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CASE REPORT

Effectiveness of afatinib after ineffectiveness of gefitinib in an advanced lung adenocarcinoma patient with a single EGFR exon 20 S768I mutation: a case report

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Abstract: Epidermal growth factor receptor-tyrosine kinase inhibitors have improved progression-free survival and overall survival in non-small-cell lung cancer (NSCLC) patients with sensitive mutations. However, response of uncommon mutation to epidermal growth factor receptor-tyrosine kinase inhibitors is still unclear. S768I is one of the uncommon mutations. A female patient with advanced NSCLC with a single S768I mutation achieved effectiveness from afatinib after showing no response to gefitinib. The patient had progression-free survival after taking afatinib for 6 months, and her follow-up is continuing. It suggests that afatinib may be a more effective treatment for NSCLC patients with a single S768I mutation, compared to first-generation tyrosine kinase inhibitors.

Keywords: NSCLC, epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs), S768I, afatinib, gefitinib

Introduction

Lung cancer is the leading cause of cancer deaths according to GLOBOCAN estimates and has caused stressful burden on the society.[1] Cancer Statistics in China revealed similar phenomenon.[2] In recent years, epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) have improved the progression-free survival (PFS) in non-small-cell lung cancer (NSCLC) patients with sensitive mutations, compared to traditional chemotherapy[3–5] (9.2–13.1 vs 4.6–6.3 months). The sensitive mutations include deletions in exon 19 or L858R mutations in exon 21, which account for 85% of all epidermal growth factor receptor (EGFR) mutations and are associated with sensitivity to EGFR-TKIs.[6,7] Different generations of EGFR-TKIs showed no significant differences in sensitive mutations. Meanwhile, the incidence rates of uncommon mutation such as G719X, S768I, L861Q, and exon 20 insertion mutations are 4%–13%,[8] and their response effects to EGFR-TKIs remain unclear.[8–10]

Exon 20 p.S768I mutation is one of the uncommon mutations. Previous reports contradict on which generation has a better effect on S768I mutation.[8–10] LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6 studies[11] showed that afatinib (Boehringer Ingelheim Pharmaceutical Co., Ingelheim, Germany) revealed benefits among eight patients who carried S768I mutation. However, only one case had the single S768I mutation. Here, we report a case of afatinib's response in an advanced NSCLC female patient who failed treatment with gefitinib (AstraZeneca plc, London, UK).

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Case report

In March 2013, a 52-year-old Chinese female with no smoking history had sudden coughs with bloody sputum and chest pain. Positron emission tomography-computed tomography (CT) taken in Peking Union Medical College Hospital showed a mass in the left upper lung sized 39×49 mm^2 and the standard uptake value was 5.8. Meanwhile, several masses sized 8 mm in the mediastinum were observed without increased radioactive uptake. On April 16, 2013, upper left lung resection and mediastinal lymph node dissection were performed. Finally, the patient was diagnosed with lung adenocarcinoma on the left upper lobe with stage IIa (pT2aN1M0), as shown in Figure 1. Molecular pathology suggested EGFR exon 20 p.S768I mutation (2303G>T). Also, in her family, her father and one uncle died of lung cancer and another uncle died of kidney cancer.

From June to October 9, 2013, the patient was treated with adjuvant chemotherapy in another hospital (pemetrexed plus cisplatin, but the dose was unknown) for four therapy circles. Chest CT scan showed no recurrence. However, on October 10, 2014, a regular chest CT scan showed a new mass with a diameter of 10 mm in the left upper lung and several new masses in the right lung with a maximum diameter of 4 mm, that is, metastasis in mediastinal 4R, 4L, six regions, and left pleural effusion.

From October 2014 to December 2016, the patient accepted four-line therapies with chemotherapies and bevacizumab. Among the treatments, the fourth line treatment maintained 15 cycles and the patient benefited the longest PFS lasting for 14 months (Table 1). On December 30, 2016, a circulating tumor DNA liquid biopsy by the Amplification Refractory Mutation System was performed. And the result was the same as the surgical specimen two years ago (Figure 2). Because afatinib was not available in China at that time, we recommended the first-generation EGFR-TKI gefitinib (250 mg/day) with bevacizumab. One month later, the chest CT scan revealed that the metastases increased widely in both lungs, indicating that gefitinib was of primary resistance (Figure 3A and B). On March 3, 2017, the patient started taking afatinib (40 mg/day) with bevacizumab. The chest CT scan revealed the metastases shrank obviously after 1 month (Figure 3C). After 3 months, the patient had two-grade diarrhea and one-grade rash on the back neck. The efficacy evaluation was partial response. Now, the patient has PFS for 6 month (Table 1).

The patient has signed written informed consent for publishing the case details and any accompanying images.

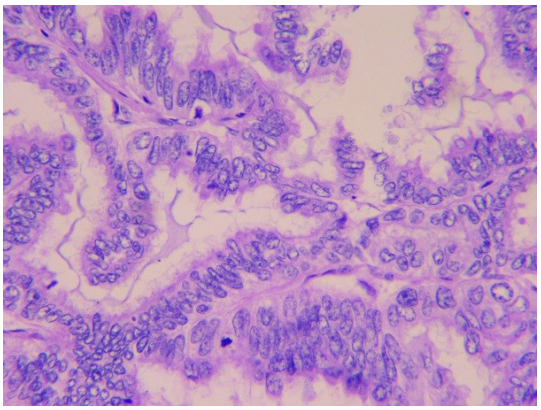


Figure 1 High-power magnification of a tumor specimen shows adenocarcinoma (400×).

Discussion

The patient was diagnosed with left lung adenocarcinoma without sensitive EGFR mutation. The initial stage was IIa, and the margin was negative. According to the National Comprehensive Cancer Network (NCCN) Guideline,[12] chemotherapy was recommended as the adjuvant therapy. After four cycles of therapy and 16-month disease-free survival, locoregional recurrence and distant metastases occurred. Chemotherapy or bevacizumab combined with chemotherapy was recommended according to the NCCN Guideline.[12]

According to the NCCN Guideline, bevacizumab, a humanized monoclonal antibody against vascular endothelial growth factor, can be used as the first-line therapy for lung adenocarcinoma until the disease progressed.[12] Many classic clinical studies[13–16] also proved its efficacy in NSCLC, compared with traditional chemotherapy. The classic ECOG4599[16] and BEYOND[13] studies have proved that bevacizumab with carboplatin/paclitaxel was well tolerated and resulted in a clinically meaningful treatment benefit in Chinese patients with advanced nonsquamous NSCLC. Table 1 shows the survival benefits from chemotherapy or bevacizumab.

When the disease progressed, the tissue samples could not be obtained due to the poor physical strength of the patient, so we performed circulating tumor DNA liquid biopsy, which was the feasible sample for EGFR mutation analysis.[17,18] EGFR exon 20 S768I mutation was detected just like before. Hellmann et al[19] reported a case whose mass spectrometry genotyping revealed EGFR S768I mutation among surgical specimens in 2001, 2003, and 2013, respectively. Besides, erlotinib had resulted in partial radiographic response until T790M mutation occurred.

To the best of our knowledge, this is the first case wherein a patient with S768I mutation received first- and second-generation EGFR-TKIs successively, and the response was completely different. The S768I mutation is a rare subset of

Table 1 Detailed medications and treatment

Time periods	Treatment	Line	Cycle	RECIST	PFS (month)
From November 2014 to January 2015	Fosfamide 2 g days 1–3 and pemetrexed 800 mg day 4, every 21 days	1	2	PD	–
From March 17 to April 18, 2015	Navelbine 40 mg day 1/day 8 and carboplatin 400 mg day 2 and bevacizumab 400 mg day 1, every 21 days	2	6	PR	4
From May 12 to July 29, 2015	Navelbine 40 mg day 1/day 8 and oxaliplatin 150 mg day 2 and bevacizumab 400 mg day 1, every 21 days				
From September 2 to October 19, 2015	Gemcitabine 1.8 g day 1/day 8 and bevacizumab 400 mg day 1, every 21 days	3	1		
	Gemcitabine 1.8 g day 1, every 21 days		1	PD	–
From November 9, 2015, to October 12, 2016	Paclitaxel 210 mg day 1 and bevacizumab 400 mg day 1, every 21 days	4	15	PR	14
From November 11 to December 7, 2016	Paclitaxel 180 mg day 1 and oxaliplatin 150 mg day 1 and bevacizumab 400 mg day 1, every 21 days		2	PD	–
From January 14 to February 14, 2017	Gefitinib 250 mg/day and bevacizumab 400 mg day 1, every 21 days	5	1	PD	–
From March 3, 2017 to until now	Afatinib 40 mg/day and bevacizumab 400 mg day 1, every 21 days	6	4	PR	6

Abbreviations: PD, progressive disease; PFS, progression-free survival; PR, partial response; RECIST, response evaluation criteria in solid tumors.

EGFR mutants located in exon 20 (incidence 1%–2%).[10,20] Common mutations including exon 19 deletions and L858R in exon 21 have shown sensitivity to EGFR-TKIs, no matter which generations they are.[6,7] However, the effects of uncommon EGFR mutations such as S768I mutation remain largely unknown. Although the analysis of LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6[11] proved that eight patients with S768I mutation all showed partial remission with afatinib, the limitation is obvious since the sample size was small and only one patient had single S768I mutation. In addition, Kuiper et al[21] and Beau-Faller et al[22] discovered that the disease control rate (DCR) was better with EGFR-TKIs for complex mutations than for a single mutation. Although some cases could be explained because they carried attractive mutations such as 19 deletions or L858R in exon 21 simultaneously, most conditions remain unclear.

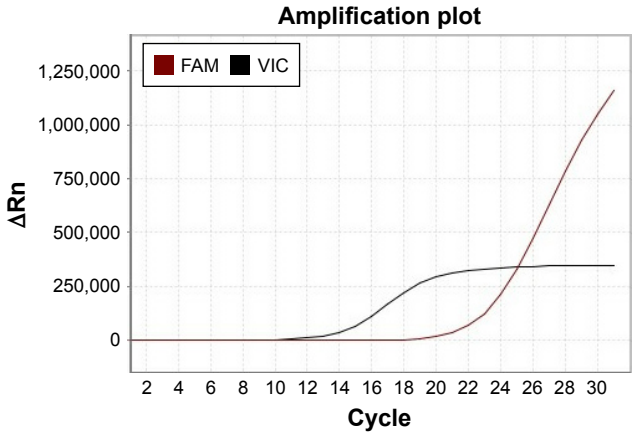


Figure 2 Circulating tumor DNA liquid biopsy shows S7689I mutation by the ARMS.

The female patient carried single S768I mutation according to two molecular pathologic tests. The effects of first- and second-generation EGFR-TKIs were completely different. To evaluate the effect of the single S768I mutation on the response to TKIs, we reviewed the previous cases and studies (Table 2). Table 2 shows that all the patients accepting afatinib showed partial remission or stable disease. The DCR is 100%. By contrast, the DCR of patients who accepted the first-generation TKIs such as erlotinib, gefitinib, and icotinib was 46.2%. Our case showed similar result. In addition to clinical researches, some experimental studies confirmed the value of different TKIs on S768I mutation. Tanizaki et al[23] examined the sensitivity of Ba/F3 cells expressing EGFR (L858R) or EGFR (S768I) to EGFR-TKIs by calculating the median inhibitory concentration (IC_{50}) values and a ratio relative to those for cells expressing EGFR (L858R). The result was inspiring because the IC_{50} values of afatinib were minimal. Regarding the IC_{50} ratios, the second-generation drugs' ratios were much smaller than those of the first- and the third-generation drugs. Kancha et al[24] and Banno et al[25] carried out similar experiments and drew similar conclusions. Therefore, S768I mutation is more sensitive to the second-generation TKI (afatinib) than the first-generation TKIs (erlotinib, gefitinib, and icotinib).

Up to now, 6-month PFS was achieved from afatinib combined with bevacizumab. The NEJ002 study[26] found that the median survival time of patients treated with gefitinib, platinum, and pemetrexed or docetaxel was around 3 years. Previous studies proved the benefits of EGFR-TKIs combined with anti-vascular endothelial growth factor therapy, such as bevacizumab and apatinib.[27–29] Furthermore, the

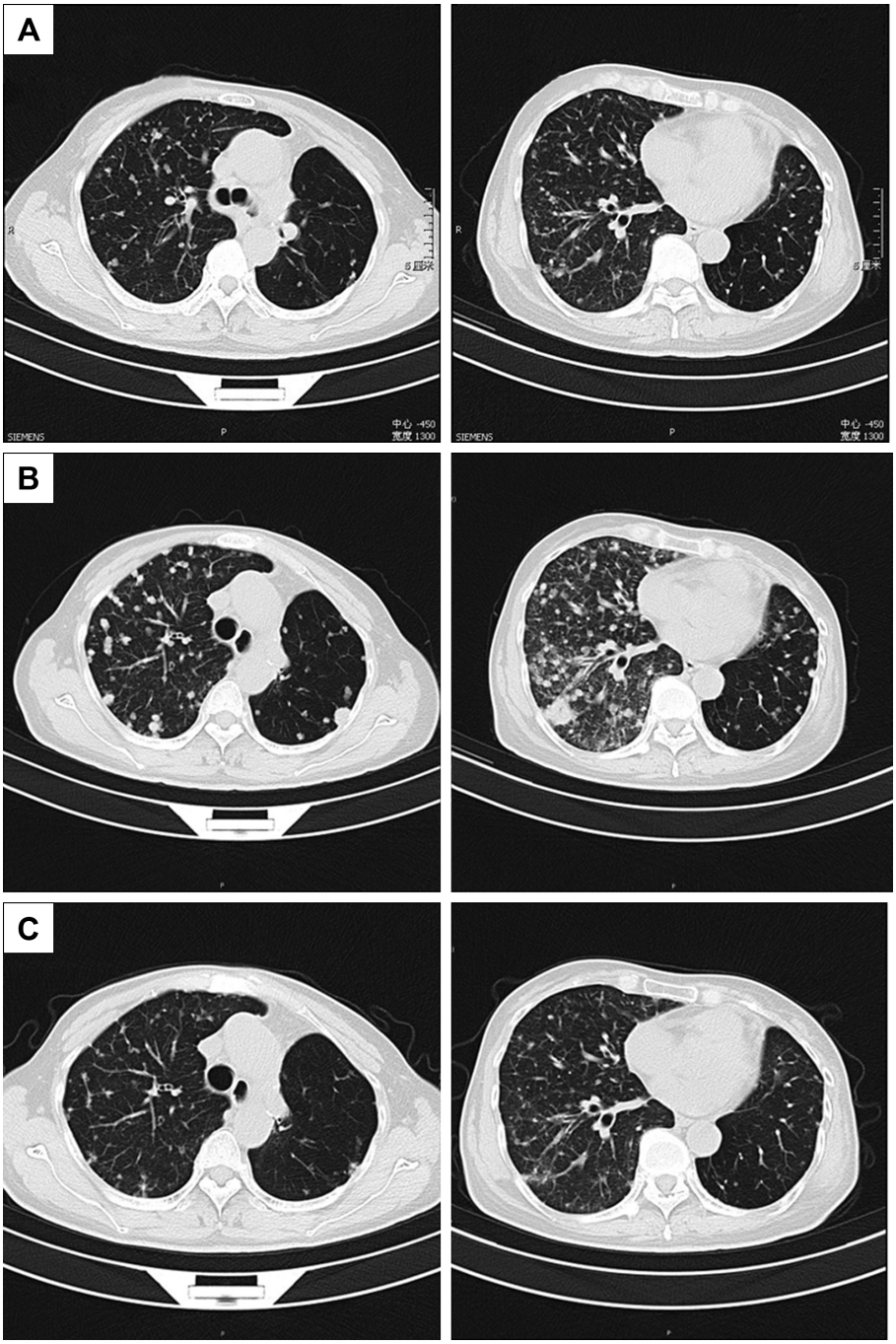


Figure 3 Thoracic computed tomography (CT) before taking gefitinib (**A**); after taking gefitinib , metastases increased widely in both lungs (**B**); after taking afatinib for one month, the metastases shrank obviously (**C**).

European Society for Medical Oncology[30] recommends bevacizumab combined with erlotinib as the first-line therapy for metastatic NSCLC. Comprehensive treatment could bring benefits to advanced NSCLC patients.

T790M mutation accounted for half of the known mechanisms of resistance.[31] Patients with single S768I mutation also acquired secondary T790M mutation.[19,32] Meanwhile, another clinical case[33] reported that patients with L858R mutation showed resistance after TKI therapy and secondary S768I mutation occurred in repeated molecular pathology. May be the occurrence of secondary S768I mutation could be the potential resistance mechanism.

Conclusion

Our case indicates that the second-generation TKI (afatinib) could be better than the first-generation TKI (gefitinib). Afatinib may be an effective treatment for NSCLC patients with single S768I mutation. Comprehensive treatment could

Table 2 Summary of reported clinical response to TKIs in patients harboring the single EGFR S768I mutation

Author	Year	n	Nationality	Age	Sex	Smoking	Stage	EGFR-TKI	Prior therapy	Line	RECIST	PFS
Masago et al[34]	2010	1	Japanese	81	M	37 pack-years	IV	Gefitinib	–	2	PR	461 days
Lund-Iversen et al[35]	2012	1	Norwegian	73	F	Former	IV	Erlotinib	Chemotherapy	2	PD	1 month
Weber et al[36]	2014	1	Danish	–		–	IV	Erlotinib	Chemotherapy	2	PD	1 month
Hellmann et al[19]	2014	1	American	–	–	5 pack-years	IV	Erlotinib	–	1	PR	8 years
Pallan et al[37]	2014	2	Afro-Caribbean	56	M	1 pack-year	IV	Gefitinib	–	1	PD	6 weeks
			Caucasian	65	F	20 pack-years	IV	Erlotinib	Chemotherapy	2	PD	2 months
Chiu et al[38]	2015	6	Taiwanese	–	–	–	–	Gefitinib or erlotinib	–	–	2PD, 2PR, 2SD	–
Heigener et al[39]	2015	1	German	–	–	–	–	Afatinib	–	–	SD	–
Yang et al[40]	2015	1	Chinese	56	F	–	IV	Afatinib	–	1	PR	5 months
Yang et al[11]	2015	1	–	–	–	–	–	Afatinib	–	–	PR	–
Leventakos et al[41]	2016	1	–	–	–	–	IV	Gefitinib	–	–	PD	3 months
Klughammer et al[42]	2016	1	–	–	–	–	–	Erlotinib	–	–	PR	–
Cheng et al[43]	2016	1	Chinese	59	F	–	IV	1G-TKI	–	–	PR	8.6 months
Kobayashi et al[44]	2016	1	Japanese	61	F	–	IV	Afatinib	–	11	PR	12 months
Zhang et al[45]	2017	1	Chinese	64	M	–	–	Icotinib	–	2	SD	31 months
Zhu et al[46]	2017	1	Chinese	52	F	–	IIIa	Gefitinib	–	1	SD	8.8 months
Russo et al[32]	2017	1	Italian	65	M	–	IV	Afatinib	–	1	PR	3 months

Abbreviations: 1G, first-generation; EGFR, epidermal growth factor receptor; F, female; M, male; PD, progressive disease; PFS, progression-free survival; PR, partial response; RECIST, response evaluation criteria in solid tumors; SD, stable disease; TKI, tyrosine kinase inhibitor.

bring benefits to advanced NSCLC patients. However, further clinical data are required for patients with advanced NSCLC harboring a single S768I mutation in order to provide more powerful evidences.

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Author contributions

HD, HC, YP, and YQ were responsible for collection and assembly of the patient's data. HD, YP, QL, JZ, WS, CS, and CL performed data analysis and literature searching. All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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