HER2-amplified metastatic lung adenocarcinoma responds to fourth-line pyrotinib therapy: A case report

KAN GONG*, YI YANG*, HUAN HUANG, XUNJIE KUANG and XUEQIN YANG

Cancer Center, Daping Hospital, Army Medical University, Chongqing 400042, P.R. China

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Abstract. Despite the success of anti-HER2 therapy in patients with breast cancer with HER2 amplification or HER2 overexpression, the results of clinical trials on anti-HER2 therapy for lung cancer have not been satisfactory. The aim of the present study was to report a case of a non-smoker, female patient diagnosed with stage IIIA lung adenocarcinoma harboring *HER2* amplification. The disease progressed despite surgery and multiple lines of chemotherapy, plus trastuzumab or lapatinib. The pan-ErbB inhibitor pyrotinib (400 mg/day) was commenced as a fourth-line regimen, and the patient achieved complete response with a time to progression (TTP) of 6 months. After the lung adenocarcinoma progressed, pyrotinib was continued, along with anlotinib and nivolumab. The patient achieved stable disease (SD) status with another 6 months of TTP. The overall survival of the patient was 28 months. Therefore, the present case suggests that the development of novel drugs may provide new and effective therapeutic regimens for lung cancer with HER2 amplification.

Introduction

Novel insights into gene mutations in lung adenocarcinoma have led to the molecular-stratified therapy of the disease. Fewer than 5% of patients with lung adenocarcinoma harbor HER2 (also known as ErbB2) alterations. Those with HER2 mutations have poorer survival outcomes compared with lung adenocarcinoma harboring other gene mutations, mandating tailored HER2-directed therapies in this subset of patients (1-3). The majority of HER2 mutations occur in HER2 exon 20 as a duplication or insertion mutation (4). The overall response rate of anti-HER2 therapy with HER2 inhibitors, including poziotinib, pyrotinib, and afatinib, ranges from 30 to 50% (5-7). In addition to HER2 gene mutations, the mechanisms of HER2 activation include HER2 amplification or overexpression. Despite the success of anti-HER2 therapy in patients with breast cancer with HER2 amplification or overexpression, the results of clinical trials on anti-HER2 therapy for patients with lung cancer have failed (8).

The aim of the present study was to report a case of stage IIIA lung adenocarcinoma in a non-smoker female patient with primary chemoresistance who achieved partial response (PR) with anti-HER2 therapy using trastuzumab and lapatinib and complete response (CR) with pyrotinib after disease progression.

Case report

A 53-year-old Chinese, non-smoker, female patient with no family history of cancer was diagnosed pathologically with lung adenocarcinoma after undergoing thoracoscopic left upper lobectomy and hilar and mediastinal lymph node dissection at Daping Hospital (Chongqing, China) in March 2018. The TNM classification of the disease was T2N2M0 and stage IIIA. A CT scan after two cycles of pemetrexed (500 mg/m^2, day 1) plus platinum (75 mg/m^2, day 1, every 3 weeks) revealed mediastinal lymph node and liver metastases. Magnetic resonance imaging of the brain revealed no intracranial metastasis. The CEA level increased to 180 ng/ml (normal reference value range: 0-5 ng/ml). The patient was switched to a second-line regimen with albumin-conjugated paclitaxel (260 mg/m^2, once every 3 weeks), platinum and bevacizumab (7.5 mg/kg, once every 3 weeks). However, the CEA level continued to increase (414 ng/ml). After one treatment cycle, the CT examination revealed a new liver lesion. Next-generation sequencing (NGS) of the surgical specimen revealed HER2 amplification (gene copy number: 11), HER2 mutation (1.46%; F616L is not an exon 20 mutation), ErbB4 mutation (24.41%), TP53 mutation (33.57%), and other mutations (Table I). The tumor mutation burden was 17.9/Mb. Supplementary immunohistochemistry (IHC) examination revealed HER2 overexpression (3+; Fig. S1). The third-line regimen was commenced in June 2018 with four courses of lapatinib

Correspondence to: Professor Xueqin Yang, Cancer Center, Daping Hospital, Army Medical University, 10 Changjiang Zhi Road, Yuzhong, Chongqing 400042, P.R. China
E-mail: yangxueqin@hotmail.com

*Contributed equally

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; TTP, time to progression; PFS, progression-free survival; CEA, carcinoembryonic antigen; NGS, next-generation sequencing; ORR, objective response rate; NSCLC, non-small lung cancer; OS, overall survival

Key words: NSCLC, HER2 amplification, pyrotinib

(1,250 mg/day) and one course of trastuzumab (75 mg/m^2, once every 3 weeks), in addition to docetaxel (75 mg/m^2, once every 3 weeks), platinum, vinorelbine (25 mg/m^2, days 1 and 8, every 3 weeks) and capecitabine (1,250 mg/m^2 twice a day, days 1-14, every 3 weeks). The patient achieved PR. The disease progressed with left axillary lymph node metastasis detected on CT scan in November 2018. The fourth-line regimen was then initiated, with pyrotinib (400 mg/day) combined with irinotecan (220 mg/m^2, once every 3 weeks), and oxaliplatin (130 mg/m^2, once every 3 weeks). After two cycles, the regimen was changed to pyrotinib monotherapy at 400 mg/day. The patient achieved CR in February 2019. The metastatic foci in the liver and mediastinal lymph nodes disappeared, and the CEA levels returned to normal. The main treatment-associated side effect was grade 2 diarrhea.

The time to progression (TTP) of the patient was 6 months. The disease started to progress slowly, after six cycles of pyrotinib therapy. CT scans performed in April 2019 revealed new lesions in the liver, and the CEA level increased to 40 ng/ml. The regimen was switched to afatinib (40 mg/day). After 1 month, the disease rapidly progressed with a marked increase in CEA (639 ng/ml) and CA125 (1,255 U/ml; cutoff value <35 U/ml) levels. A CT scan revealed slight progression in the lesions in the chest, but the liver lesions markedly progressed. A liver biopsy was performed in June 2019. NGS was performed using the same method as before. The results revealed HER2 amplification (gene copy number: 23), and more gene mutations (Table II). No ErbB4 mutations were identified. The tumor mutation burden increased to 26.66/Mb. Programmed death-ligand 1 (SP142) was negative as detected by IHC. As the results showed high copy number of HER2, high TMB, and high rates of chemotherapy-resistant gene mutations [such as KEAP1 (9) and NOTCH1 (10)], pyrotinib (480 mg/day) was continued, along with anlotinib (12 mg/day, days 1-14, every 3 weeks) and nivolumab (3 mg/kg, once every 2 weeks). The disease remained stable until December 2019, and the patient achieved another 6 months of TTP. The patient eventually succumbed to the disease in July 2020. The overall survival was 28 months. The changes in CT images and CEA levels over the course of treatment are shown in Figs. 1 and 2. The treatment regimens and responses are summarized in Table SI.

Table I. Gene mutational profile in a patient with lung adenocarcinoma by next-generation sequencing of DNA obtained from surgical specimens.

Genes	Mutation sites	Frequency, %	Amplification (copy no.)
HER2	F616L[a]	1.46	11
ErbB4	N280I	24.41	
GATA1	S12P	1.17	
GNAS	T386P	1.82	
KIT	M1R	2.58	
KIT	A621S	21.79	
MSH3	K281fs	1.73	
TP53	G154V	33.57	
VEGFA	L139R	1.08	

[a]This mutation is not a classic activating mutation and unlikely to be responsible for the responsiveness to HER2-targeted therapy.

Table II. Gene mutational profile of lung adenocarcinoma by next-generation sequencing of DNA from biopsy specimen after disease progression.

Genes	Mutation sites	Frequency, %	Amplification (copy no.)
HER2			23.69
PIGF			3.6
ACAD5B	G360A	12.61	
AXIN1	T332S	39.39	
ARID1A	P65Rfs*36	72.87	
CD79A	W34R	25.52	
CDKN2A	151-1G>T	50.78	
CREBBP	D539G	19.31	
FAT1	G1318	24.81	
FLT3	W105C	23.4	
IRF4	G314V	47.34	
KIT	A621S	36.94	
KEAP1	R234P	75.63	
KMT2A	G2409V	71.49	
NOTCH1	P2199S	44.87	
PIK3CA	E218Tfs*7	13.17	
PRKCI	I124L	14.52	
PRKCI	Y125C	14.61	
RPTOR	M280V	35.67	
TP53	G154V	67.9	
WT1	G216R	57.51	

Discussion

Pyrotinib, a pan-ErbB blocker, has shown activity against EGFR (IC_{50}, 5.6±3.9 nM), HER2 (IC_{50}, 8.1±2.3 nM) and ErbB4 (11). By covalently binding with ATP-binding sites of intracellular kinase regions, pyrotinib inhibits the formation of homologous/heterodimer and auto-phosphorylation of HER family members, thus blocking the activation of the RAS/RAF/MEK/MAPK and PI3K/AKT signaling pathways and restricting tumor development (11). Based on the results of a phase II trial, the drug was conditionally approved in August 2018 in China for combination with capecitabine in patients with HER2-positive advanced or metastatic breast cancer previously treated with anthracyclines or taxane-based chemotherapy (12); however, it has not yet been approved by the US Food and Drug Administration. Second-line therapy with pyrotinib was found to be superior to lapatinib in patients with breast cancer previously treated with trastuzumab [progression-free survival (PFS): 18.1 vs. 5.6 months, respectively], probably due to the fact that pyrotinib targets more signaling molecules compared with lapatinib, which only acts on EGFR and HER2 (13,14). However, to the best of our knowledge, whether pyrotinib is effective in patients with lung

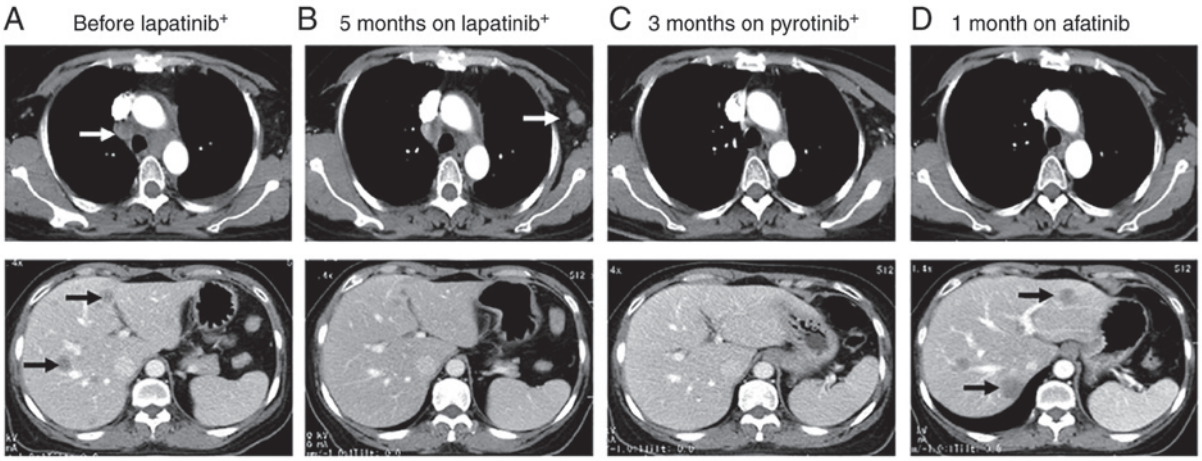

Figure 1. A 53-year-old female Chinese non-smoker was diagnosed with stage IV adenocarcinoma of the left lung with HER2 amplification on next-generation sequencing. CT images of the chest (upper panels) and upper abdomen (lower panels) are shown. (A) CT scan after two cycles of pemetrexed plus platinum revealed mediastinal lymph node metastasis and liver metastasis. After one cycle of albumin-conjugated paclitaxel, platinum and bevacizumab, the patient was treated with lapatinib plus chemotherapy. (B) The patient achieved partial response after treatment with lapatinib plus chemotherapy; however, 5 months later, the disease progressed with left axillary lymph node metastasis. (C) The patient achieved complete response 3 months after pyrotinib plus chemotherapy. (D) The disease started to slowly progress 6 months after pyrotinib therapy. The regimen was switched to afatinib; however, one month later, the disease progressed with the appearance of new hepatic lesions. Arrows, target lesions; +, plus chemotherapy.

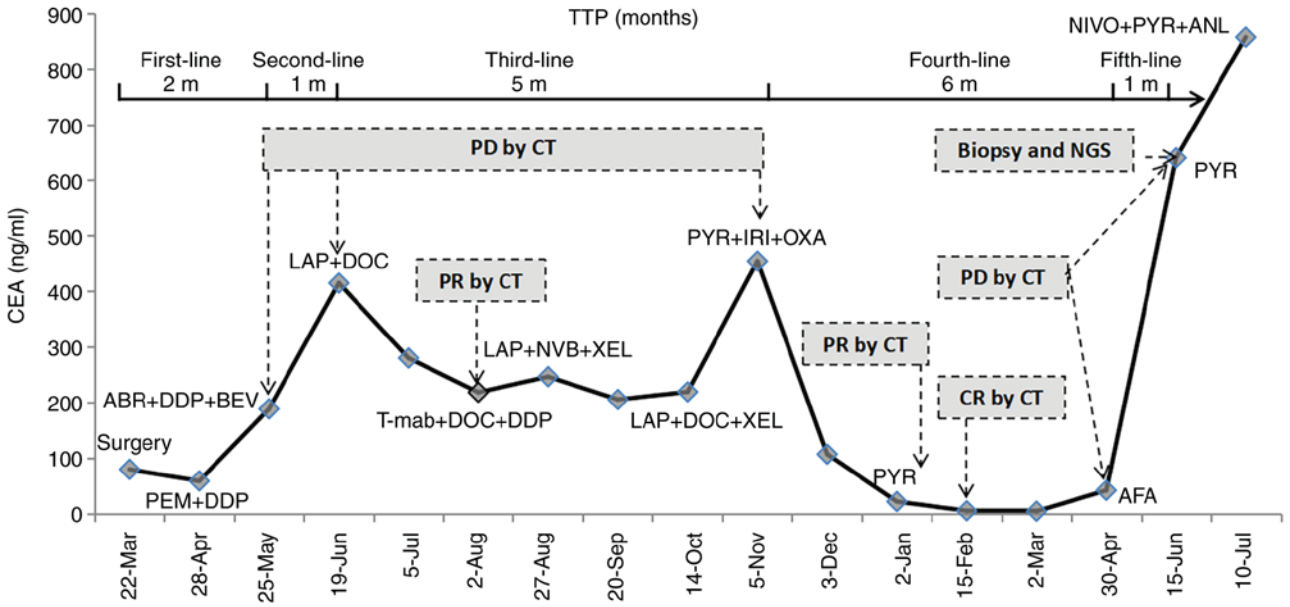

Figure 2. Changes of CEA levels over time. PEM, pemetrexed; DDP, cisplatin; ABR, abraxane; LAP, lapatinib; DOC, docetaxel; T-mab, trastuzumab; NVB, navelbine; XEL, xeloda; PYR, pyrotinib; IRI, irinotecan; OXA, oxaliplatin; AFA, afatinib; NIVO, nivolumab; ANL, anlotinib; TTP, time to progression; PD, progressive disease; CR, complete response; PR, partial response; CEA, carcinoembryonic antigen.

cancer with HER2 amplification has not been reported to date. Experience from breast cancer has shown that some patients who were treated with trastuzumab or lapatinib developed primary resistance to anti-HER2 therapy. Therefore, clinically, in patients with breast cancer, both trastuzumab and lapatinib are administered in combination with chemotherapy in most cases, except for trastuzumab monotherapy in the adjuvant setting. The present case had HER2 amplification with ErbB4 mutation. The patient also harbored a F616L mutation, which is not a classic activating mutation and is unlikely to be responsible for the responsiveness to HER2-targeted therapy. The patient was treated with four different HER2 inhibitors and at least five chemotherapeutic regimens. However, chemotherapy was ineffective during the first- and second-line treatment. The patient achieved PR with lapatinib, but developed primary resistance to trastuzumab. However, pyrotinib was effective, leading to CR, particularly after resistance to lapatinib. Afatinib, which is also a pan-ErbB (EGFR/HER2/ErbB4) inhibitor, has been reported to be effective in a case of bladder cancer with HER2 amplification (15). After progression, the patient in the present case was switched to afatinib. However, the disease rapidly progressed, indicating that afatinib may not be suitable for patients resistant to pyrotinib. Diarrhea is the most common adverse effect observed with tyrosine kinase

inhibitors targeting EGFR/HER2. The incidence of diarrhea in patients treated with pyrotinib plus capecitabine in breast cancer was 96.9%, mainly grade 1-2, with 15.4% of patients developing grade 3 diarrhea (14). The main adverse effect experienced by our patient was also diarrhea, which indicates that the adverse effects of pyrotinib in patients with lung cancer may be similar to those in patients with breast cancer.

HER2 amplification has been implicated as an oncogenic driver in lung cancers by The Cancer Genome Atlas (16). Although therapy targeting HER2 amplification or protein overexpression in lung cancer has long been explored, it is far less effective compared with breast cancer, and less effective compared with lung cancer with HER2 mutation. The objective response rate (ORR) of trastuzumab plus chemotherapy in lung cancer with HER2 amplification has been reported to be lower compared with that of chemotherapy alone (17,18). Other new agents, including trastuzumab plus pertuzumab [ORR: 12.5% (2/16)] (19) and trastuzumab emtansine [ORR: 0 (0/8); 20% (4/20)] (20,21) exhibited low efficiency in patients with HER2 amplification or overexpression [IHC (3+), FISH (+), or NGS (copy number increased)]. The pan-HER blocker dacomitinib was also found to be ineffective in lung cancer with HER2 amplification (0/4) (22). The use of other tyrosine kinase inhibitors, including lapatinib, niratinib, afatinib and pyrotinib, have not been reported in NSCLC. Anti-HER2 therapy targeting HER2 amplification in lung cancer has been characterized by low efficacy, for which there are possibly two main reasons: First, the HER2 signaling pathway in lung cancer is more complicated compared that in breast cancer. As HER2 does not have a known endogenous ligand for its extracellular domain, it activates downstream signaling pathways by forming heterodimers with other ErbB family receptors (23). Other ErbB family members (for example, ErbB4 mutation in this case) affect HER2 signaling, and targeting a single signaling molecule is not sufficient in lung cancer with HER2 amplification. Second, concurrent gene mutations in lung cancer contribute to the poor efficacy of HER2 therapy. In addition to HER2 amplification, the present case had a TP53 mutation in the early stage of therapy and a KEAP1 mutation in the resistance stage. Concomitant TP53 or KEAP1 mutations have been reported in patients with EGFR mutations (24-26). The PFS of patients with these mutations receiving EGFR tyrosine kinase inhibitors was significantly shorter compared with that of patients without mutations. It was hypothesized that TP53 mutation contributed to the shorter TTP in our patient in the first- and subsequent second-line anti-HER2 therapy. Thus, HER2 amplification or overexpression as a single parameter is an insufficient predictive biomarker in NSCLC.

There are currently no reports on the resistance mechanism of pan-ErbB blockers in HER2-amplified NSCLC. The resistance mechanism of lapatinib and niratinib in HER2-amplified breast cancer has been reported to be associated with bypass activation, such as HER2 mutations and mutations in other ErbB family genes (27). In the present case, the inferred resistance mechanisms are as follows: The first is the insufficient ability to inhibit the HER2 signaling pathway, as the copy number of HER2 was higher than before and there was a mutation of PIK3CA. The second is bypass activation, which includes mutations in CDKN2A, Notch1 and KEAP1. However, it does not appear to be associated with mutations in the ErbB family gene.

Our current case suggests that the development of novel drugs may offer new and effective therapeutic regimens for lung cancer with HER2 amplification. Clinical trials or studies should be conducted to investigate the efficacy of novel therapeutic regimens for lung cancer with HER2 amplification.

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Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available due to protection of patient privacy and biosecurity reasons, but are available from the corresponding author on reasonable request.

Authors' contributions

KG and XY made the diagnosis and wrote the manuscript. YY, HH and XK created the tables and figures. KG and YY treated and followed up the patient, and they have also seen and can confirm the authenticity of all the raw data. All the authors have read, carefully revised and approved the final version of this manuscript.

Ethics approval and consent to participate

The present case report was approved by the Ethics Committee of Daping Hospital, Army Medical University, Chongqing, China [no. 2019(116)]. Written informed consent was obtained from the patient.

Patient consent for publication

Written informed consent was obtained from the patient for publication of the case details and any associated images.

Competing interests

The authors declare that they have no competing interests.

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