Response to First-Line Osimertinib Treatment in Non–Small-Cell Lung Cancer With Coexisting G719A and Primary T790M Epidermal Growth Factor Receptor Mutations

Tomoo Ikari, Jun Sakakibara-Konishi, Gaku Yamamoto, Hidenori Kitai, Hidenori Mizugaki, Hajime Asahina, Eiki Kikuchi, Naofumi Shinagawa

Clinical Practice Points

- Osimertinib is a third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) that is effective treatment for non–small-cell lung cancer (NSCLC) with EGFR–TKI-sensitizing and *EGFR* T790M-resistance mutations.
- The efficacy of osimertinib for uncommon mutations or compound mutations is unknown.
- We describe a case of NSCLC with the *EGFR* G719A mutation and primary T790M mutation exhibiting response to osimertinib.

Clinical Lung Cancer, Vol. 20, No. 4, e531-3 © 2019 Elsevier Inc. All rights reserved.
Keywords: Compound mutation, *EGFR* mutation, EGFR-TKI, Lung adenocarcinoma, Uncommon mutation

Introduction

Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are a mainstay in the treatment of advanced unresectable non–small-cell lung cancer (NSCLC).[1,2] Activating *EGFR* mutations are the primary predictive factors of EGFR-TKI therapy outcome.[1] The most frequent and clinically significant *EGFR* mutations include exon 19 deletion (del) and exon 21 L858R, but in addition to these, exon 18 G719A mutations constitute a major part of uncommon mutations.[3] *EGFR* exon 20 T790M mutations are the most frequent mechanism of acquired drug resistance to first- and second-generation EGFR-TKIs. In rare cases, primary T790M mutation is detected in the untreated EGFR-TKI patients and is more likely to coexist with other *EGFR* mutations.[4] Osimertinib is a third-generation, irreversible EGFR-TKI that is selective for sensitive *EGFR* and T790M resistance mutations. However, the efficacy of osimertinib in uncommon mutations is unknown. We encountered a case involving the treatment of a treatment-naive patient with coexisting G719A and primary T790M *EGFR* mutations, for whom osimertinib treatment was effective.

First Department of Medicine, Hokkaido University Hospital, Sapporo, Japan

Submitted: Mar 3, 2019; Revised: Apr 2, 2019; Accepted: May 4, 2019; Epub: May 11, 2019

Address for correspondence: Jun Sakakibara-Konishi, PhD, MD, Hokkaido University Hospital, First Department of Medicine, North 15, West 7, Kita-ku, Sapporo 060 8638, Japan
Fax: +81-11-706-7899; e-mail contact: konishj@med.hokudai.ac.jp

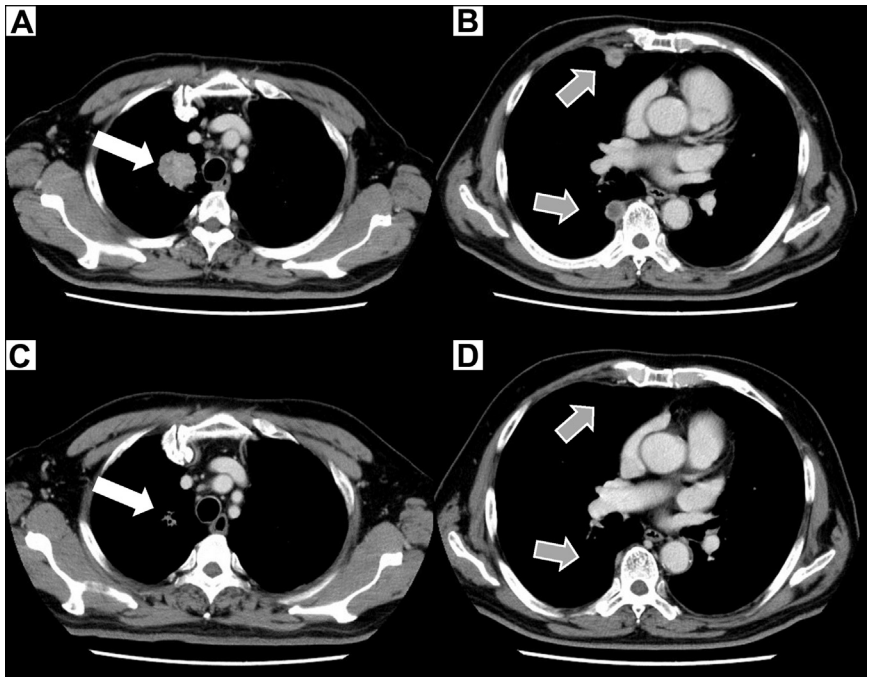
Case

A 70-year-old man, former smoker, was referred to our hospital because of an abnormal chest shadow. He had smoking history of 60 pack-years. Computed tomography (CT) examination at the first visit revealed a tumor shadow with a large diameter of 34 mm at right S1. Multiple mediastinal lymph node enlargements, and multiple pleural nodules were also observed (Figure 1A and B). Adenocarcinoma was detected using cytological examination of the tracheal branch lymph node, which was obtained by transbronchial needle aspiration. The patient was diagnosed with primary adenocarcinoma of the lung (cT2aN2M1a: pleural metastasis, stage IVA, according to the eighth edition of the/International Union for Cancer Control/American Joint Committee on Cancer tumor, node, metastases staging system). Exon 18 G719X and exon 20 T790M mutations of the *EGFR* were detected in the same specimen using the Scorpion amplification refractory mutation system (Hokkaido University Hospital, Hokkaido, Japan). We also submitted the tissue for Cancer Genome Screening Project for Individualized Medicine in Japan (SCRUM-JAPAN), in which G719A and T790M mutations were observed in Oncomine comprehensive assay version 3 (National Cancer Center Hospital East, Chiba, Japan).

First-line therapy with osimertinib (80 mg once daily) was started as first-line therapy in August 2018. Grade 2 rash according to the

1525-7304/$ - see frontmatter
https://doi.org/10.1016/j.cllc.2019.05.002

Figure 1 (A) and (B) Thoracic Computed Tomography (CT) Images of the Patient at Baseline. CT Images of the Chest Showing a Primary Tumor With a Large Diameter of 34 mm at Right S1 and Multiple Pleural Nodules. (C) and (D) Thoracic CT Images of the Patient 4 Months After Starting Osimertinib Treatment Show That the Primary Tumor Measured up to 13 mm and the Same Pleural Metastatic Lesions Have Disappeared. White Arrows Indicate Primary Tumors. Gray Arrows Indicate Pleural Nodules



Common Terminology Criteria for Adverse Events version 4.0 was observed 1 week after the start of osimertinib administration, but it was managed with the use of external steroid medicine. Initial CT evaluation after 1 month of treatment revealed significant tumor response in the primary tumor and all metastatic lesions, lasting 4 months (Figure 1C and D).

Discussion

We report the case of coexisting G719A and primary T790M *EGFR* mutations, which exhibited a significant response to osimertinib in clinical practice.

Common mutations such as exon 19 del and exon 21 L858R have shown remarkable response to *EGFR*-TKIs.[5-7] However, uncommon mutations including G719A resulted in varying efficacies of EGFR-TKIs.[8] Moreover, multiple *EGFR* mutations were observed within single tumor samples, which were referred to as compound mutations, and the significance of these mutations have not been determined. G719A was reported to frequently coexist with other mutations and tends to combine with S768I or L861Q.[9-11] Coexistence of G719A and primary T790M has been reported in a few cases.[12,13] However, their characteristics and the outcome of EGFR-TKI treatment remains unknown.

In post hoc analysis from 3 clinical studies of afatinib (A Phase II Single-arm Trial of BIBW 2992 in Non-small Cell Lung Cancer Patients With EGFR Activating Mutations [Lux Lung 2], A randomized, Open-label, Phase III study of afatinib versus pemetrexed and cisplatin as first-line treatment for patients with advanced adenocarcinoma of the lung harboring EGFR-activating mutations [Lux Lung 3], A Randomized, Open-label, Phase III Study of BIBW 2992 Versus Chemotherapy as First-line Treatment for Patients With Stage IIIB or IV Adenocarcinoma of the Lung Harbouring an EGFR Activating Mutation [Lux Lung 6]), a second-generation EGFR-TKI, 8 patients had only G719X and there were 5 patients with S768I, 3 patients with L861G, and 2 patients with T790M in the G719X group (n = 18). In the G719X group, objective response, median progression-free survival (PFS), and median overall survival were 77.8%, 13.8 months, and 26.9 months, respectively.[12] Although individual data about 2 patients with G719X and T790M were not shown, the G719X group appeared to be sensitive to afatinib treatment. However, patients harboring a T790M mutation revealed a median PFS of 2.7 months and median overall survival of 9.2 months with afatinib treatment.[12] Pre-existence of the T790M mutation resulted in insensitivity toward first- or second-generation EGFR-TKIs, even in the presence of sensitive mutations.[14,15]

Osimertinib is a third-generation EGFR-TKI that was designed to target sensitive mutations and T790M resistance mutation.[16] The A Phase III, Double-blind, Randomised Study to Assess the Safety and Efficacy of AZD9291 Versus a Standard of Care Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor as First Line Treatment in Patients With Epidermal Growth Factor Receptor Mutation Positive, Locally Advanced or Metastatic Non

Small Cell Lung Cancer (FLAURA) trial shows that in patients with previously untreated common *EGFR* mutation-positive advanced NSCLC, osimertinib treatment resulted in significantly longer PFS than did standard *EGFR*-TKIs.[17] Because patients with uncommon mutations were excluded from the FLAURA trial, the therapeutic effect on cases with those mutations is not certain. Recently, a phase II study (An open-label, multicenter, phase II single arm trial of osimertinib in non-small cell lung cancer patients with uncommon EGFR mutation [KCSG-LU15-09]) to evaluate the efficacy and safety of osimertinib for patients with uncommon mutations was reported. Patients with G719A/C/D/S/X mutation (10/19) had partial response, indicating that osimertinib was effective.[18]

In the Safety, Tolerability, Pharmacokinetics and Anti-tumour Activity of AZD9291 in Patients With Advanced Non Small Cell Lung Cancer Who Progressed on Prior Therapy With an Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Agent (AURA) study, 7 treatment-naive patients with primary T790M mutations together with L858R were included and 6 of them had a partial response to osimertinib, which suggested that osimertinib also exhibited antitumor efficacy for primary T790M mutations in the same way as for T790M resistance mutations.[19] On the basis of AURA trials and afatinib data, we chose osimertinib to treat our patient when we considered first-line therapy. Moreover, Hunter et al reported that 2 untreated patients with G719A and primary T790M mutations responded to the first-line osimertinib treatment. In this report, 1 patient had a partial response, which is ongoing at 5 months and another patient had stable disease at 15 months.[13] This report was consistent with our case. Although a similar report has been published previously, our present case report provides the optimal treatment for enhancing osimertinib efficacy in patients with primary T790M and uncommon mutations.

Conclusion

Although further studies are necessary to evaluate the effects of osimertinib on uncommon or compound mutations, first-line osimertinib might offer significant benefits to patients with coexisting G719A and primary T790M mutations.

Acknowledgments

The authors thank Dr Koichi Goto (Department of Thoracic Oncology, National Cancer Center Hospital East, Kashiwa, Japan) and Dr Shingo Matsumoto (Department of Thoracic Oncology, Exploratory Oncology Research and Clinical Trial Center, National Cancer Center), who performed and managed next-generation sequencing analysis in SCRUM-JAPAN.

Disclosure

The authors have stated that they have no conflicts of interest.

References

1. Kobayashi S, Boggon TJ, Dayaram T, et al. *EGFR* mutation and resistance of non–small-cell lung cancer to gefitinib. *N Engl J Med* 2005; 352:786-92.
2. Castellanos E, Feld E, Horn L, et al. Driven by mutations: the predictive value of mutation subtype in *EGFR*-mutated non–small-cell lung cancer. *J Thorac Oncol* 2017; 12:612-23.
3. Kobayashi Y, Togashi Y, Yatabe Y, et al. EGFR exon 18 mutations in lung cancer: molecular predictors of augmented sensitivity to afatinib or neratinib as compared with first- or third-generation TKIs. *Clin Cancer Res* 2015; 21:5305-13.
4. Li W, Qiu T, Guo L, et al. Primary and acquired EGFR T790M-mutant NSCLC patients identified by routine mutation testing show different characteristics but may both respond to osimertinib treatment. *Cancer Lett* 2018; 423:9-10.
5. Mitsudomi T, Morita S, Yatabe Y, et al. Gefitinib versus cisplatin plus docetaxel in patients with non–small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. *Lancet Oncol* 2010; 11:121-8.
6. Rosell R, Carcereny E, Gervais R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced *EGFR* mutation-positive non–small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol* 2012; 13:239-46.
7. Maemondo M, Inoue A, Kobayashi K, et al. Gefetinib or chemotherapy for non–small-cell lung cancer with mutated *EGFR*. *N Engl J Med* 2010; 362:2380-8.
8. Wu JY, Yu CJ, Chang YC, et al. Effectiveness of tyrosine kinase inhibitors on "uncommon" epidermal growth factor receptor mutations of unknown clinical significance in non–small-cell lung cancer. *Clin Cancer Res* 2011; 17:3812-21.
9. Kohsaka S, Nagano M, Ueno T, et al. A method of high-throughput functional evaluation of *EGFR* gene variants of unknown significance in cancer. *Sci Transl Med* 2017; 9:eaan6566.
10. Kobayashi Y, Mitsudomi T. Not all epidermal growth factor receptor mutations in lung cancer are created equal: perspectives for individualized treatment strategy. *Cancer Sci* 2017; 107:1179-86.
11. Kobayashi S, Canepa HM, Bailey AS, et al. Compound *EGFR* mutations and response to *EGFR* tyrosine kinase inhibitors. *J Thorac Oncol* 2013; 8:45-51.
12. Yang JCH, Sequist LV, Geater SL, et al. Clinical activity of afatinib in patients with advanced non–small-cell lung cancer harbouring uncommon *EGFR* mutations: a combined post-hoc analysis of LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6. *Lancet Oncol* 2015; 16:830-8.
13. Ancevski Hunter K, Friedland DM, Villaruz LC, et al. First-line osimertinib in patients with treatment-naive somatic or germline *EGFR* T790M-mutant metastatic NSCLC. *J Thorac Oncol* 2018; 13:e3-5.
14. Ramalingam SS, Yang JC, Lee CK, et al. Osimertinib as first-line treatment of *EGFR* mutation-positive advanced non–small-cell lung cancer. *J Clin Oncol* 2018; 36:841-9.
15. Zhang B, Wang S, Qian J, et al. Complex epidermal growth factor receptor mutations and their responses to tyrosine kinase inhibitors in previously untreated advanced lung adenocarcinomas. *Cancer* 2018; 124:2399-406.
16. Mok TS, Wu YL, Ahn MJ, et al. Osimertinib or platinum-pemetrexed in *EGFR* T790M-positive lung cancer. *N Engl J Med* 2017; 376:629-40.
17. Soria JC, Ohe Y, Vansteenkiste J, et al. Osimertinib in untreated *EGFR*-mutated advanced non–small-cell lung cancer. *N Engl J Med* 2018; 378:113-25.
18. Cho JH, Sun J, Lee S, et al. An open-label, multicenter, phase II single arm trial of osimertinib in NSCLC patients with uncommon *EGFR* mutation (KCSG-LU15-09). *J Thorac Oncol* 2018; 13:10 (abstract 10.05).
19. Suzanne J, James CY, Pasi AJ, et al. *EGFR* mutation analysis for prospective patient selection in two phase II registration studies of osimertinib. *J Thorac Oncol* 2017; 12:1247-56.