Afatinib as first-line treatment for advanced lung adenocarcinoma patients harboring HER2 mutation: A case report and review of the literature

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Keywords
Afatinib; first-line treatment; HER2 mutation; lung cancer.

Abstract
HER2 mutations are a rare group of driving genes that respond to HER2 targeted therapy, particularly afatinib. No more than 20 such cases have been reported, but afatinib was used after first-line chemotherapy. We present the case of a never-smoking female patient diagnosed with stage IV lung adenocarcinoma harboring a Her2 exon 20 inserted mutation who achieved a durable response (12 months) to first-line afatinib treatment. We review the literature concerning afatinib therapy in this rare cohort of mutated lung cancer patients.

Introduction
Human epidermal growth factor 2 (HER2, erbB-2/neu) is a member of the erbB receptor tyrosine kinase family. It is a plasma membrane-bound receptor tyrosine kinase, containing extracellular membrane binding, transmembrane, and intracellular domains. HER2 is activated by homodimerization or heterodimerization with other erbB-2 family members, especially EGFR.1,2 HER2 combined with EGFR can increase the potential for receptor phosphorylation and thus activate downstream signaling pathways, including mitogen-activated protein kinase (MAPK), phosphoinositol 3-kinase (PI3K/Akt), phospholipase Cγ, protein kinase C (PKC), and signal transducer and activator of transcription (STAT). These signaling pathways promote cell proliferation and resist apoptosis, which is correlated to uncontrolled cell growth in oncogenesis.3,4 The principal mechanisms of oncogenic activation of HER2 are HER2 gene amplification, gene mutation, and HER2 protein overexpression.5 Oncogenic activity of HER2 mutations have been reported in a large spectrum of malignancies including breast, ovarian, bladder, salivary gland, endometrial, pancreatic, and non-small cell lung cancers.6

Afatinib is an oral HER family blocker, which can covalently bind and irreversibly block ErbB receptor family members.7 It displays a manageable toxicity profile and promising results in several retrospective studies targeting mutated HER2 exon 20 in non-small cell lung cancer (NSCLC).5

Herein, we report a stage IV lung adenocarcinoma patient harboring a HER2 exon 20 inserted mutation who was treated with afatinib as first-line treatment and achieved progression-free survival (PFS) of 12 months with ongoing treatment. To the best of our knowledge, this is the first report of first-line afatinib treatment achieving a partial response (PR) in an NSCLC patient with a HER2 exon 20 insertion mutation.

Case report
A 57-year-old, non-smoking woman was diagnosed with stage IV lung adenocarcinoma in July 2017 after undergoing a left pleural biopsy by wedge resection of the lower lobe of the left lung. The tumor node metastasis...
(TNM) classification of this patient was T3aN0M1a, because of ipsilateral lobe and pleural metastases. The pathological result from lung tissue biopsy was infiltrating lung adenocarcinoma. Immunohistochemical results showed positive thyroid transcription factor-1 (TTF-1), negative ALK, cytokeratin (CK)-7, and CK-10. No intracranial metastasis was observed on brain magnetic resonance imaging. A mutation frequency of 28.2% exon 20 ERBB2 activated mutation (p.G776delinsVC) was found in the tumor DNA extracted from the original diagnostic biopsy by next-generation sequencing (NGS), performed by Cancer-Hope (Genomicare, Shanghai, China). A CTNNB1 with p.S45P activated mutation was also detected at a frequency of 16.03%. Testing was conducted to identify any other common mutations, such as EGFR, KRAS, NRAS, MET, ALK, ROS1, and RET, however, the results were negative. The patient had not previously been administered chemotherapy or targeted therapy.

Treatment with afatinib (40mg/day) was commenced in August 2017. One month later, computed tomography showed a radiological PR with the patient advising relief of the chest pain (Fig 1). She was followed-up at outpatient visits every two months and achieved a continuous PR until July 2018, the latest return visit. Afatinib treatment is ongoing. The major treatment-related side effects observed were diarrhea, oral ulcers, and grade 1 skin adverse events.

**Discussion**

HER2 kinase domain mutation occurs in 1–4% of lung adenocarcinomas as oncogenic driver mutations.®

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**Figure 1** (a,b) Computed tomography (CT) images taken on 28 July 2017 when the patient arrived at our outpatient facility for the first time. Multiple lesions were observed on both sides of the lung. (c,d) CT images taken on 27 August 2017 after orally administration of afatinib 40 mg/day for one month. Shrinkage of the lesions was observed, particularly in the upper lobe of the left lung.
Oncogenic mutations of HER2 mostly present in non-smoking female patients diagnosed with advanced lung adenocarcinoma.\textsuperscript{5–14} Similar to EGFR mutations in NSCLC, HER2 mutations most frequently occur in tyrosine kinase domains, but cases involving the extracellular domain and transmembrane domain (TMD) have been reported.\textsuperscript{15} The most common subtype of HER2 mutation is exon 20 in-frame YVMA insertion (HER2[YMVA]), which is found in over 50% of all HER2 mutant lung cancer patients.\textsuperscript{12} The percentage of exon 20 in-frame insertions has been reported to be as high as 89–100% by several large cohort studies.\textsuperscript{13,14,16–18} Gow et al. retrospectively analyzed 888 Asian lung cancer patients via gene sequencing to detect a number of driver gene mutations, including HER2. Forty lung adenocarcinoma patients were HER2 mutation positive and all were exon 20 insertion alterations. A\textsuperscript{775_G776} ins YVMA and P\textsuperscript{780_Y781} ins GSP were the two most prevalent mutation subtypes (n = 22 and n = 4, respectively).\textsuperscript{19}

Afatinib exhibits antitumor efficacy by downregulating the phosphorylation of HER2 and EGFR, together with downstream signaling in HER2 mutant NSCLC. Moreover, it induces an anti-proliferative effect through G1 arrest and apoptotic cell death.\textsuperscript{20} Increased HER2 phosphorylation, as well as increased sensitivity to afatinib, have also been observed in transfected Ba/F3 cells with HER2 (P\textsuperscript{780_Y781} ins GSP) mutation, indicating the possible treatment efficacy of afatinib.\textsuperscript{21}

De Greve et al. reported the first evidence of clinical benefit from afatinib treatment in 2011.\textsuperscript{22} Three patients diagnosed with advanced lung adenocarcinoma were detected with HER2 mutations. They were administered afatinib 50 mg/day (2 accompanied by paclitaxel) and all achieved significant tumor regression, with an afatinib-related PFS of 3–15 months. De Greve et al. subsequently conducted a phase II clinical study to evaluate the effects of afatinib or afatinib plus paclitaxel for the treatment of lung adenocarcinoma. Notably, one patient receiving afatinib monotherapy achieved a confirmed PR, as well as one patient treated with combination therapy who had a confirmed PR of 41.9 weeks.\textsuperscript{23} Since these studies, few cases of lung adenocarcinoma patients harboring HER2 mutation have been reported (Table 1). Of the 24 reported cases (F: 16 vs. M: 8), three patients were light smokers, one male patient was a heavy smoker, and the remaining 15 patients were never-smokers (5 were unclear). Seventeen (71%) patients' genetic sequences were altered with exon 20 insertions. Five harbored TMD mutations and also responded to afatinib, with no significant difference to those with exon 20 insertions. Unlike other patients who were treated with no more than 50 mg/day afatinib, three patients underwent pulse afatinib therapy with oral 280mg once a week. It is worth mentioning that these three patients did not experience any rash, which is a common drug-related side effect of afatinib. The PFS durations were 11 and 5 months; PFS was not available in the third patient.\textsuperscript{25} Twenty patients achieved evaluable afatinib-related PR or stable disease (SD), with a median PFS of 5.25 months (range: 1–18).

Three of the 24 patients received afatinib as first-line therapy, including our patient, who achieved PFS of 12 months with ongoing afatinib therapy. Of the other two patients, one harbored a TMD V659E mutation and the other an exon 20 insertion (YVMA\textsuperscript{776–779} ins) and both had SD after afatinib treatment. Our patient is the only reported case with an exon 20 YVMA insertion to achieve a continuous PR.

Large cohort studies have reported similar clinical characteristics of lung cancer harboring HER2 mutations as these case reports. Mazieres et al. retrospectively identified 65 NSCLC patients diagnosed with a HER2 in-frame insertion in exon 20. Favorable responses were observed, with a 100% disease control rate in patients administered afatinib (n = 4, SD or PR).\textsuperscript{13} Furthermore, Mazieres et al. also conducted the European EUHER2 study to determine the efficacy of multiple drug therapy for HER2 exon 20 insertion mutated lung adenocarcinoma patients. Eleven patients were treated with afatinib and the median PFS was 3.9 months. No significant advantage of HER2-TKI treatment was observed compared to traditional chemotherapy.\textsuperscript{14}

Although rarely occurring, mutations in the TMD have also attracted research attention. Ou et al. prospectively analyzed the tumor cells of 8551 lung adenocarcinoma patients and identified 15 cases of HER2 TMD mutations (V659E/D, G660D), two of which harbored concurrent Erbb2 receptor tyrosine kinase 2 gene amplification. Interestingly, three of the four patients with TMD mutations administered first or second-line afatinib developed partial or metabolic responses for 5–18 months, indicating the potential benefit not only to kinase domain but also TMD mutation patients.\textsuperscript{33}

In conclusion, we report the only known case of a patient with the most common YVMA mutation, HER2 alteration, administered first-line afatinib to achieve a continuous PR for at least 12 months, which is longer than the median PFS (6.9 months) acquired by pemetrexed/cisplatin.\textsuperscript{24} Our results, together with two other first-line afatinib treatment cases, indicate that large cohort studies should be conducted to investigate the efficacy and drug-related adverse events of first-line afatinib compared to traditional first-line chemotherapy with pemetrexed/cisplatin for the treatment of HER2 positive lung adenocarcinoma patients.
| No. | Age, y | Gender | Smoking status | Histologic subtype | Stage | ERBB2/HER2 Alteration | Systemic Therapy | Best Response | PFS |
|-----|--------|--------|----------------|-------------------|-------|----------------------|----------------|--------------|-----|
| 1   | 72     | F      | Never          | Lung ADC          | III   | Exon 20 mutation (p. Tyr772_Ala775dup) | Carbo/Gem X8 cycles | Partial remission then SD | 3 mo |
| 22  | 62     | F      | Never          | Lung ADC          | pT2N1 | Exon 20 mutation (p. Gly776Leu) | Afatinib *3 mo | PR then PD | 8 mo |
| 3   | 49     | F      | Never          | Lung ADC          | IV    | Exon 20 insertional duplication (p.Gly778_Pro780dup) | Cis/Gem | Objective response | 15 mo |
| 22  | 48     | F      | Never          | Lung ADC          | IV    | Exon 20 mutation (P780_Y781insGSP) | Peme/Cis *6 cycles | Partial remission | 4 mo |
| 5   | 55     | M      | Never          | Lung ADC          | IV    | Exon 20 mutation (p.A775_G776insYVMA) | Docetaxel *8 cycles | PR | 10 mo |
| 6   | 65     | M      | Never          | Lung ADC          | IV    | Exon 20 insertion (A775_G776insYVMA) | Carboplatin *7 cycles | PR | 10 mo |
| 7   | 64     | F      | 5-pack-year    | Lung ADC          | IV    | Exon 20 insertion (V747_G748insGSP) | Carboplatin *5 mo | PR | 11 mo |
| 8   | 71     | F      | Never          | Lung ADC          | IV    | Exon 20 insertion (E740_A741insAYVM) | Afatinib (280 mg once weekly) | PR | 5 mo |
| No. | Age, y | Gender | Smoking status | Histologic subtype | Stage | ERBB2/HER2 Alteration | Systemic Therapy | Best Response | PFS |
|-----|--------|--------|----------------|-------------------|-------|-----------------------|-----------------|--------------|-----|
| 9\(^{26}\) | 58 | F | NP | Solid predominant | NP | Exon 20 insertion (GSP781-783ins) | Gem/cis *4.6 mo | SD | 5.5 mo |
| 10\(^{26}\) | 70 | F | NP | Papillary predominant | NP | Exon 20 insertion (YVM76-779ins) | Peme/carbo*2.8 mo | SD | 3.5 mo |
| 11\(^{26}\) | 60 | M | NP | Micropapillary predominant | NP | Exon 20 insertion (YVM76-779ins) | Afatinib *4 mo | SD | 4 mo |
| 12\(^{26}\) | 66 | M | NP | Papillary predominant | NP | Exon 20 insertion (YVM76-779ins) | Docetaxel/platinum*1 mo | PD | NA |
| 13\(^{27}\) | 67 | F | Never | Lung ADC | NP | Exon 20 insertion (A775_G776insYVMA) | Carbo/Pem, then Pem maintenance *9 mo | PR | 1 mo |
| 14\(^{27}\) | 36 | F | Never | Lung ADC | NP | Exon 20 insertion (exact sequence unknown) | Carbo/Pem/Beva, then maintenance *4.5 mo | PR | 6.5 mo |
| 15\(^{38}\) | 41 | M | Heavy Smoker | Lung ADC | IV | HER2 exon 8 5310Y (c.929C>A(p.Ser310Tyr)) | Gem/Carbo *4 cycle | NA | 7 mo |
| 16\(^{38}\) | 50 | F | Never | Lung ADC | IV | Exon 20 mutation (c.2437A>G) | Gem*3cycle | NA | NA |
| 17\(^{31,31}\) | 56 | F | 1,2-pack-year | | | | | PR | 4 mo |
| 18\(^{31}\) | 52 | F | NA | Adeno of the ampulla of Vater | Metastatic to lung | G660D and S310F | Gem/Cis | PD | NA |
| 19\(^{31}\) | 45 | F | Never | Lung ADC | Metastatic to bone | HER2 V777_G778insGSP | Cis/Peme*7 mo | PR | 7 mo |
| 20\(^{31}\) | 62 | F | Never | NSCLC | NA | V659E | First-line afatinib | PR | 5 mo |
| 21\(^{31}\) | 54 | M | Never | NSCLC | NA | V659E | Second-line afatinib | PR | 18 mo |
Disclosure

No authors report any conflict of interest.

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