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CASE REPORT

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Efficacy of the apatinib and icotinib combination therapy in the treatment of icotinib-resistant advanced lung adenocarcinoma: A case study

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Competing interests

The authors declare no conflicts of interest.

Abbreviations

HER2: human epidermal growth factor receptor 2; Met: mesenchymal epithelial transition factor; RAS: rat sarcoma; FGFR1: fibroblast growth factor receptor 1; MAPK1: mitogen-activated protein kinase 1 VEGF: vascular endothelial growth factor.

Citation

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Abstract

A patient with advanced lung adenocarcinoma who was unable to tolerate chemotherapy was controlled after combined treatment with apatinib. This case provides a basis for the treatment of this disease using this method. Methods: The diagnosis of patients with lung adenocarcinoma stage IV period, age, detection of EGFR mutations, line for treatment in September there progress, a large number of pleural effusions, the right lung neoplasm, cisplatin and interleukin-2 pleural perfusion chemotherapy, line again. Assessment of the EGFR gene exon 20 single did not identify a missense mutation (T790M not mutation). Patients with high collar, poor health, refused chemotherapy. Subsequently, we administered oral treatment of apatinib at 250 mg/day. Conclusion: Apatinib combined with EGFR-TKI targeted therapy is effective for lung adenocarcinoma. Moreover, adverse reactions can be controlled.

Key Words: Apatinib, EGFR-TKI, Lcotinib hydrochloride tablets, agedness, lung adenocarcinoma

Introduction

Lung adenocarcinoma is a common type of non-small cell lung cancer, treated mainly by surgery, chemotherapy, and targeted therapy. The recent years brought rapid changes in the use of targeted therapy drugs in response to the increasing occurrence of treatment failures due to drug resistances. Our study describes the case of an elderly female patient with poor constitution, intolerance for intravenous chemotherapy, epidermal growth factor receptor (EGFR) mutations, but without T790M mutation, who developed resistance to icotinib monotherapy. After combining the icotinib with the small molecular antiangiogenic drug, apatinib, her tumor shrank, and her progression-free survival (PFS) has reached 7 months. Our results provided valuable evidence for the clinical application of the small molecular antiangiogenic drug, apatinib mesylate.

Clinical information

On the 22th of June 2017 a 74-year-old female was admitted at our department due to distending pain in the right side of her dorsal region for half a year, with exacerbation during the previous month. The plain and enhanced chest scans performed have found a 5 × 4 cm space-occupying tumor in the right lower lung-lobe, mediastinal lymph node metastases, and pleural effusion in the right hemithorax (Figure 1). The enhanced magnetic resonance imaging of the brain and the systemic bone scan did not reveal any metastases, but the carcinoembryonic antigen (CEA) level was very high (210 ng/ml). During the genetic testing of the pleural effusion, genomic alterations were found in several exons of the EGFR： E18(wild-type), E19 (mutant), E20-1, E20-2, E20-3 (wild-type), E21-1 (wild-type), E21-2 (wild-type) and the microscopical exam of the fluid has found adenocarcinomatous cells. The definitive diagnosis was lung cancer (right, adenocarcinoma, peripheral, cT2N2M1a stage IV), EGFR-TKI mutation. For a period of eight months (from the 22th of June 2017 to the 27th f February 2018) the patient received oral icotinib in doses of 125 mg, three times per day (tid). At the subsequent reexamination her computed tomography (CT) chest scan showed a slight reduction in the tumor's size (reduced by 4.8 cm) and decrease of the pleural effusion quantity, warranting the diagnosis of stable disease. Also, the CEA level lowered to 15 ng/ml (Figure 2). The main adverse reactions to the icotinib treatment included facial rash, constipation, and mild oral mucositis. No significant myelosuppression was seen and the hepatic and renal functions were normal. Because the patient complained about the exacerbation of chest tightness and shortness of breath for the following month, another chest CT was performed on the 30th of March 2018 revealing a large quantity of pleural effusion and atelectasis of the right lung, without distal metastases (Figure 3). Also, the CEA level increased again, to 243 ng/ml. The genetic testing of the sample obtained from the pleural fluid drained by right side thoracentesis diagnosed the absence of the T790M mutation. Three doses of Cisplatin (30 mg/dose) andinterleukin-2 (160IU/mL) were administered by intrathoracic perfusion, a few days apart (biw), which led to the decrease of the pleural effusion. Because the patient has not tolerated the intravenous chemotherapy (due to her old age and poor constitution), a combination therapy with icotinib (125mg three times pei day (tid)) and apatinib mesylate (250 mg/dose, qd) treatment was decided. The follow-up reexamination, two weeks later (on the 14th of April 2018) (Figure 4), found a slight reduction in the tumor size, decreased pleural effusion, and CEA 57 ng/ml, thus the patient's state was described as partial remission. The second follow-up exam, on the 20th of August 2018, showed the complete resorption of the pleural

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effusion, a marked decrease in the tumor size (reduced by 3 cm) (Figure 5), and the tumor marker (CEA) decreased to 10 ng/ml. The patient did not undergo any subsequent reexamination. The main adverse reactions of the combination therapy included hypertension but with the normalization of the blood pressure after ACER or ARD drug treatment; hand-foot syndrome, and proteinuria. Myelosuppression and gastrointestinal reactions were absent.

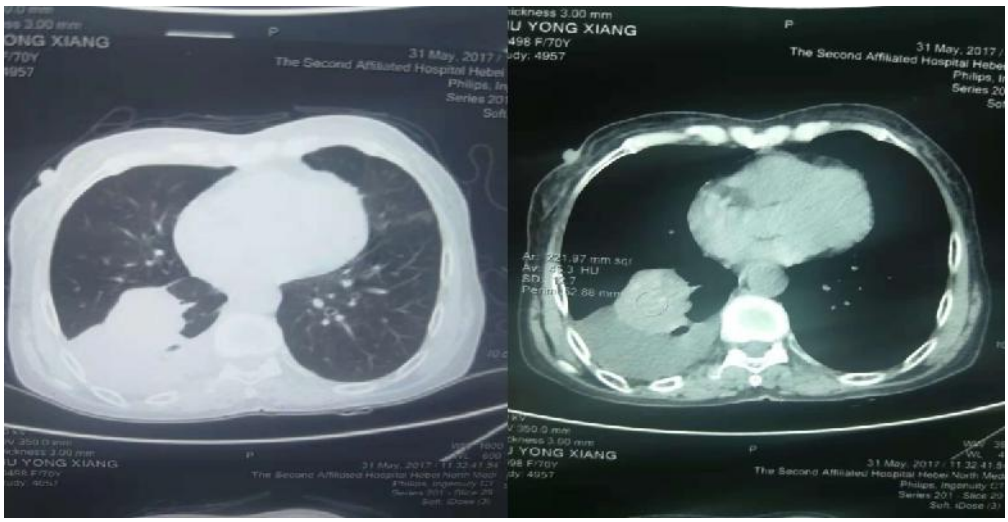

Figure 1: Before treatment (05-31-2017)

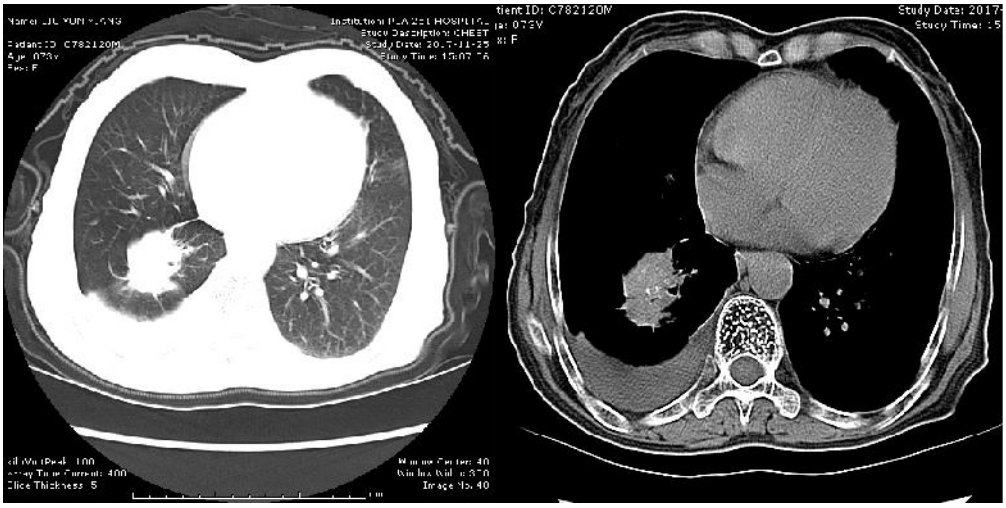

Figure 2: After treatment (11-02-2017)

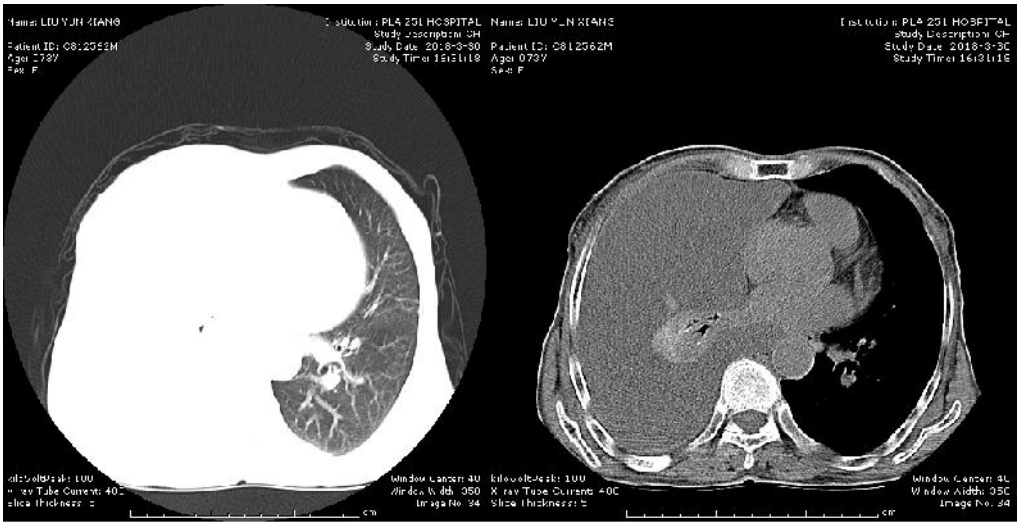

Figure 3: Date 03-30-2018

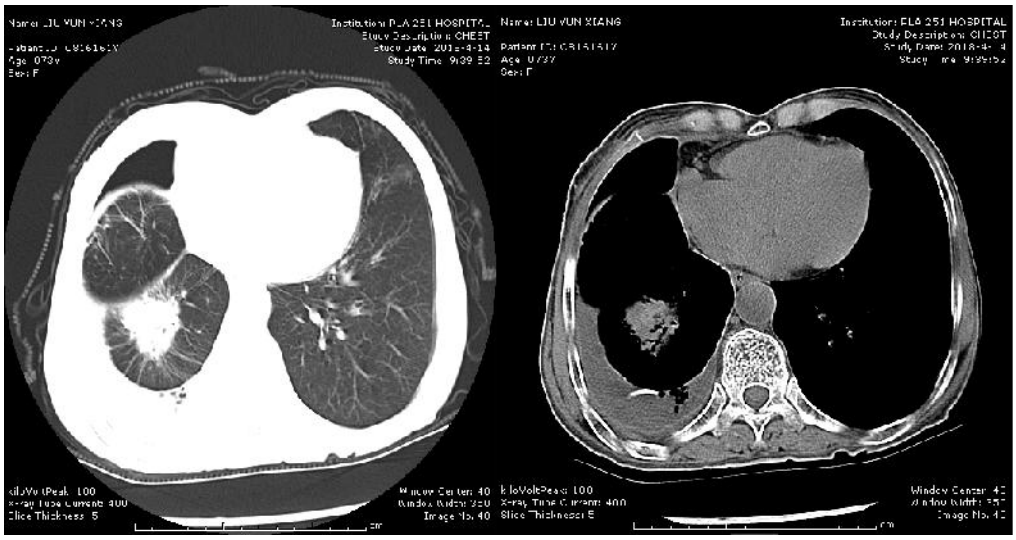

Figure 4: After intrathoracic perfusion (04-14-2018)

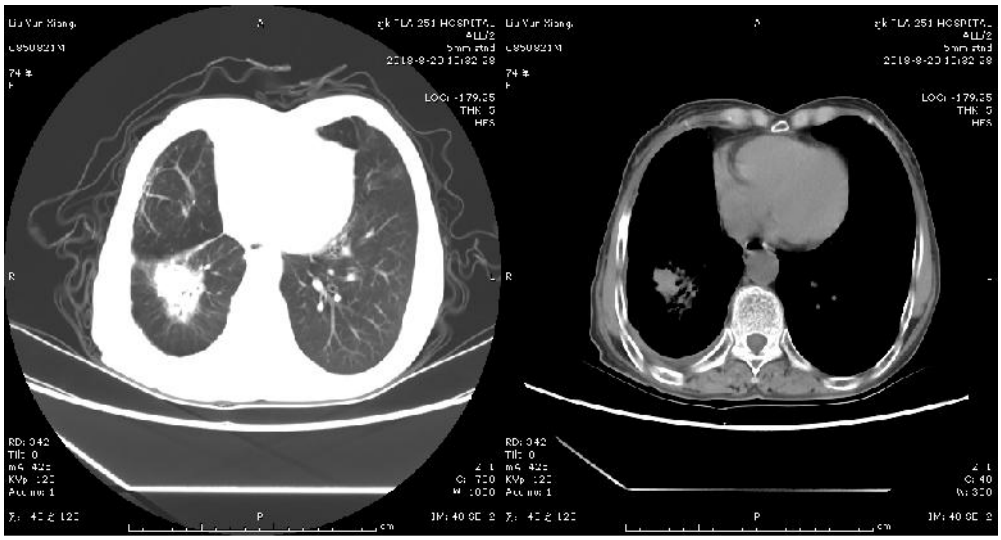

Figure 5: After combination therapy with icotinib and apatinib (08-20-2018)

Table 1 Tumor sizes （dates）

	03-30-2018	04-14-2018	08-20-2018
Primary lesion (cm)	5 × 7	4 × 3	2 × 3.3
Pleural effusion	Large quantity	Quantitative reduction	Further quantitative reduction
Tumor marker (ng/ml)	243	57	10
Distal metastases	Absent	Absent	Absent

Discussion

Lung adenocarcinoma accounts for 80% of non-small cell lung cancers (NSCLC) and its biological characteristics are slow growth, early metastasis, and low sensitivity to chemotherapy and radiotherapy. Advanced NSCLC has a natural disease course of 4–6 months. According to surveys [1], the prevalence of female Asian non-smoker lung adenocarcinoma patients with genetic mutations is 60%. Mutations in the EGFR tyrosine kinase domain mainly occur at exons 19–21, of which the mutations in exons 19 and 21 are more important. In particular, the positive exon 19 mutation suggests good efficacy of the molecular targeted drugs. The epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) drugs are recommended as first-choice therapy for elderly advanced NSCLC patients with EGFR mutations [2].

Icotinib hydrochloride is a small molecular EGFR-TKI targeted antineoplastic drug with complete intellectual property rights in China. The median PFS of icotinib is 137 days and the median time to progression is 154 days, demonstrating the efficacy of icotinib. The main reason for tumor progression is resistance to targeted therapy drugs. Most patients who receive first- and second-generation EGFR-TKI will develop resistance after 10–12 months. The most common drug resistance mechanism is a missense mutation in exon 20 of EGFR (T790M mutation). At present, third-generation EGFR-TKIs targeting the T790M mutation include AZD9291, HM61713, CO-1686. However, patients will develop drug resistance after 10 months of treatment with third-generation EGFR-TKIs [3]. Another drug resistance mechanism is C-Met. Currently, the phase I clinical trial on C-Met inhibitors has started and shown clear efficacy. In future phase

II clinical trials, patients with C-Met amplification or overexpression will be specifically selected and the efficacy of C-Met inhibitors is expected to be 40% and above. In addition, drug resistance mechanisms also include alternative pathway activation, including human epidermal growth factor receptor 2 (HER2) and mesenchymal epithelial transition factor (Met) amplification, v-raf murine sarcoma viral oncogene homolog B1 (BRAF) V600E mutation, rat sarcoma (RAS) mutation, fibroblast growth factor receptor 1 (FGFR1) amplification, phosphatase and TENsin homolog (PTEN) deletion, and mitogen-activated protein kinase 1 (MAPK1) amplification. The last mechanism consists in pathological changes but this is rare.

Apatinib mesylate is an oral small molecule antiangiogenic drug that exhibits highly selective inhibition of the tyrosine kinase activity on the vascular endothelial growth factor receptor 2 (VEGFR-2) and blocks the signaling pathway after the vascular endothelial growth factor (VEGF) binds to its receptor. This strongly inhibits tumor angiogenesis, resulting in antineoplastic effects. VEGF is the most potent growth factor that acts directly on vascular endothelial cells known so far, is the most important factor in many angiogenesis signaling pathways, and it is intimately associated with tumor progression [4]. A phase III clinical trial published in 2018 by the American Society of Clinical Oncology showed that antiangiogenic treatment combined with TKI can effectively improve the PFS of patients. Currently, treatments targeting tumor angiogenesis have become an important strategy in tumor treatment. The clinical applications of apatinib are broad and effective in many tumors, including NSCLC and small cell lung cancers. Combination therapy with apatinib was effective in the studied patient who developed resistance to oral EGFR-TKIs: the tumor decreased in size, the quantity of pleural effusion reduced, and the patient's life quality increased. This efficiency was based on three factors: (1) Apatinib is effective against the NSCLC itself through the inhibition of common downstream signaling pathways. The production of malignant pleural effusion may be due to pleural invasion by the malignant tumor or pleural metastases, tumor angiogenesis, active VEGF, tumor growth, and changes in tumor vasculature basic structure and genes. Hence, inhibiting VEGF can have antineoplastic effects and control pleural effusion. (2) Apatinib combined with TKI has synergistic effects: TKIs mainly target tumor cells while antiangiogenic drugs mainly target the tumor microenvironment, especially a decrease in tumor neovascularization, leading to the normalization of the tumor's vasculature. (3) Reversal of TKI resistance: Apatinib can inhibit the growth of tumor blood vessels, improving the tumor microenvironment, which has cross-talk effect with inhibitory signaling pathways. Therefore, the clinically observed synergistic effects of apatinib and TKI prove the theoretical basis for the TKI resistance reversal. Professor Xia Song of Shaanxi Provincial Cancer Hospital reports that TKI combined with apatinib had an efficacy of 20% and disease control rate of 100% in 18 advanced lung cancer patients with TKI resistance. According to the above studies, the small molecular antiangiogenic drug (apatinib mesylate) combined with the original TKI treatment has improved efficacy in elderly lung adenocarcinoma patients without T790M mutation and the adverse reactions are few.

In conclusion, apatinib combined with EGFR-TKI has shown some efficacy, few adverse reactions, and high safety, thus it can improve the patient's quality of life and prolong asymptomatic survival, all of which makes this combination therapy worthy of promotion.

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