Turk Thorac J 2022; 23(5): 364-365 DOI: 10.5152/TurkThoracJ.2022.22034

Letter to the Editor

Response to Afatinib in a Common EGFR-Mutated Lung Adenocarcinoma with a Very Rare Combination of Compound Mutations

Hiroaki Satoh[1], Kunihiko Miyazaki[2], Yoshiharu Sato[3], Nobuyuki Hizawa[4]

[1]Division of Respiratory Medicine, Mito Medical Center, University of Tsukuba, Tsukuba, Japon
[2]Division of Respiratory Medicine, Ryugasaki Saiseikai Hospital, Tsukuba, Japon
[3]DNA Chip Research Inc., Tokyo, Japan
[4]Division of Respiratory Medicine, Faculty of Clinical Medicine, University of Tsukuba, Tsukuba, Japon

Cite this article as: Satoh H, Miyazaki K, Sato Y, Hizawa N. Response to afatinib in a common EGFR-mutated lung adenocarcinoma with a very rare combination of compound mutations. *Turk Thorac J.* 2022;23(5):364-365.

Received: *February 15, 2022* ***Accepted:*** *June 10, 2022* ***Available Online:*** *August 8, 2022*

To the Editor,

A 76-year-old woman was referred to our hospital due to a nodule detected by mass screening. Biopsy specimens from the lesion showed epidermal growth factor receptor (EGFR)-mutated (exon 21 858R) adenocarcinoma. She underwent surgical resection; however, a year later, intrapulmonary metastases were discovered. Therefore, afatinib therapy was initiated as first-line therapy. The best response to afatinib was evaluated as "partial response," and progression-free survival (PFS) was 24 months. Then, she received chemotherapy for 6 months, erlotinib and bevacizumab for 5 months, and nivolumab for 3 months. After these treatments, pleural dissemination and accumulation of pleural fluid developed. EGFR mutation was re-evaluated using cancer cells in the pleural fluid to confirm the presence or absence of the T790M gene mutation. Cytological diagnosis was adenocarcinoma, and T790M gene was not detected. Afatinib was given for 3 months, but the best therapeutic effect was "stable disease," and the patient died 4 months after re-administration of afatinib. Overall survival was 42 months.

We undertook a detailed analysis of compound mutations and the content ratio of tumor cells and relative allele frequency (RAF) in pathological specimens obtained by surgical resection using Non-overlapping Integrated Read Sequencing System (NOIR-SS) (DNA Chip Research Inc. Tokyo, Japan).[1,2] Briefly, DNA was extracted from the slices of formalin fixed paraffin embedded (FFPE) tissue block of the patient using a Maxwell® RSC DNA FFPE kit (Promega, Madison, Wis, USA). 50 ng of DNAs were fragmented by Covaris focused-ultrasonicator (Woburn, Mass, USA), and molecular-barcoded next-generation sequencing (NGS) library was constructed by the NOIR-SS method as described previously.[1,2] Constructed library was sequenced using the Ion Chef/Ion S5 platform with Ion 540 chip (Thermo Fisher Scientific, Waltham, Mass, USA). In this patient, in addition to exon 21 L858R of the main mutation, L861Q and C797S were also found as compound mutations. The RAF for L861Q and C797S was 12% and 15%, respectively.

With the advancement of NGS technology, information on compound mutations in patients with common EGFR mutations has become available.[1,2] In catalogue of somatic mutations in cancer (COSMIC) database v94 (COSMIC Catalog of Somatic Mutations in Cancer, https://cancer.sanger.ac.uk> cosmic), 3169 patients had compound mutations with L858R. Only 10 of them had L861Q. Thus, among L858R-mutated patients, those with L861Q as a compound mutation were rare. In addition, to the best of our knowledge, there were no L858R-mutated patients who had L861Q and C797S as compound mutations.

In patients with the common EGFR mutant exon 21 L858R, their PFS and OS were evaluated as around 11 months and 24-32 months, respectively.[3-5] On the other hand, in a large database of 693 patients treated with afatinib for the treatment of NSCLC harboring uncommon EGFR mutations, median time to treatment failures in patients with major uncommon mutations, those with compound mutations, and those with other uncommon mutations were 10.8, 14.7, and 4.5 months, respectively.[6] The exact mechanism of the favorable outcome in our patient was unknown; however, the presence of these compound mutations seems to be unlikely and adversely affects the therapeutic effect of TKIs. Afatinib is considered to be a drug with therapeutic power that surpasses the situation with these compound mutations. It is speculated that the EGFR mutation by NGS will be clarified in more detail in the future. We considered that afatinib might be one of the drugs to be selected for the treatment of patients with complicated EGFR mutation backgrounds such as this patient.

Corresponding author: Hiroaki Satoh, e-mail: hirosato@md.tsukuba.ac.jp

Ethics Committee Approval: This study was approved by the institutional ethics committee of Mito Medical Center, University of Tsukuba: NO18-46; Ryugasaki Saiseikai Hospital: No. 201904.

Informed Consent: Written comprehensive informed consent at the time of admission for obtaining pathological specimens was obtained from the patient.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – H.S., K.M., Y.S., N.H.; Design – H.S., Y.S., N.H.; Supervision – H.S., N.H.; Funding – H.S.; Materials – H.S., K.M.; Data Collection and/or Processing – H.S., K.M.; Analysis and/or Interpretation – H.S., Y.S.; Literature Review – H.S., N.H.; Writing – H.S.; Critical Review – Y.S., N.H.

Acknowledgments: The authors thank Yoshio Iwakawa for his important research advice.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: The support for biomarker analysis was provided by Nippon Boehringer Ingelheim Co Ltd (Tokyo, Japan).

REFERENCES

1. Kukita Y, Ohkawa K, Takada R, Uehara H, Katayama K, Kato K. Selective identification of somatic mutations in pancreatic cancer cells through a combination of next-generation sequencing of plasma DNA using molecular barcodes and a bioinformatic variant filter. *PLoS One*. 2018;13(2):e0192611. [CrossRef]
2. Kukita Y, Matoba R, Uchida J, et al. High-fidelity target sequencing of individual molecules identified using barcode sequences: de novo detection and absolute quantitation of mutations in plasma cell-free DNA from cancer patients. *DNA Res*. 2015;22(4):269-277. [CrossRef]
3. Sequist LV, Yang JC, Yamamoto N, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. *J Clin Oncol*. 2013;31(27):3327-3334. [CrossRef]
4. Wu YL, Zhou C, Hu CP, et al. Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small cell lung cancer harbouring EGFR mutations (LUX-Lung 6): an open-label, randomised phase 3 trial. *Lancet Oncol*. 2014;15(2):213-222. [CrossRef]
5. Yang JC, Wu YL, Schuler M, et al. Afatinib versus cisplatin-based chemotherapy for EGFR mutation-positive lung adenocarcinoma (LUX-Lung 3 and LUX-Lung 6): analysis of overall survival data from two randomised, phase 3 trials. *Lancet Oncol*. 2015;16(2):141-151. [CrossRef]
6. Yang JC, Schuler M, Popat S, et al. Afatinib for the treatment of NSCLC harboring uncommon EGFR mutations: a database of 693 cases. *J Thorac Oncol*. 2020;15(5):803-815. [CrossRef]