 mg d1; bevacizumab 500 mg d1, 21 days repeated) from 26 October 2017 to 22 November 2017. Stable disease was confirmed after the four cycles of chemotherapy, with a slight reduction in the size of the lesion in the dorsal segment of the lower lobe of the right lung. However, the disease status reverted to progressive disease after two further cycles of maintenance therapy with pemetrexed plus bevacizumab, whereby the CT scan on 5 December 2017 confirmed a tumor (3.2×2.1cm) in the dorsal segment of the lower lobe of the right lung (the primary lesion) and a massive pleural effusion in the right chest.

After a genetic test using tissues was conducted, an EGFR-19Del (NM-00522.3(EGFR):c.2236-2250del(p.Glu746-

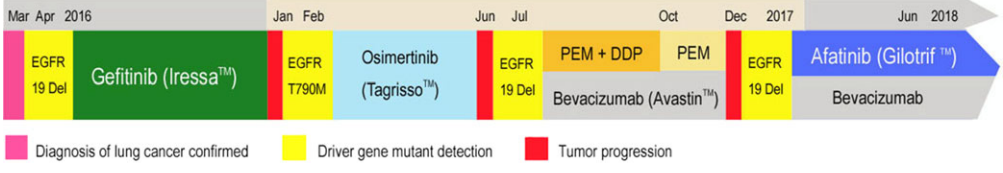

Figure 1. Timeline of treatment. The patient was treated with Gefitinib (Iressa™), Osimertinib (Tagrisso™), Bevacizumab (Avastin™), Afatinib (Gilotrif™).

Ala750del)) mutation (with an abundance of 78.91%) and a MET mutation and the amplification of FGFR1, ALK, ERBB2, NTRK1, DDR2, BRCA1, SMO, ROS1, etc., were confirmed on 23 December 2017. The patient accepted and started treatment with second generation TKI (afatinib, Gilotrif™) plus bevacizumab (500 mg d1, 21 days repeated) from 14 December 2017. A CT review scan confirmed a tumor (2.0×2.0 cm) in the dorsal segment of the lower lobe of the right lung and an obvious reduction of the pleural effusion; these improvements were evaluated as PR. The recent CT scan confirmed the PR response on 12 April 2018, with a PFS of afatinib treatment exceeding 6 months till this report had been drafted. The whole treatment course is presented in Fig. 1, a variation of the CT image is presented in Fig. 2, all the samples and sequencing results of each EGFR mutation test are presented in supplementary table 1.

Discussion

The T790M-EGFR mutation is a common mutation following resistance to first generation TKIs, with an incidence of about 50-60%[5,14]; subsequent mutations after secondary resistance are varied.[10] This case documents a rare mutation pattern where the main driver gene reverted to the original 19Del-EGFR mutation after developing resistance against third generation TKI. The patient was confirmed to have the exact same mutation as the original (NM-00522.3(EGFR):c.2236-2250del(p.Glu746-Ala750del), after receiving third-line treatment

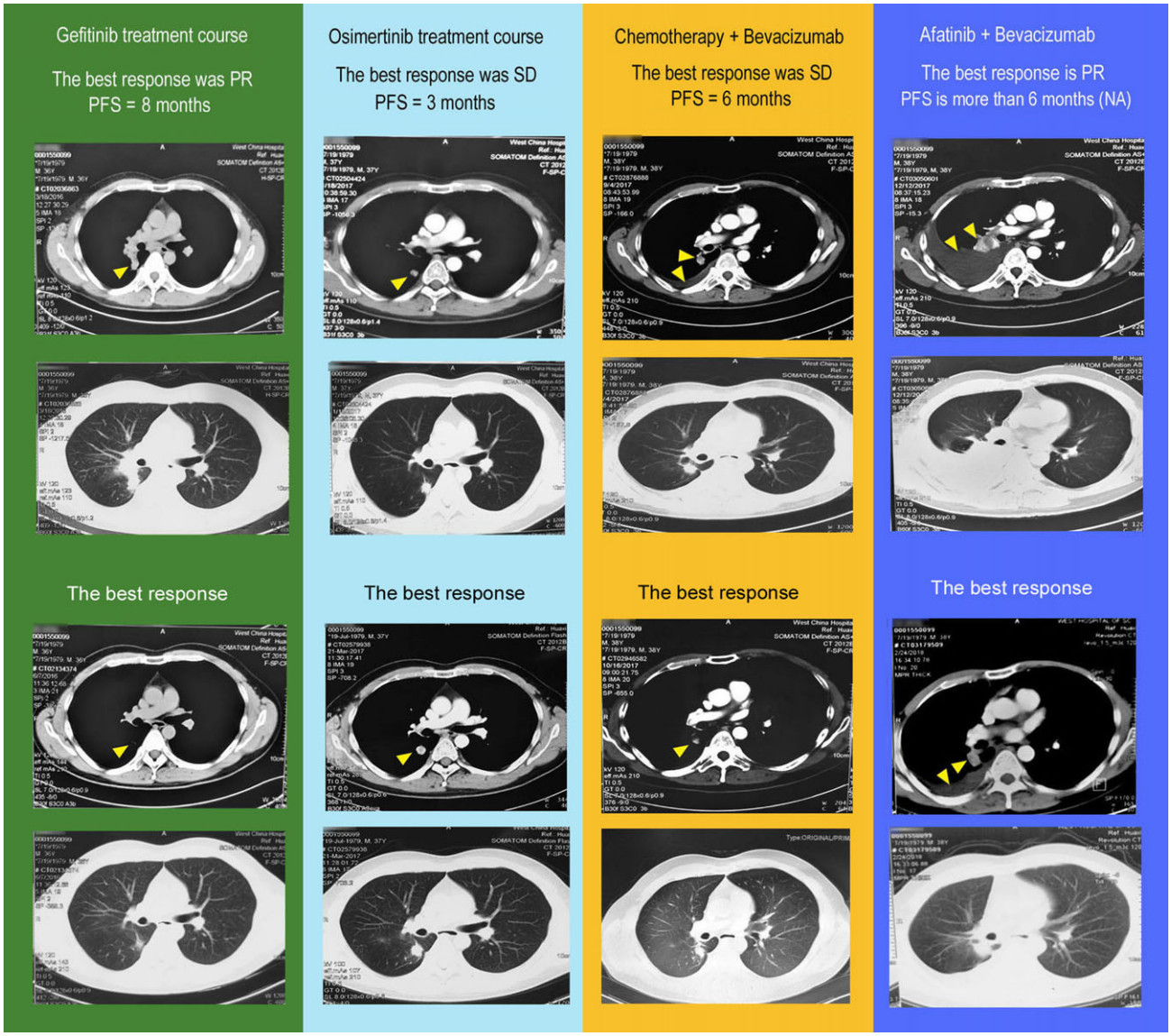

Figure 2. CT scan and response evaluation of the four lines of treatment. Line 1 and Line 3: mediastinal window; Line 2 and Line 4: lung window.

with chemotherapy following development of secondary resistance against third generation TKI. Although new mutations appeared in the last genetic test, the main driver was still the original mutation. The possible mechanisms of resistance against osimertinib include both EGFR-dependent and EGFR-independent resistance mechanisms,[9–13] but the mutation switching back to the original 19Del mutation is not included.

Given that the abundance of the EGFR-19Del mutation was confirmed to be 0.33% in plasma and 78.91% in tissue before and after chemotherapy, respectively, we were unable to determine whether chemotherapy had contributed to the increase in the observed frequency of the EGFR-19Del mutation. Further studies are required to illustrate the role of chemotherapy or antiangiogenic drugs in the moderation of mutation change.

The first-, second-, and third-line treatments for this patient were prescribed according to the guideline. Stable disease was achieved following third-line chemotherapy treatment with pemetrexed combined with cisplatin plus bevacizumab, after the patient developed secondary resistance to third generation TKI. Unfortunately, the disease continued to progress despite two further cycles of maintenance therapy with pemetrexed plus bevacizumab. After progressive disease was reported, the patient received second generation TKIs (afatinib) plus bevacizumab as fourth-line treatment and finally achieved PR. This final treatment choice was made without explicit guidance from the existing guideline. This treatment decision successfully extended the PFS and overall survival of this patient with phase IV NSCLC. This case study demonstrates a possible novel treatment option that can be considered in future clinical practice and management of refractory lung cancer.

Afatinib as a second generation TKI is an irreversible inhibitor of the EGFR and HER2 inhibitor, and was approved to be used in treatment of TKI-naive patients with NSCLC with sensitive EGFR mutation or patients with NSCLC progression after cisplatin-based chemotherapy.[15] PR was obtained in this case following treatment with Afatinib, possibly because of the sensitivity of the driver 19Del mutation, although the ERBB2 amplification might also contribute to the sensitivity.

Conclusion

This case presents a patient with stage IV NSCLC harboring an EGFR 19Del mutation derived from a secondary T790M mutation, who responded to afatinib as fourth-line treatment. The possibility of the driver mutation gene reverting to the original mutation after a series of alterations is indicated. This case illustrates that therapy targeting the main driver gene may make response to treatment more likely when the mutation varies through several lines of treatment. It may also warrant genetic re-testing during treatment into routine review when faced with disease progression or relapse.

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Supplementary data

Supplementary data are available at *Precision Clinical Medicine* Journal online.

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Conflict of interest statement

None declared.

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