Case Report

Pyrotinib in the treatment of advanced lung adenocarcinoma with *HER2* exon 20 mutation: a case report and literature review

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Abstract: The lung cancer poses a great threat to the patients' health and social activities. Luckily, epithelial growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) have greatly improved the response of patients getting EGFR-mutated non-small cell lung cancer (NSCLC), but the targeted therapy of human epidermal growth factor receptor 2 (*HER2*) mutations in lung cancer is still being explored; however, the effectiveness of drugs for *HER2*-mutant NSCLC is unsatisfactory. This article reported the diagnosis and treatment of a case of advanced lung adenocarcinoma with erb-b2 receptor tyrosine kinase 2 (*ERBB2*, also known as *HER2*) exon 20 mutation. A 65-year-old women received concurrent chemoradiotherapy postoperatively after a lesion was found in her lung. A new metastatic lesion then appeared in the lung 8 months later and she diagnosed with stage IV lung adenocarcinoma; The gene detection found the patient carried a non-frameshift insertion mutation of *HER2* exon 20, According to the test result, the patient received pyrotinib, and the new lesion in the lung disappeared soon. The progression-free survival (PFS) of the patient was up to 26 months. The clinical study reported a such successful application of pyrotinib in a patient with *HER2*-mutated advanced lung adenocarcinoma, the case indicated that pyrotinib may provide a longer survival time for such patients.

Keywords: Lung cancer; human epidermal growth factor receptor 2 (*HER2*); pyrotinib; case report

Submitted Oct 26, 2021. Accepted for publication Dec 20, 2021.
doi: 10.21037/apm-21-3468
View this article at: https://dx.doi.org/10.21037/apm-21-3468

Introduction

Lung cancer is a common malignant tumor, accounting for more than 230,000 illnesses and 130,000 deaths in the United States in 2021 (1). This results a huge burden on society, and also poses a great threat to the health of individuals. The traditional treatment for non-small cell lung cancer (NSCLC) mainly includes surgery, chemotherapy, and radiotherapy; however, these provide limited benefit to patients (2). The emergence of targeted therapy in the 21st century has changed this pattern. A large number of clinical studies have shown that people with genetic mutations will obtain a longer survival time by taking the corresponding targeted drugs (3). However, anti-human epidermal growth factor receptor 2 (*HER2*) therapy has offered limited progress for lung carcinoma patients with *HER2* mutations. Statistically, the incidence of *HER2* mutations in lung cancer only accounts for approximately 3%, and is more common in women, Asians, non-smokers, and lung adenocarcinoma pathologies. A safe and effective approach is urgently needed for these patients (4). And activating mutations of *HER2* have been observed in 1.7% of lung adenocarcinomas (5). Pyrotinib is an orally administered irreversible dual panErbB

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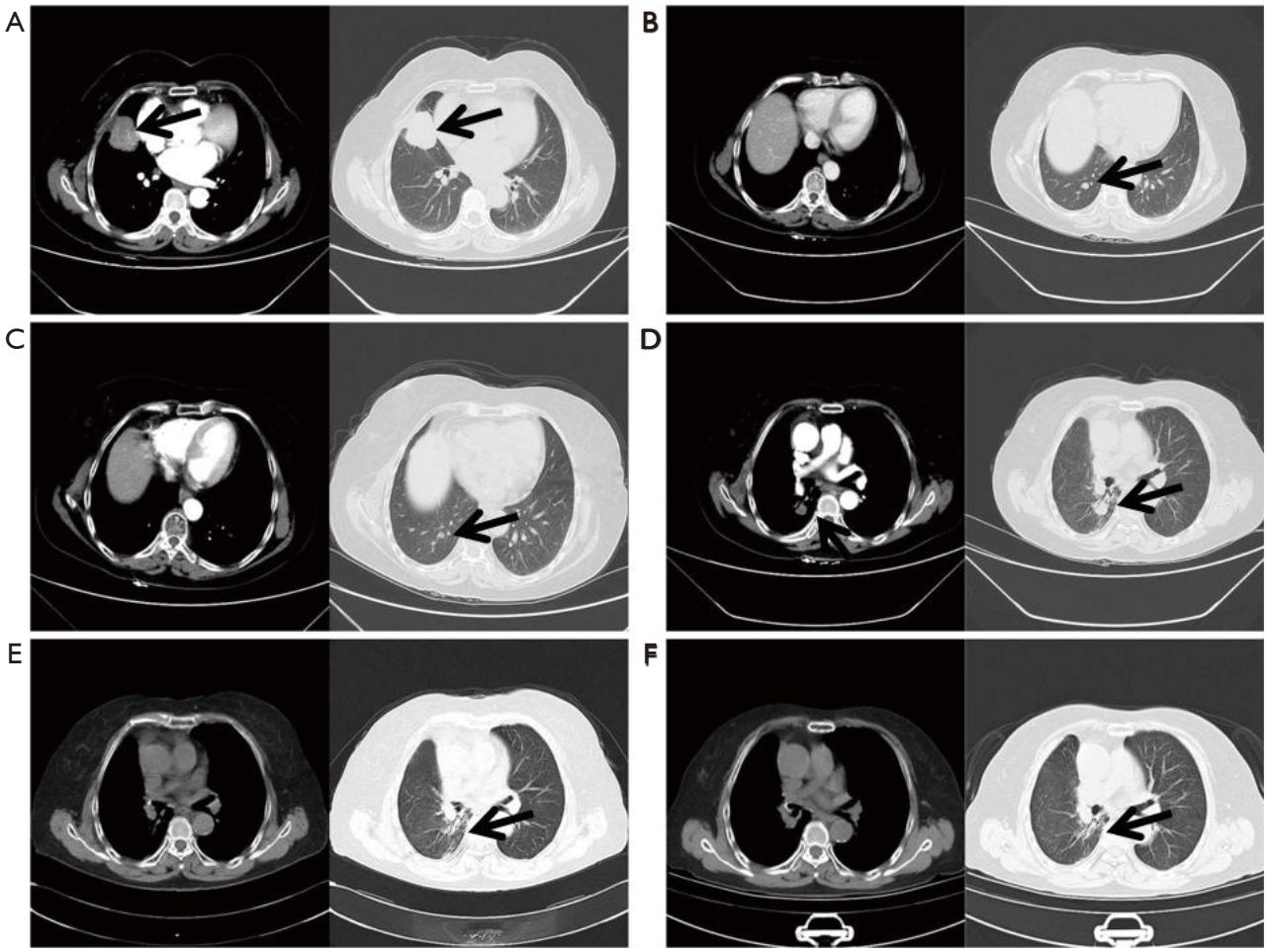

Figure 1 CT scans of the patient before pyrotinib and follow-up after pyrotinib treatment. The meaning of arrows is the location of the lesion. (A) September 27, 2017: physical examination of chest CT, tumor size is 4 cm × 3.5 cm × 3 cm; (B) October 18, 2018: new lesion in the lower right lung; (C) January 27, 2019: CT images after treatment of the right lower lung lesion; (D) April 23, 2019: new lesion in the right hilar; (E) November 28, 2019: CT images after pyrotinib treatment; (F) April 26, 2021: CT images during pyrotinib treatment. CT, computed tomography.

tyrosine kinase inhibitor (TKI) developed by Shanghai Hengrui Pharmaceutical (a subsidiary of Jiangsu Hengrui Medicine) for the treatment of advanced solid tumors with overexpression of *HER2* (6). In this report, we share the case of a *HER2*-mutant advanced lung adenocarcinoma patient treated with pyrotinib for 26 months who achieved stable disease. We present the following article in accordance with the CARE reporting checklist (available at https://dx.doi.org/10.21037/apm-21-3468).

Case presentation

A mass was found in the right lung of a 65-year-old female through chest computer tomography (CT) on September 27, 2017 (*Figure 1A*). She had 2-year history of hypertension, and did not have any specific history of smoking or malignant tumor. A radical resection of the right middle lung lobe and lymph node dissection was performed on October 5, and pathology results indicated invasive adenocarcinoma with 4 cm × 3.5 cm × 3 cm mass invading the pericardium, as well as one positive lymph node in the third group, visceral pleura, pericardium, and nerves were also invaded. Moreover, a vascular tumor embolism was found. Based on the above pathological results, and combined with the American Joint Committee on Cancer (AJCC) 7th edition guidelines, this patient's

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tumor (T) lymph node (N) metastasis (M) staging was classified as pT3N2M0 (stage IIIA). On October 30, 2017, concurrent chemoradiation was applied [pemetrexed 500 mg/m^2 + cisplatin 75 mg/m^2, every 3 weeks (q3w), four cycles; radiotherapy dose: 95% planning target volume =56 Gy/28 F]. On October 18, 2018, a 0.8 cm solid nodule was discovered in the lower lobe of the right lung (*Figure 1B*) and the carcinoembryonic antigen (CEA) had elevated to 12.69 ng/mL. The patient received four cycles of AP (pemetrexed 500 mg/m^2 + cisplatin 75 mg/m^2, q3w) (*Figure 1C*), followed by four cycles of P (pemetrexed 500 mg/m^2, q3w).

On April 23, 2019, another solid nodule appeared on the right hilar (*Figure 1D*) and the CEA was also elevated to 16.09 ng/mL, but the patient refused chemotherapy. Gene detection was performed via next-generation sequencing using paraffin sections of tissues from the right middle lower mass (*Table 1*), and the result indicated that the patient carried a non-frameshift insertion mutation of *HER2* exon 20 with *HER2*-p. Tyr772 _Ala775dup, and the frequency was 30.9%. She was diagnosed with stage IV lung adenocarcinoma with a *HER2* exon 20 mutation. Pyrotinib (400 mg/qd) was administered and without stopping. At the time of writing this report, the patient's condition was stable (*Figure 1E,1F*). The patient has experienced one side effect (mild diarrhea). *Figure 2* shows the entire treatment process. All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

HER2, a member of the EGFR family, triggers a network of downstream signaling pathways and mediates cell division, adhesion, movement, and death when it binds to the *HER2* receptor, resulting in the occurrence of malignant tumors (7). *HER2* mutations have been detected in approximately 2–4% of NSCLC patients, 90% of which are insertions of exon 20 (8). Y772_A775dup mutation accounts for 47.7% and G778_P780dup mutation accounts for 11.6% (9). Our patient, an elderly Asian female with *HER2*-mutant advanced lung adenocarcinoma, carried a common insertion mutation of *HER2* exon 20 with *HER2*-p. Tyr772 _Ala775dup.

It has been reported that the median duration of response (mDoR) of *HER2*-mutant metastatic lung cancer patients receiving anti-*HER2* therapy is only 2.2 months (10). Several pan-*HER* inhibitors, such as afatinib (11), dacomitinib (12), neratinib (13), and poziotinib (14) provide limited efficacy. The fifth edition of the 2021 NCCN guidelines recommends T-DM1 and DS-8201 as targeted therapies for *HER2*-mutant NSCLC; however, treatment is limited due to the unavailability of drugs. Pyrotinib is a new type of irreversible TKI, which shows a strong anti-tumor effect to inhibit cell proliferation, leading to *HER2* overexpression *in vivo* and *in vitro* (15,16). A phase 3 clinical trial (17) found that *HER2*-mutant metastatic breast cancer patients treated with trastuzumab and taxanes before receiving pyrotinib plus capecitabine had significantly improved progression-free survival (PFS) compared with those receiving lapatinib plus capecitabine (12.5 *vs.* 6.8 months, respectively). Therefore, pyrotinib has been approved as a second-line treatment for *HER2*-positive metastatic breast cancer in China. It behaves well in breast cancer and also provides positive results in *HER2*-positive lung cancer. In a phase II trial, 15 *HER2*-mutant advanced NSCLC patients treated with pyrotinib had an objective response rate (ORR) of 53.3% and a median overall survival (mOS) of 6.4 months (18). In another phase II study (19), patients with stage IIIB and IV *HER2*-mutant lung adenocarcinoma treated with platinum-based chemotherapy prior to being enrolled to receive pyrotinib had a PFS of 6.9 months and a mOS of 14.4 months. In the 2021 ASCO online annual meeting (20), it was reported that the ORR of applying pyrotinib combined with apatinib for *HER2*-mutant advanced NSCLC reached 45.5%, and the ORR of patients with brain metastases was 46.2%. The above research illustrates the feasibility of pyrotinib for the treatment of *HER2*-mutant NSCLC.

Moreover, the side effects of pyrotinib are controllable. Treatment-related adverse events (TRAEs) of any grade were reported in 59 patients (98.3%), with most of these being grades 1 or 2. The most common TRAEs were diarrhea (91.7%), elevated blood creatinine (30.0%), vomiting (28.3%), elevated alanine aminotransferase (15.0%), and elevated aspartate aminotransferase (15.0%). Grades 3–4 TRAEs occurred in 17 patients (28.8%), and the most common TRAE was diarrhea (17), which usually occurred on the fourth day and remained for 2–3 days after taking pyrotinib. Symptomatic treatment or reducing the dose of pyrotinib was found to relieve symptoms. For our

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Table 1 Genes in April 2019

Gene	Type of mutation	Nucleotide changes	Amino acid changes	Frequency	Chromosome	Exon
ERBB2	Non-frameshift insertion mutation	C. 2313_2324dup	p. Tyr772 _Ala775dup	30.9%	17	20|27
TP53	Missense mutation	c. 584T>C	P. Ile195Thr	19.7%	17	6|11
KRAS, EGFR, BRAF	No mutations					
ALK, ROS1, RET	No gene fusion					
MET	No gene amplification/gene mutation					

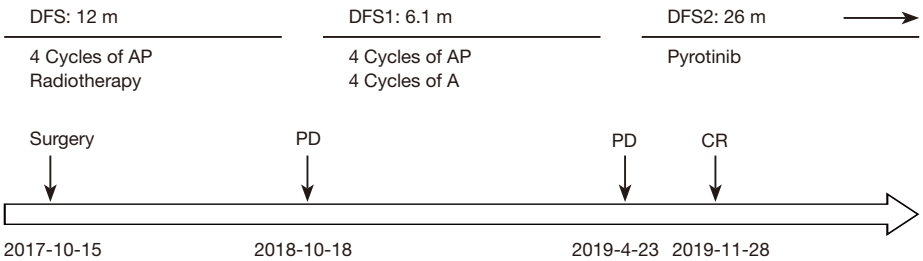

Figure 2 The entire treatment process. DFS, disease-free survival; AP, pemetrexed and cisplatin; PD, progressive disease; CR, complete response.

patient, the side effect was mild diarrhea, and no grade III or IV adverse reactions appeared. Due to the accessibility and benefits of pyrotinib, we applied the new novel generation of targeted drug to the patient. The patient's condition has been stable for over 26 months with mild side effects, and we will continue focus on the patient's treatment. We make a suggestion that pyrotinib might be a potential treatment for patients with *HER2*-positive advanced adenocarcinoma because of the favorable response and clinical benefit.

However, there are some limitations in this study that should be noted. Firstly, although pyrotinib has provided long-term benefits to this patient, the mechanism of pyrotinib resistance and the reason behind *HER2* resistance mutations can be explored if the patient becomes resistant to pyrotinib in the future. Secondly, there are few clinical research statistics on III *HER2*-mutant NSCLC, and further studies should be conducted to demonstrate the efficacy and safety of pyrotinib.

Conclusions

Pyrotinib may provide longer-term survival for *HER2* mutation-positive NSCLC, and needs to be further applied clinically.

Acknowledgments

Funding: This work was supported by Ningbo Science and Technology Bureau of Zhejiang Province (2021S116).

Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://dx.doi.org/10.21037/apm-21-3468

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/apm-21-3468). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and

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accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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(English Language Editor: A. Kassem)

Cite this article as: Luo Y, Yao B, Huang P, Zhao Y, Chen J. Pyrotinib in the treatment of advanced lung adenocarcinoma with *HER2* exon 20 mutation: a case report and literature review. Ann Palliat Med 2021;10(12):12906-12910. doi: 10.21037/apm-21-3468

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