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CASE REPORT

Heterogeneity of the resistance to gefitinib treatment in a non-small cell lung cancer patient with active epidermal growth factor receptor mutation

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Abstract

We report the case of a 37-year-old male non-small cell lung cancer patient with an active epidermal growth factor receptor (EGFR) mutation who received gefitinib as first-line treatment. After 13.7 months, the patient experienced disease progression and was treated with platinum-based doublet chemotherapy plus gefitinib for 5.4 months. A subsequent lung biopsy showed cMET overexpression; therefore, the patient received a cMET inhibitor with the gefitinib. The response in the different lesions of several organs was diverse. Stable disease was achieved in the lung lesion; however, the liver metastases enlarged. A liver biopsy found T790M mutation in EGFR exon 20, thus, third generation EGFR-tyrosine kinase inhibitors were used and a partial response was achieved.

Introduction

In advanced non-small cell lung cancer (NSCLC) patients, the median overall survival (OS) with platinum-based doublet chemotherapy is less than a year. The introduction of target drugs, such as gefitinib, erlotinib, afatinib, and crizotinib has achieved survival rates of more than two years in NSCLC patients with driver gene mutations.[1] Beyond progression there is still chance for patients to received targeted treatment, which is determined according to the resistance mechanism.[2]

Case report

A 37-year-old male patient presented to our hospital complaining of a cough that had lasted two months. The patient had never smoked and had no family history of cancer. His Eastern Cooperative Oncology Group performance status (PS) score was 1. The right supraclavicular lymph node could be touched during the physical examination. Positron-emission tomography-computed tomography (PET/CT) taken on 11 September 2012 showed right lower lung cancer with multiple metastases to the bilateral lung, right supraclavicular lymph node, and liver metastases. A biopsy of the lymph node taken on 15 September 2012 determined adenocarcinoma with an epidermal growth factor receptor (EGFR) exon 19 mutation, detected by the real time-polymerase chain reaction (RT-PCR). The diagnosis was cT4N3M1a (lung) stage IV right lower lung adenocarcinoma.

From 26 September 2012 the patient received gefitinib and achieved a partial response (PR). A CT scan taken on 8 November 2013 confirmed progressive disease (PD). The progression-free survival (PFS) rate was 13.7 months. He was enrolled in the IMPRESS trial and received six cycles of pemetrexed/cisplatinum chemotherapy with gefitinib from 20 November 2013.[3] Stable disease (SD) was initially achieved; however, PD was confirmed on 3 May 2014 with PFS of 5.4 months. The second biopsy from the primary lesion in the lung taken on 20 May 2014 showed

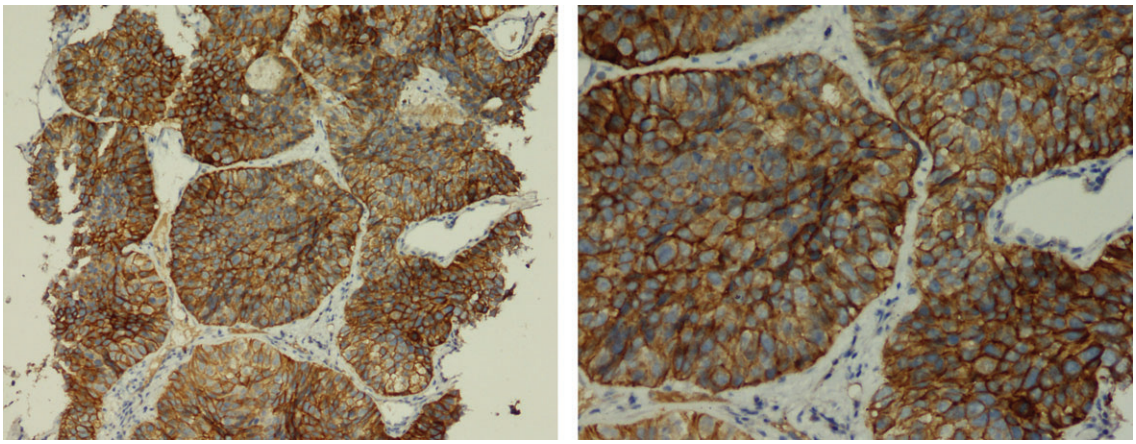

Figure 1 Immunohistochemistry of the mesenchymal epithelial transition gene expression.

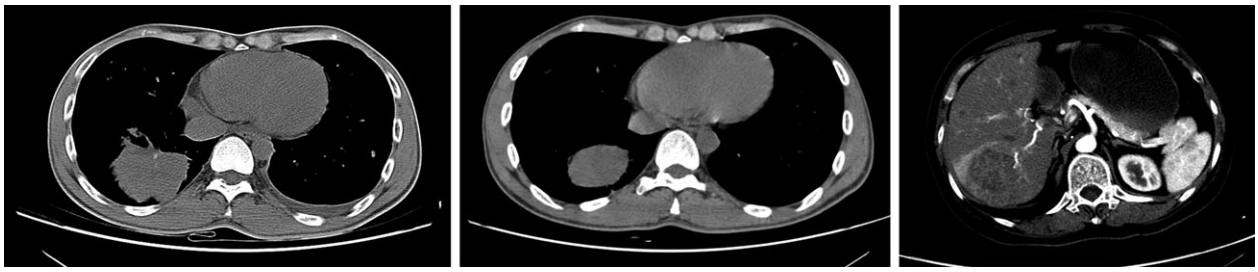

Figure 2 Image evaluation before and after the cMET inhibitor treatment.

adenocarcinoma with EGFR exon 19 mutation but no exon 20 mutation, detected by RT-PCR. Mesenchymal epithelial transition (MET) immunohistochemistry (IHC) was positive (Fig 1) and fluorescence in situ hybridization (FISH) was negative. The patient was enrolled in a clinical trial and treated with cMET inhibitor INC280 plus gefitinib from 12 June 2014. SD was achieved. On 7 October 2014, the primary lesion in the lung was reduced, while a new lesion appeared in the liver (Fig 2). The PFS was 3.8 months. A biopsy of the liver tumor was performed on 20 October 2014, which confirmed that the adenocarcinoma had metastasized from the lung, with EGFR exon 20 T790M mutation detected by RT-PCR. IHC and FISH of cMET were negative. From 5 January 2015, the patient was enrolled in a third generation EGFR-tyrosine kinase inhibitor (TKI) trial (NCT02330367) and was treated with avitinib (AC0010). The patient achieved PR.

Discussion

In the past, the standard treatment for advanced NSCLC patients has been first-line platinum-based doublet chemotherapy and second-line chemotherapy. After the introduction of EGFR-TKIs for NSCLC, patients with EGFR positive mutation have benefitted from longer PFS than with chemotherapy.[1] After the progression of the first-line EGFR-TKIs, doublet chemotherapy became the standard treatment, presenting an opportunity at subsequent biopsy to determine the resistance mechanism.[2] The major resistance mechanism was related to the secondary mutation (T790M) of the EGFR gene at exon 20.[4] Another mechanism was cMET alteration, including overexpression, amplification, or mutation.[4] The cMET inhibitor and the third generation EGFR-TKIs focused on T790M were developed to solve the problem of resistance.[5,6]

The patient in this case received gefitinib as first-line treatment and achieved PFS of 13.7 months. After progression, he received platinum doublet chemotherapy, with PFS of 5.4 months. A subsequent lung biopsy showed cMET overexpression. After the patient was administered the cMET-inhibitor, a different response was observed between the lung lesion and the liver metastases. A liver biopsy confirmed heterogeneity between the two sites. A T790M mutation of EGFR exon 20 was found in the liver metastases, which was not found in the lung lesion. The patient received third generation EGFR-TKIs focused on the T790M mutation and achieved PR. He received different target therapy drugs according to the gene alteration

during different periods, including gefitinib for the EGFR active mutation, cMET inhibitor for the cMET overexpression, and third-generation EGFR-TKIs for the T790M mutation. The heterogeneity of the tumor was another consideration after the progression of target therapy.[7] A different strategy was required to deal with the different responses to treatment.[8] The subsequent biopsy was helpful to determine the reason for the resistance. After targeted treatment, the patient has now survived more than three years.

In conclusion, we report a case of heterogeneity in the resistance to EGFR-TKI. A subsequent biopsy can determine the different mechanisms of different tumor locations, and then targeted treatment toward the driver gene alteration can be administered.

Acknowledgments

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Disclosure

No authors report any conflict of interest.

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