Successful Treatment of a Patient with Lung Adenocarcinoma Harboring Compound EGFR Gene Mutations, G719X and S768I, with Afatinib

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Mutations in the gene encoding epidermal growth factor receptor (EGFR) are the most frequent driver mutations in lung adenocarcinoma in Japan. Exon 19 deletion and L858R mutation in exon 21 are the most common EGFR mutations. Uncommon mutations, such as G719X, S768I, and L861Q, and compound mutations, combinations of 2 common or uncommon mutations, have also been reported. EGFR tyrosine kinase inhibitors (TKIs) are effective against cancers harboring common mutations; however, their efficacy against cancers with uncommon or compound mutations remains unclear. We report the case of a 67-year-old man with lung adenocarcinoma (clinical stage IIIA [cT1N2M0]), harboring an uncommon compound mutation, G719X and S768I. The cancer progressed within 2 months of initial chemoradiotherapy. Treatment with afatinib (40 mg/day) produced a partial response, which was maintained for 17 months with continued treatment. A literature review revealed that lung cancer with G719X/S768I compound mutation exhibited good response to EGFR-TKIs, even better than that of lung cancers with single uncommon mutations.

Key words: Epidermal growth factor receptor, Epidermal growth factor receptor-tyrosine kinase inhibitor, Gene mutation, Lung cancer

INTRODUCTION

Drugs targeting individual driver mutations significantly improve the prognosis of non-small cell lung cancer. Mutations in the gene encoding epidermal growth factor receptor (EGFR) are the most frequent driver mutations in lung adenocarcinoma in East Asia, including Japan. Two common mutations, exon 19 deletion mutation and exon 21 L858R point mutation, account for approximately 85% of all EGFR gene mutations [1–3], whereas exon 20 insertions (6%), G719X (3%), S768I (1%), L861Q (1%), and exon 19 insertions (0.6%) are uncommon [4]. Uncommon mutations, especially T790M and S768I in exon 20, are associated with lower sensitivity to first-generation EGFR-tyrosine kinase inhibitors (TKIs) [5–7]. Therefore, patients with uncommon mutations are often excluded from clinical trials of second- and third-generation EGFR-TKIs.

Compound mutations, usually consisting of a common and an uncommon mutation, occur in 2%–25% of EGFR mutation-positive lung cancers [8–15]. Compound mutations involving 2 uncommon mutations are rare, and clinical data of EGFR-TKIs for cases with compound uncommon mutations are scarce. Herein, we report the case of a patient with lung adenocarcinoma harboring compound uncommon EGFR mutations, G719X in exon 18 and S768I in exon 20, who showed a favorable response to treatment with a second-generation EGFR-TKI, afatinib.

CASE REPORT

A 67-year-old man, a former smoker of 60 pack-years, was admitted for treatment of relapsed lung adenocarcinoma. Eight months before admission, he was diagnosed with lung adenocarcinoma in the upper lobe of the left lung (clinical stage IIIA [cT1N2M0]). Compound EGFR mutations of exon 18 G719X and exon 20 S768I were identified in a cytological sample from the primary tumor using cobas® EGFR Mutation Test v2 test (Roche Molecular Systems, Inc., USA). Two months after 4 courses of chemotherapy with cisplatin and vinorelbine with concurrent thoracic radiotherapy (70 Grey), multiple metastases appeared in the brain, lungs, right adrenal gland, and right iliac bone.

On admission, he presented with no symptoms of dyspnea or pain, and his Eastern Cooperative Oncology Group performance status was zero. Mild neutropenia, anemia, renal dysfunction, and increased serum levels of carcinoembryonic antigen (CEA; 3135 ng/mL) were observed. Computed tomography showed multiple intrapulmonary nodules, a right adrenal mass, and brain tumors (Figure A–C). Treatment with afatinib (40 mg per day) was initiated.

Two months later, the serum CEA level was reduced to 42 ng/mL, and the size of lung and adrenal gland metastases was reduced to fulfill the criteria of partial response in the Response Evaluation Criteria in Solid Tumor version 1.1 (Figure D–F). Due to grade 2 diarrhea and peritonitis based on Common Terminology

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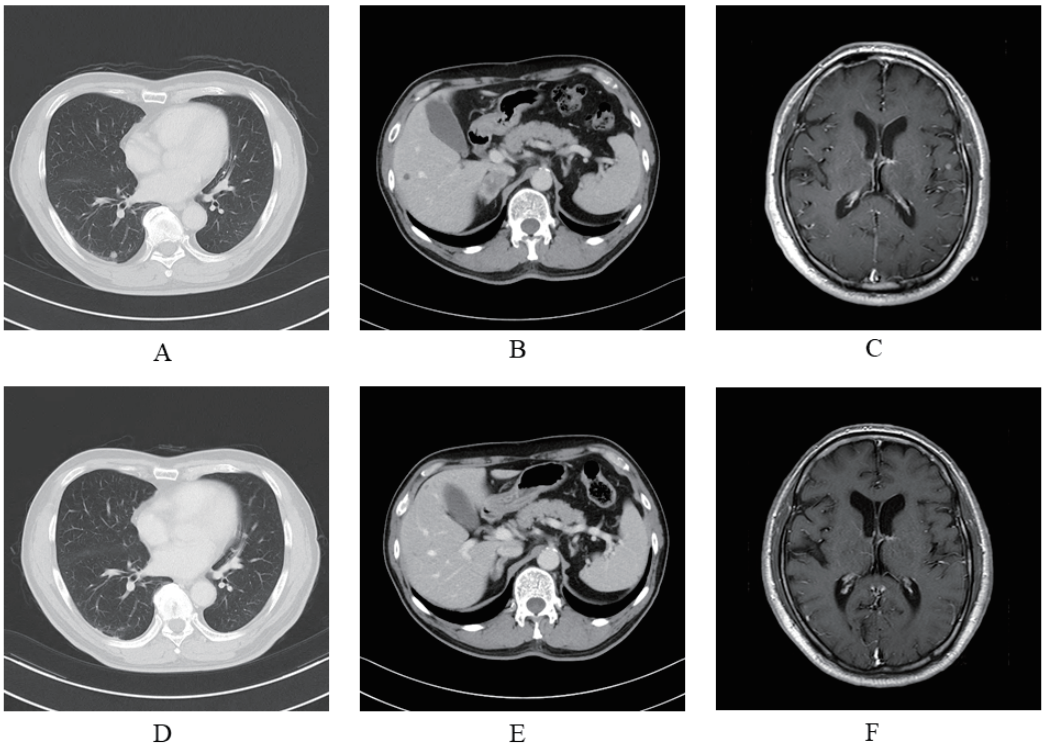

Figure A 67-year-old man with lung adenocarcinoma (cT1N2M0) demonstrated multiple intrapulmonary nodules (A), a right adrenal mass (B, 35 × 22 mm), and metastatic brain tumors (C) 2 months after the first-line treatment with thoracic irradiation and 4 courses of chemotherapy with cisplatin and vinorelbine. Two months after the initiation of afatinib (40 mg/day), intrapulmonary nodules (D) and metastatic brain tumors (F) disappeared, and the right adrenal mass (E) shrank to a size of 23 × 8 mm in diameter.

Criteria for Adverse Events version 4.0, the dose of afatinib was reduced to 20 mg per day. Afatinib treatment was continued for 17 months until the regrowth of metastatic lesions in the right adrenal gland and iliac bone and the appearance of new vertebral metastases.

DISCUSSION

We report a case of lung adenocarcinoma with EGFR mutations, G719X and S768I, wherein long-term progression-free survival (PFS) was achieved with afatinib treatment. The G719X (G719A, G719S, G719C) mutation is seen in ~3% of the lung adenocarcinoma cases [4]. *In vitro* studies have shown that G719X-harboring tumors respond well to gefitinib, erlotinib, and afatinib. S768I, found in 1% of lung adenocarcinoma cases [4], is associated with resistance to the first-generation EGFR-TKIs, but with a relatively fair response to afatinib [16].

A previous report suggested that a combination of 2 uncommon mutations is associated with poorer prognosis (median PFS: 6.5 months) than are combinations of 2 common mutations (median PFS: 10.1 months) or of a common and an uncommon mutation (median PFS: 10.5 months) [17]. However, a favorable response to EGFR-TKIs has been demonstrated in cases harboring a G719X + S781I compound mutation (Table) [4, 9, 17–28]. One study reported the overall response rate (ORR) of the first-generation EGFR-TKIs to be 36.8% for cases with G719X alone (n = 78), 33.3% for S768I alone (n = 7), and 50% for G719X/S781I compound mutation (n = 10) [20]. When 3 types of rare mutations (G719X, S781I, and L861Q) were analyzed in combination, the median PFS for patients with compound mutations was significantly longer than that of patients with a single mutation (11.9 vs. 6.5 months, $p < 0.01$) [20]. Kate *et al.* [26] reported that the ORR of EGFR-TKIs was 50% for G719X alone (n = 5), 0% for S768I alone (n = 2), and 66.6% for G719X/S768I compound mutation (n = 3). The median PFS was 9.1 months for G719X/S768I compound mutation, 9.0 months for G719X alone, and 1.0 months for S768I alone [26]. In another study, similar trends in the efficacy of first- and second-generation EGFR-TKIs were observed; the disease control rate for cases with a compound mutation of G719X, S781I, L861Q (100%, n = 4) was not inferior to those with a single mutation (83.8%, n = 37) [9].

A similar trend was observed for the response to osimertinib; ORR was 51.9% for cases with single rare mutations (G719X, L861Q, S781I, n = 27) and 75% for the cases with compound mutations (n = 4) [28]. An *in vitro* study using cell lines co-expressing G719X and S768I also showed good response to afatinib, suggesting that G719X mutation causes favorable changes in the three-dimensional structure of EGFR protein with S768I mutation, enhancing the binding of EGFR-TKI [29].

In conclusion, the efficacy of EGFR-TKIs in lung cancers harboring rare compound EGFR mutations cannot be predicted from the data of each single mutation. An appropriate choice of EGFR-TKI and prediction of its therapeutic effect can be obtained from the results of *in vitro* experiments using cell lines and accumulated case reports.

Table Efficacy of EGFR-TKIs in cases with G719X + S768I compound mutation

Study (year) [ref]	Type of mutations	No. of patients	Medications	PR	SD	PD	Efficacy
Lund-Iversen *et al.* (2012) [18]	G719X + S768I	1	Gefitinib	1	0	0	
Kobayashi *et al.* (2013) [9]	G719A + S768I	2	Erlotinib	2	0	0	
Svaton *et al.* (2015) [19]	G719X + S768I	1	Gefitinib	1	0	0	
Chiu *et al.* (2015) [20]	G719X + S768I	10	Gefitinib or Erlotinib	5	5	0	
Xu *et al.* (2016) [21]	G719X + S768I	2	EGFR-TKI	1	1	0	
	G719C + S768I	1					PFS 25.0 months
Kuiper *et al.* (2016) [22]	G719A + S768I	1	EGFR-TKI	0	0	1	
Kobayashi *et al.* (2016) [4]	G719X + S768I/L861Q	13	1G EGFR-TKI	9			
Chen *et al.* (2017) [23]	G719X + S768I	2	EGFR-TKI	0	2	0	
Zhang *et al.* (2017) [24]	G719X + S768I	5	EGFR-TKI				DCR 90.9%, ORR 22.7%, median PFS 7.6 months[a]
Watanabe *et al.* (2018) [25]	G719X + S768I	1	Afatinib				no progression up to 12 months
Yu *et al.* (2018) [17]	G719X + S768I	3	1G EGFR-TKI	2	1	0	
			Erlotinib	1	0	0	
Kate *et al.* (2019) [26]	G719X + S768I	2	Gefitinib				PFS 0.26 months, OS 0.26 months
Zhang *et al.* (2019) [27]	G719X + S768I	5	EGFR-TKI				DCR 90.9% (10/11), ORR 27.3% (3/11)[b]
Cho *et al.* (2019) [28]	G719X + S768I	2	Osimertinib				ORR 53%, median PFS 8.2 months[c]

EGFR-TKI, epidermal growth factor tyrosine kinase inhibitor; IG, first generation; DCR, disease control rate; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; PD, progressive disease; SD, stable disease

[a] 14 cases of G719X alone, 2 cases of G719X + L858R, and 1 case of G719X + E709A

[b] including S768I alone and S768I + L858R

[c] including G719X alone and G719X + L861Q

CONFLICT OF INTEREST

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