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BEDSIDE TO BENCH REPORT

Efficacy generated by afatinib in a lung adenocarcinoma patient harboring *HER2* S310Y mutation

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ABSTRACT

Afatinib exhibits therapeutic efficacy for lung adenocarcinoma patients harboring *HER2* exon 20 insertions. *HER2* S310Y single site substitution was discovered in recent years and afatinib efficacy for adenocarcinoma patients harboring S310Y mutation has not been reported. We presented a case of a 41-year-old male patient with lung adenocarcinoma harboring the *HER2* S310Y mutation obtained clinical response to the treatment of afatinib, an oral *HER* family blocker. After the treatment of afatinib, the patient achieved partial response (PR) in chest lesions and almost complete response (CR) in intracranial lesions. He experienced progressive disease (PD) with liver metastasis and achieved a progression-free survival (PFS) of 5 months. He continually treated with afatinib after CT guided percutaneous radiofrequency ablation to eradicate the hepatic tumor cells and achieved stable disease (SD). In this study, we reported the first clinical evidence of efficacy generated by afatinib, the irreversible *HER* family inhibitor, targeting *HER2* S310Y single site mutation in lung adenocarcinoma.

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Introduction

Gene alterations of human epidermal growth factor 2 (*HER2/ERBB2*) occur in 1–4% of lung adenocarcinomas as oncogenic driver mutations.[1] Median overall survival of *HER2* gene variations in lung cancer patients is 1.6–1.9 years from the time of stage IV diagnosis. *HER2* mutations found in clinical patients so far are commonly consisting of an in-frame insertion YVMA (p.A775_G776insYVMA) in exon 20, located in kinase domain of HER2 protein.[2] Afatinib is an oral HER family blocker, which covalently binds and irreversibly blocks all kinase-competent HER family members.[3] Afatinib displays a manageable toxicity profile and promising results in several retrospective studies targeting mutated HER2 exon 20 in non-small-cell lung cancer (NSCLC).[4]

Although the exon 20 mutation in HER2 kinase domain has been already well characterized, mutations in extracellular domain (ECD) were poorly investigated. HER2 S310 single site substitution was located in the ECD of HER2 and first discovered by a comprehensive genetic study.[5] S310Y mutation has been identified in a few NSCLC patients,[6,7] but no clinical efficacious drug targeting this mutation has been reported. Herein, we reported the first clinical evidence of efficacy generated by afatinib targeting *HER2* exon 8 S310Y mutation in a lung adenocarcinoma patient.

Case presentation

A 41-year-old male with a smoking index of 200 (20 cigarettes/day for 10 years) presented to the outpatient clinic in May 2015, with intermittent cough and left chest pain for 2 months. Chest computed tomography (CT) revealed a mass arising from the lingual segment in the left upper lobe of lung. Neither mediastinal lymph nodes enlargement nor pleural thickening was observed. No bilateral pulmonary effusion appeared. Wedge resection was performed in left upper lung under double lumen intubation thoracoscopy. During the operation, he was founded the invasive adenocarcinoma in left lung and pleural nodules and diaphragm. The patient was diagnosed as stage IV left upper lung adenocarcinoma.

This patient was treated with chemotherapy by gemcitabine (1600 mg, D1, D8) and carboplatin (500 mg, D2) for 4 cycle, followed by gemcitabine alone (1600 mg, D1, D8) for 3 cycle after operation. He presented with chemotherapy-induced side effects of anorexia and myelosuppression. He achieved stable disease (SD) and experienced progressive disease (PD) 11 months later with enlarged left lung lesion (Figure 1A) and brain metastasis (Figure 2A). Positron emission tomography-computed tomography (PET-CT) revealed an increase in pulmonary lesion number, accompanied with the involvement of supraclavicular fossae lymph node and left pleura and thoracic vertebra. Magnetic resonance imaging (MRI) revealed intracerebral metastasis.

Capture-based targeted sequencing of assessing plasma circulating tumor DNA (ctDNA) and tissue biopsy were performed. NGS revealed the harboring of *HER2* exon 8 S310Y missense mutation NM_004448.3(*HER2*):c.929C>A(p.Ser310Tyr) with allelic fraction (AF) of 0.57% in liquid biopsy and

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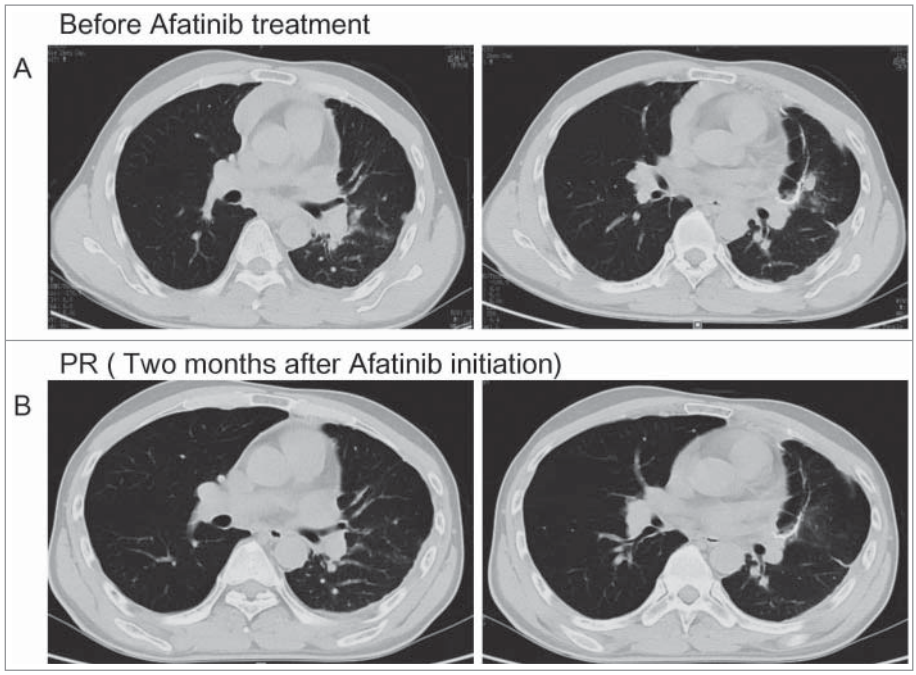

Figure 1. Chest computed tomography scan revealed the tumor response to afatinib. (A) The progressive disease status of lung lesion before afatinib treatment. (B) The partial response of lung lesions after afatinib treatment.

38.9% in tissue sample (Figure 3). No other afatinib targeted mutations were identified. From May 2016, the patient was treated with afatinib (40 mg), the irreversible HER family inhibitor. Shortly after initiation of treatment, the patient experienced rapid clinical symptom relief. He displayed side effects of mild skin rash, fatigue and loss of appetite during the treatment of afatinib. He achieved partial response (PR) in lung lesion and almost complete response (CR) in intracranial lesions two months after the initiation of afatinib. Head and chest CT scan revealed decreased number of left lung lesions, shrinkage of pleura nodules and mediastinum lymph nodes (Figure 1B), accompanied with nearly tumor-free in brain (Figure 2B).

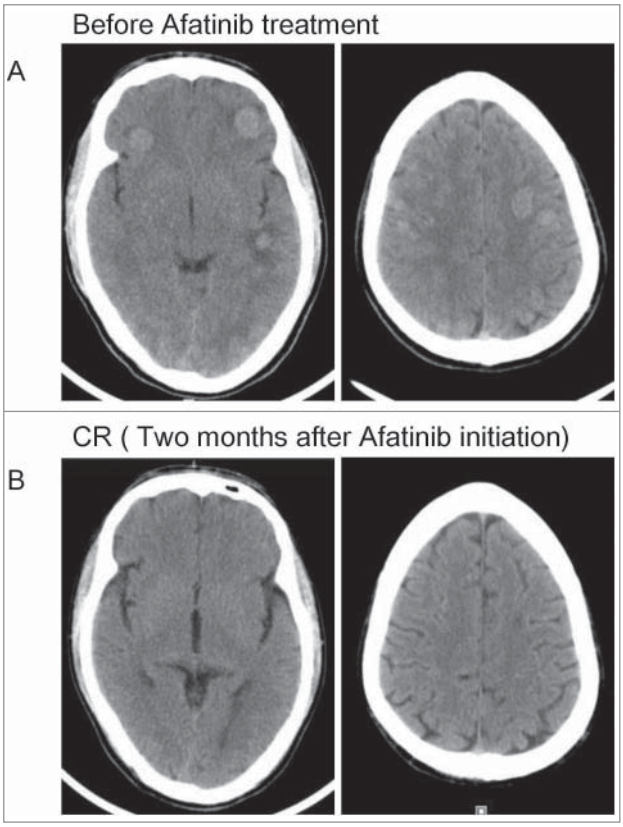

Figure 2. Head computed tomography scan revealed the tumor response to afatinib. (A) The progressive disease status of intracranial lesions before afatinib treatment. (B) Complete response of intracranial lesions after afatinib treatment.

However, this patient experienced progressive disease (PD) with enlarged lung lesion and increasing pleural effusion in October 2016. He also experienced hepatic metastasis, resulting a progression-free survival (PFS) of 5 months. Capture-based NGS revealed *HER2* exon 8 S310Y mutation in hepatic puncture biopsy (AF = 15.2%). The hepatic tumor was treated with CT guided percutaneous radiofrequency ablation. At the same time, he was continued with ongoing afatinib treatment (40 mg, QD) and his extra-hepatic lesion achieved stable disease (SD) with slow progression. Unfortunately, he experienced enlarged lung lesion and developed brain metastasis 5 months later in March 2017. The patient passed away a few weeks later.

Discussion

HER2 aberrances, which can lead to phosphatase inhibition or structure change of receptors, can be oncogenic and been identified in several malignancies.[8] Afatinib, can covalently binds to *HER2* and irreversibly inhibits its enzymatic activity, provides an effective, long-lasting blockade of aberrant *HER2* receptor signaling in multiple types of cancer.[9-12] Here, we presented the first case of a lung adenocarcinoma patient harboring *HER2* S310Y mutation, effectively treated with afatinib.

With the rapid development of targeted therapy, *HER2* inhibitors has dramatically revolutionized and widely

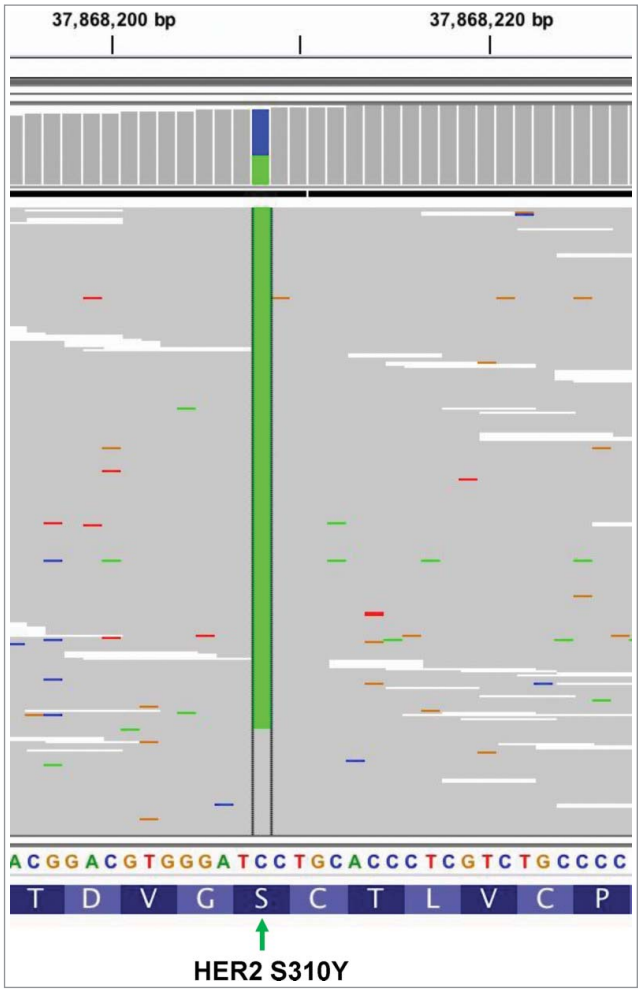

Figure 3. The Intergrative Genomics Viewer (IGV) screenshots displayed the reads from ctDNA sequencing and revealed the harboring of *HER2* S310Y. Different nucleobase types were presented with different colors. Adenine (A) is presented by green, cytosine (C) is indicated by blue, guanine (G) is yellow, and thymine (T) is red. The green column in the middle indicates position of the mutated nucleobase (929C>A). The mutation of *HER2* S310Y in terms of nucleobase and amino acid level occurred as 929C>A and Serine310 to Tyrosine, respectively [NM_004448.3(*HER2*):c.929C>A(p.Ser310Tyr)].

applied to *HER2* mutant lung cancer patients. *HER2* exon 20 insertions were the most common subtype accounting for the majority (50–80%) of *HER2* mutant lung cancer.[13,14] This tyrosine kinase domain mutation can cause constitutive phosphorylation and activation of HER2 receptor by altering the ATP-binding pocket, resulting in oncogenic activity of HER2.[15] The responses to afatinib have been reported in several studies with tumors harboring the YVMA exon 20 insertion.[16]

Extracellular domain mutations of *HER2,* S310F and S310Y, were discovered in cancer patients recent years and speculated to result in hydrophobic interactions and non-covalent dimerization, thus subsequently activate the downstream signaling pathways.[7] To date, limited number of targeted therapy studies focusing on *HER2* S310F have been reported. A breast cancer patient with *HER2* S310F mutation responded well to trastuzumab monotherapy with decrease in the size of liver and bone metastases within 3 months of initiating treatment.[17] An extramammary paget's disease patient associated with adnexal adenocarcinoma harboring *HER2* S310F was reported to achieve continuing partial response to lapatinib and capecitabine therapy.[18]

Nevertheless, to the best of our knowledge, the efficacy of afatinib to *HER2* S310Y mutation in NSCLC patients has not been reported before. In our case, after afatinib treatment, the lung adenocarcinoma patient obtained PR in chest lesion and almost CR in intracranial lesions, accompanied with significant symptoms relief. Although the patient experienced PD five months later, he continually achieved longer duration of treatment with afatinib in other lesions after the local ablative therapy. In this study, we provided the first clinical evidence of afatinib to be efficacious for lung adenocarcinoma patients harboring *HER2* S310Y mutation, which served as guidance for *HER2*-associated targeted therapy. Further investigation of highly effective and tolerable *HER2* therapies will be highly expected to carry out in order to expand treatment options for HER2 ECD mutant cancer patients.

In our presented case, the patient harboring *HER2* S310Y mutation was negative for *HER2* amplification, assessed by both NGS and fluorescence in situ hybridization (FISH). In addition, HER2 protein overexpression was also negative in this patient detected by immunohistochemical staining (IHC). This case demonstrated that *HER2* S310Y was independent of *HER2* amplification and protein overexpression in this patient, acting as a functional driver mutation for tumorigenesis and responded to afatinib treatment. Many researches also focus on the coincidence of the gene mutation, amplification and protein overexpression. Li et al. reported that *HER2* mutation was not overlapped with *HER2* amplification and HER2 protein overexpression.[19] However, the co-existence of *HER2* amplification was observed in four of eight,[20] three of thirty-four,[21] and two of six[22] of *HER2* mutated lung cancer patients. Previous studies of the underlying associations of *HER2* mutation, copy number amplification and HER2 protein overexpression have not reached a unanimous conclusion. Therefore, further efforts are still needed to interrogate the complexity of *HER2* alterations and the associations of *HER2* mutation, amplification and protein overexpression in cancers.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

Informed consent statement

This study was approved by the Institutional Review Board at the Shenzhen People's Hospital. The patient provided informed consent and gave permission to this study.

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