Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.2152-18
Intern Med 58: 1625-1627, 2019
http://internmed.jp

【 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 chemotherapies, 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

(Intern Med 58: 1625-1627, 2019)
(DOI: 10.2169/internalmedicine.2152-18)

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

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Received: September 18, 2018; Accepted: December 3, 2018; Advance Publication by J-STAGE: February 1, 2019
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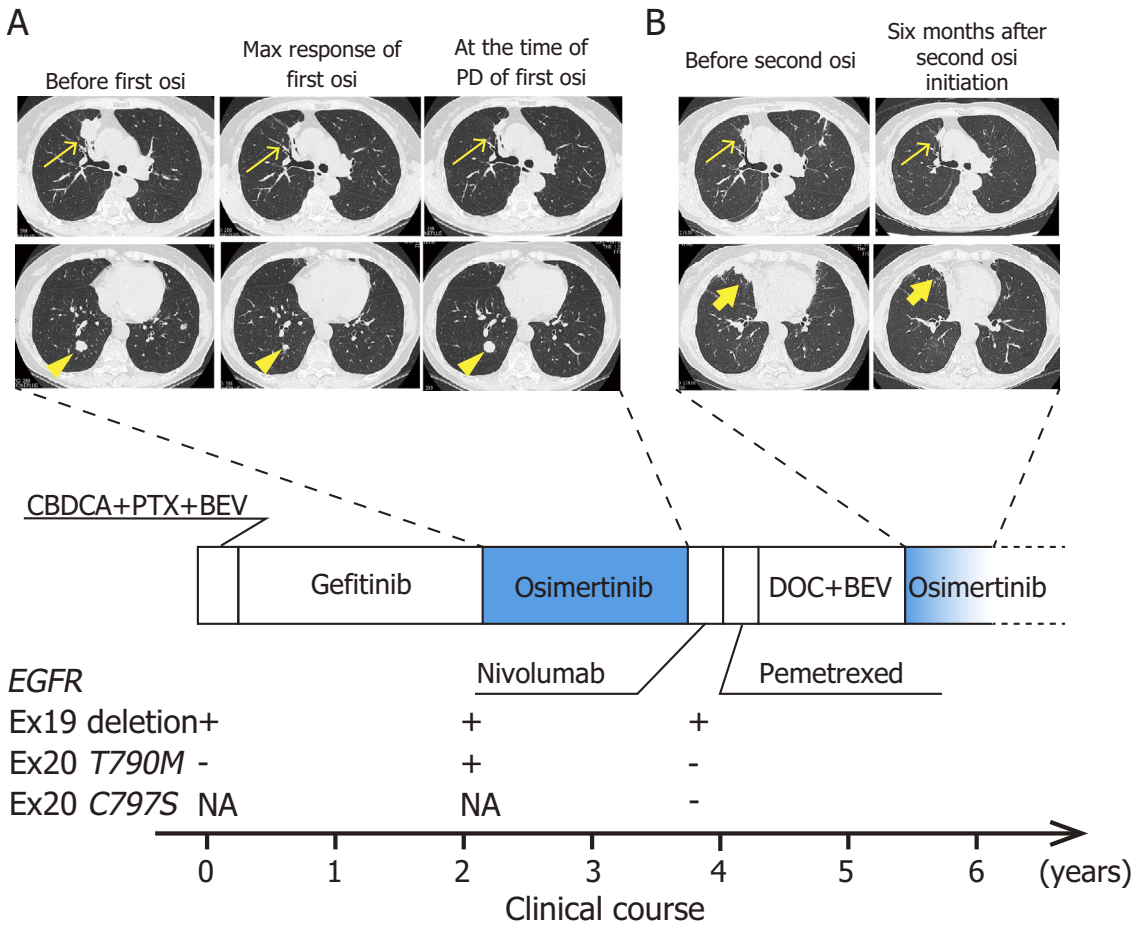

Figure. **A: Chest computed tomography image before and after the first challenge with osimertinib. The upper columns show the primary lesion (yellow arrow), while the lower columns show the pulmonary metastases (yellow triangle). B: Chest computed tomography image before and after the readministration of osimertinib. The upper columns show the primary lesion (thin yellow arrow), while the lower columns show the pulmonary dissemination (bold yellow arrow). osi: osimertinib, PD: progressive disease, CBDCA: carboplatin, PTX: paclitaxel, BEV: bevacizumab, DOC: docetaxel, EGFR: epidermal growth factor receptor, Ex: exon, NA: not assessed**

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 Medience, 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 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.

The authors state that they have no Conflict of Interest (COI).

Financial Support

This research received a specific grant from JSPS Grants-in-Aid for Scientific Research (Grant-in-Aid for Young Scientists (B): KAKEN 16K19454) (K.O.), JSPS Grants-in-Aid for Scientific Research (Scientific Research (B): KAKEN 15H04830) (K. O. and K.K.).

Acknowledgement

We are grateful to Hiromi Nakashima and Kyoko Maeda for their technical support. We also thank our laboratory colleagues for the useful discussions.

References

1. Mok TS, Wu YL, Ahn MJ, et al. Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer. N Engl J Med **376**: 629-640, 2017.
2. Tomizawa Y, Fujita Y, Tamura A, et al. Effect of gefitinib re-challenge to initial gefitinib responder with non-small cell lung cancer followed by chemotherapy. Lung Cancer **68**: 269-272, 2010.
3. Thress KS, Paweletz CP, Felip E, et al. Acquired EGFR C797S mutation mediates resistance to AZD9291 in non-small cell lung cancer harboring EGFR T790M. Nat Med **21**: 560-562, 2015.
4. Le X, Puri S, Negrao MV, et al. Landscape of EGFR -dependent and -independent resistance mechanisms to osimertinib and continuation therapy post-progression in EGFR-mutant NSCLC. Clin Cancer Res **24**: 6195-6203, 2018.
5. Oxnard GR, Hu Y, Mileham KF, et al. Assessment of resistance mechanisms and clinical implications in patients with EGFR T790M-positive lung cancer and acquired resistance to osimertinib. JAMA Oncol **4**: 1527-1534, 2018.
6. Asahina H, Oizumi S, Inoue A, et al. Phase II study of gefitinib readministration in patients with advanced non-small cell lung cancer and previous response to gefitinib. Oncology **79**: 423-429, 2010.
7. Costa DB, Nguyen KS, Cho BC, et al. Effects of erlotinib in EGFR mutated non-small cell lung cancers with resistance to gefitinib. Clin Cancer Res **14**: 7060-7067, 2008.
8. Chmielecki J, Foo J, Oxnard GR, et al. Optimization of dosing for EGFR-mutant non-small cell lung cancer with evolutionary cancer modeling. Sci Transl Med **3**: 90ra59, 2011.
9. Abbosh C, Birkbak NJ, Wilson GA, et al. Phylogenetic ctDNA analysis depicts early-stage lung cancer evolution. Nature **545**: 446-451, 2017.
10. Chaudhuri AA, Chabon JJ, Lovejoy AF, et al. Early detection of molecular residual disease in localized lung cancer by circulating tumor DNA profiling. Cancer Discov **7**: 1394-1403, 2017.