CASE REPORT

Beneficial Effect of Osimertinib Readministration in Non-small-cell Lung Cancer Harboring an Epidermal Growth Factor Receptor (EGFR) Mutation with a History of Acquired Resistance to Osimertinib

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Abstract:
We herein report a case of the beneficial effect of osimertinib readministration in non-small-cell lung cancer (NSCLC) harboring an epidermal growth factor receptor (EGFR) mutation. A 69-year-old non-smoking woman was diagnosed with advanced NSCLC harboring an EGFR exon19 deletion and T790M. She was treated with osimertinib for two years but eventually acquired resistance. After 1.5 years of salvage chemotherapy, osimertinib was re-administered. She has been effectively and safely treated with osimertinib readministration for over 10 months. A prospective study is warranted to evaluate the efficacy and safety of osimertinib readministration in NSCLC with EGFR mutations.

Key words: osimertinib, readministration, EGFR T790M, non-small cell lung cancer

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Introduction

Osimertinib, a third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI), showed a significant objective response rate in EGFR T790M-positive non-small-cell lung cancer (NSCLC) (1). However, the development of acquired resistance is inevitable. Therapy with first-generation EGFR-TKIs has been considered a therapeutic strategy for lung tumors with EGFR mutations (2); however, no studies have examined the efficacy and safety of osimertinib readministration.

In this study, we observed the beneficial effect of osimertinib readministration in a case of NSCLC with an EGFR exon19 deletion that responded very well initially and subsequently acquired resistance to osimertinib.

Case Report

A 69-year-old non-smoking woman was diagnosed with NSCLC (adenocarcinoma, cT4N2M1a cStage IV) harboring an EGFR mutation (exon 19 deletion) with contralateral lung metastases. She was treated with carboplatin, paclitaxel, and bevacizumab as first-line therapy, followed by second-line treatment with gefitinib for 1.5 years. The primary lesion of the right upper lung and multiple lung metastases enlarged, and a re-biopsy for the primary lesion revealed that the tumors harbored EGFR exon 19 deletion and T790M. Thus, osimertinib therapy was administered and continued for over two years with a good clinical response (Figure A); however, multiple lung metastases eventually developed. She was then treated with nivolumab or pemetrexed, but the effects were very limited. As sixth-line therapy, docetaxel and bevacizumab were administered for 1.5 years, after which her multiple pleural dissemination...
worsened.

The osimertinib-resistant malignant plural effusion harbored the EGFR exon19 deletion but lost T790M and did not show EGFR C797S. Therefore, we readministered osimertinib, and the pleural dissemination reduced without any progression for over 10 months (Figure B).

**Discussion**

This is the first report of the beneficial effects of osimertinib readministration in a patient with NSCLC harboring an EGFR mutation who acquired resistance to osimertinib.

Multiple resistance mechanisms of osimertinib, including EGFR C797S, MET activation, and loss of EGFR T790M, have been reported, but a standard therapy has not been developed to overcome this resistance (3-5). A large-scale (n=143) study suggested that the time to treatment discontinuation was shorter in osimertinib-resistant tumors with a loss of EGFR T790M than in tumors with EGFR T790M (6.1 vs. 15.2 months) (5). On this point, our present patient was unusual, since the time to treatment discontinuation was approximately two years. In addition to assessing EGFR C797S using the PNA-LNA PCR Clamp method (LSI Medicine, Tokyo, Japan), we performed RNA sequencing of pleural effusion obtained from a patient with osimertinib-resistant tumors using a HiSeq Sequencing System. cDNA libraries were prepared using the TruSeq RNA Access Library Prep Kit (Illumina, San Diego, USA). Neither EGFR nor MET nor RAS gene activation was observed in our case.

A previous study reported that the median progression-free survival of gefitinib readministration was 2.4 months in NSCLC patients who initially responded to gefitinib and subsequently acquired resistance. However, some of the patients showed durable long-term disease control upon readministration (6). EGFR-TKI readministration was predicted to be more effective if an EGFR-TKI-free interval could be secured using other treatments, such as cytotoxic drugs (2, 7).

In our case, the osimertinib-free interval was 18 months, and the osimertinib-resistant malignant pleural effusion harbored...
EGFR exon19 deletion, but not the T790M or C797S mutations. A preclinical study suggested that drug-sensitive and drug-resistant EGFR-mutant cells exhibited differential growth kinetics, with the latter showing slower growth in some cases (8). This preclinical study may explain one of the reasons that the EGFR-TKI-free interval is correlated with the response to EGFR-TKI readministration. In our case, osimertinib-sensitive lung cancer cells might have regrown during the 1.5 years EGFR-TKI-free period. At present, no specific genetic predictive biomarker has been identified for EGFR-TKI readministration. However, rapid advances in liquid biopsies have enabled monitoring of the genetic status of lung tumors (5, 9, 10) and may provide a gene signature that will enable the prediction of the efficacy of EGFR-TKI readministration.

In conclusion, our patient was effectively and safely treated by readministration of osimertinib, indicating that readministration can be considered as a viable treatment option. A prospective study is warranted to evaluate the efficacy and safety of osimertinib readministration in patients with NSCLC harboring EGFR mutations who acquired resistance to osimertinib and were treated with subsequent cytotoxic chemotherapies.

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References