Case Report

Osimertinib Did Not Respond to a Pulmonary Adenocarcinoma with Triple Mutations of Epidermal Growth Factor Receptor, G719S, T790M and S768I

Seigo Minami Shouichi Ihara Tsunehiro Tanaka Hideyasu Okada
Kazuki Hashimoto Kiyoshi Komuta

Department of Respiratory Medicine, Osaka Police Hospital, Osaka, Japan

Keywords

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Abstract

Uncommon epidermal growth factor receptor (EGFR) gene mutations include G719S, T790M and S768I. T790M gatekeeper mutation is the most frequent mechanism of acquired drug resistance to first- and second-generation EGFR-tyrosine kinase inhibitors (TKIs). Osimertinib is a specific EGFR-TKI to overcome T790M resistance mutation. However, owing to a new drug and a rare mutation type, it remains unknown whether osimertinib is effective for acquired S768I. Herein, we reported a 76 year-old woman with pulmonary adenocarcinoma, which had acquired EGFR mutations of S768I and T790M in addition to original G719S after long gefitinib treatment. These mutations were detected in biopsy specimen of liver metastases. During two months of osimertinib, multiple liver metastases progressively enlarged. This case suggested that acquired S768I mutation might be resistant to osimertinib, despite of co-occurrence of T790M.

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Introduction

Epidermal growth factor receptor (EGFR) gene mutations occur in approximately 40 and 20% of non-small cell lung cancer in Asian [1] and Caucasian patients [2], respectively. The in-frame exon 19 deletions and the exon 21 L858R point mutation are the most frequent and clinically significant EGFR mutations. These two types of mutations are major and common mutations, accounting for approximately 90% of all EGFR mutations [3]. The remaining 10% of EGFR mutations is a heterogeneous group of uncommon mutations within exons 18–21, for example, exon 18 G718S, exon 20 T790M and exon 20 S768I.

Emergence of T790M gatekeeper mutation is the most frequent mechanism of acquired drug resistance to first- and second-generation EGFR-tyrosine kinase inhibitors (TKIs) [4, 5]. Osimertinib, a third-generation EGFR-TKI, is a specific drug to overcome T790M resistance mutation. On the other hand, G719X and S768I point mutations are detected in approximately 3 and 1% of EGFR mutations, respectively. First generation EGFR-TKIs provided 32 and 42% of overall response rate for G719X and S768I mutations, respectively [6]. However, the clinical efficacy of osimertinib for these uncommon mutations remains unknown due to a new drug and rare mutation types.

Herein, we reported a case with acquired mutations of S768I and T790M in addition to original G719S after gefitinib monotherapy. Osimertinib was ineffective in this patient.

Case Presentation

A 76 year-old woman was referred to our hospital three years before because of abnormal chest-X-ray shadow. She was a non-smoker and had diabetes mellitus, hypothyroidism, hypertension, atrial fibrillation and chronic renal failure (estimated glomerular filtration rate 28.4 mL/min/1.73 m² at the start of osimertinib). By video-assisted thoracoscopic mediastinal lymph node biopsy, she was diagnosed with adenocarcinoma of the left upper lobe of the lung with bilateral mediastinal lymphadenopathy (c-T2aN3M0 in the 7th TNM classification of lung cancer by the Union for International Cancer Control [UICC]). The peptide nucleic acid-locked nucleic acid PCR clamp method (by LSI medicine corporation) detected G719S mutation in EGFR exon 18 from the lymph node sample. One year after concurrent chemo-radiotherapy of cisplatin and vinorelbine, we found a new metastasis in the left adrenal gland. Carboplatin, pemetrexed and bevacizumab followed by maintenance of pemetrexed and bevacizumab achieved partial response. Serum CEA increased from 5.8 ng/mL (September 2016) up to 19.7 ng/mL (June 2017), though tumor size remained stable. Thereafter, gefitinib monotherapy started at July 2017, and maintained partial response for 14 months until we found new multiple liver metastases and enlarged left adrenal gland by abdominal plain CT scan (Fig. 1A). Immunohistochemistry of liver tumor biopsy specimens showed positive staining of CK7 and TTF-1, and weak staining of CK20 and Napsin-A. We confirmed metastatic adenocarcinoma and detected T790M and S768I with the original G719S by the Roche cobas EGFR mutation test ver 2.0 (by LSI medicine corporation). Osimertinib was initiated in August 2018. Serum CEA temporarily decreased from 448.4 ng/mL (before osimertinib) to 196.8 ng/mL (one month after), but rapidly increased to 742.6 ng/mL (two month after). Plain abdominal CT scan revealed remarkable progression of multiple liver metastases and left adrenal gland (Fig. 1B). At the same time, she suffered from Trousseau syndrome manifested by multiple cerebral infarctions. We discontinued osimertinib, and then introduced atezolizumab.

Atezolizumab also failed to control the tumor progression. One month after discontinuation of osimertinib, she died at our hospital.

Discussion

Our case was characteristics of acquired EGFR mutations of T790M and S768I, which was not responsive to osimertinib at all. In clinical course and response to osimertinib, our case was similar to the previous case reported by Nasu et al, in which osimertinib was unsuccessful for emergence of the same combination of mutations after gefitinib, erlotinib and afatinib [7]. The main lesions were the progression of primary tumor and pleural effusion and the emergence of brain metastases in the previous case [7], while our case presented with the rapid progression of multiple liver metastases and the sudden emergence of Trousseau syndrome. These two cases suggested that acquired S768I may be refractory to osimertinib and accelerate rapid progression, even if it occurs together with T790M.

Regarding EGFR-TKI naïve S768I, afatinib is expected to be more sensitive to this mutation than first-generation EGFR-TKIs. However, osimertinib remains unknown for this treatment line and mutation. There were three U.S. retrospective studies of first-generation EGFR-TKI for S768I mutation. First, in a study of compound EGFR mutations at Beth Israel Deaconess Medical Center, among 79 patients with activated EGFR mutations, two (2.5%) had combined mutations of G719A and S768I. In both of these two patients, first-line erlotinib provided partial response, but only 5–7 months of PFS and 8–10 months of OS from the start of EGFR-TKIs [8]. Second, a collected and retrospective data showed that first-generation EGFR-TKI provided 42 and 53% of overall response rate for S768I single mutation and compound mutations, respectively [6]. Third, in a study of 9 patients with S768I mutation at Mayo Clinic, among 4 patients with metastatic disease treated with erlotinib, one and two patients achieved partial response and stable disease, respectively. The PFS and OS ranged from 3 to 30 months and from 5 to more than 51 months, respectively [9]. In contrast to first-generation EGFR-TKIs, a combined analysis of LUX-Lung 2, 3 and 6 trials, including only eight patients with S768I mutation, showed that afatinib, a second-generation EGFR-TKI, was responsive in all the patients [10]. The discrepancy in response to S768I between the first- and second-generation EGFR-TKIs was consistent with an in vitro sensitivity data using Ba/F3 cells. In this in vitro study, afatinib showed very low half maximal inhibitory concentration (IC₅₀) value to S768I mutation, but both gefitinib and erlotinib had high values of IC₅₀. Osimertinib was less sensitive to S768I mutation than afatinib [6, 11]. A Korean phase II trial showed that osimertinib achieved partial response in 3 patients of 8 with EGFR-TKI naïve S768I mutation (ORR, 37.5%) [12]. There was no other clinical data of osimertinib for S768I untreated with an EGFR-TKI.

Osimertinib for S768I mutation after prior therapy with an EGFR-TKI remains unknown. Although little has been reported on acquired S768I, this mutation may be resistant to osimertinib. A pooled analysis of two phase II trials (AURA extension and AURA2) of osimertinib for 697 patients with T790M-positive NSCLC included only 10 patients (1%) with S768I mutation [13]. A real-world study in Spain (ASTRIS trial) had 5% of patients with S768I among 132 patients with T790M mutation [14]. However, these two studies have not yet opened efficacy of osimertinib for these specific patients. To our knowledge, there was only a case report of acquired S768I mutation, except for the Japanese case described above. A 43 year-old Italian woman with stage IV adenocarcinoma originally harboring L858R mutation showed an unusual mechanism of gefitinib-resistance, synchronous combination of histological trans-

formation to squamous cell carcinoma and occurrence of the S768I secondary mutation. Unlike our case, this case did not acquire T790M mutation after 8 months of gefitinib treatment and was not treated with osimertinib [15]. Thus, we should make a careful decision in osimertinib for acquired S768I mutation, even when T790M appears together.

In conclusion, our case showed acquired mutations of S768I and T790M after long term treatment with gefitinib, to which osimertinib did not respond. Osimertinib can not be expected to overcome emergence of S768I mutation together with T790M.

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Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors declare that they have no conflicts of interest.

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Minami et al.: Osimertinib Did Not Respond to a Pulmonary Adenocarcinoma with Triple Mutations of Epidermal Growth Factor Receptor, G719S, T790M and S768I

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Fig. 1. Plain abdominal CT scan showing multiple liver metastases, (A) before osimertinib, (B) two months after the start of osimertinib.