Case Report

Apatinib for EGFR-TKI and chemotherapy refractory in an advanced lung cancer patient: a case report

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Submitted Apr 09, 2018. Accepted for publication Jun 01, 2018.
doi: 10.21037/jtd.2018.06.136
View this article at: http://dx.doi.org/10.21037/jtd.2018.06.136

Introduction

In China, primary lung cancer is one of the most common malignant tumors. The data of China Cancer Center in 2015 showed that the prevalence of lung cancer was 130.2 (1/10 million) from 2006 to 2011 in China. And lung cancer has risen to be the fourth leading cause of death (1). Most patients have distant metastasis when they get initial diagnosis. Despite the rapid development of targeted and chemotherapeutic drugs, there is no standard treatment option after the patients are treated with multiple lines therapy. Apatinib is a new type of small molecule tyrosine kinase inhibitor (TKI) developed by China. It has been approved to selectively bind to vascular endothelial growth factor receptor 2 (VEGFR-2). By inhibiting VEGFR-2, apatinib could decrease VEGF-mediated endothelial cell migration, proliferation, and tumor microvascular density (2-4). A Phase III trial of Apatinib in patients with chemotherapy-refractory advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction showed that median OS was significantly improved in the apatinib group compared with the placebo group (6.5 *vs.* 4.7 m, P=0.0149), PFS was 2.6 *vs.* 1.8 m (P<0.001) (5). A phase II clinical trial showed that apatinib compared to the placebo group, the median PFS was significantly prolonged (4.7 *vs.*1.9 months, P<0.001) after the failure of more than two lines of treatment in NSCLC (6). It is also applied to other solid tumors in clinic work. This case is about one patient treated with apatinib for EGFR-TKI and chemotherapy refractory in an advanced lung cancer patient.

Case presentation

The patient was female, 60 years old, with no other disease and no smoking history. She was admitted for dry cough and chest pain. The chest computed tomography (CT) showed the right lung occupation and pleural metastasis on Jun 2012. Bronchofiberscope was performed and pathological examination revealed adenocarcinoma of the lung (*Figure 1*). Detection of EGFR gene by tissue showed deletion of exon 19. The patient received several chemotherapy regimens and target therapy for eight lines until 14th Dec 2015 (*Table 1*). At that time, the patient had an Eastern Cooperative Oncology Group performance status (ECOG) of 2. So she received apatinib at the minimum dose of 250 mg/d. One month later, the chest CT scan showed the intrapulmonary occupation and the pleural metastasis were significant reduction. Symptoms including the cough and chest pain gradually decreased and the score of ECOG was significantly improved. The patient continued apatinib as maintaining therapy and received CT scan every 6 weeks. The effect was maintenance partial response (PR) until 24th Dec 2016 (*Figure 2*). The ninth-line progression free survival (PFS) was 12 months. But the patient kept taking apatinib until Aug 2017, the lesions were extending gradually (*Figure 3*). The patient died on Oct 2017, the overall survival (OS) was nearly 5 years. During administration of apatinib, the patient experienced grade 3 hypertension. The blood pressure increased to a maximum of 180/100 mmHg. Valsartan and nifedipine were administered and the blood pressure returned to a normal level. The patient got grade 4 platelet count

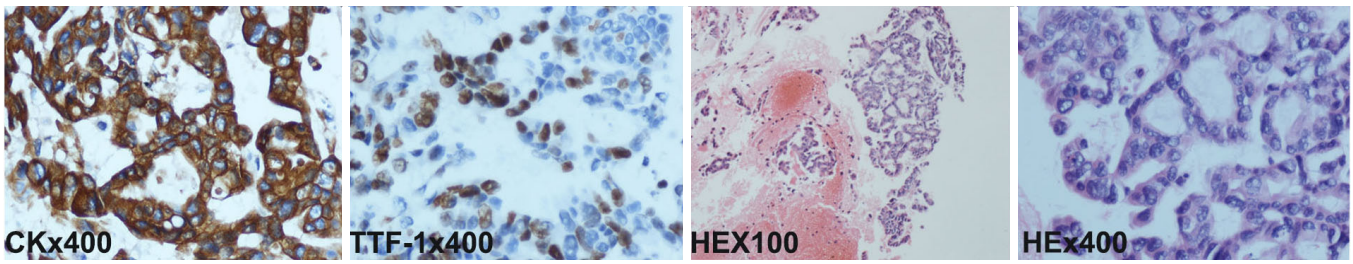

Figure 1 Histopathological and immunohistological findings of the primary lung. The original lung tumor was confirmed to be adenocarcinoma according to the typical morphology and positivity of thyroid transcription factor 1 (TTF1) and cytokeratin (CK) 7. Hematoxylin and eosin staining (HE) showed well-differentiated adenocarcinoma.

Table 1 Previous treatments from first-line to eight-line

Line	Regimen	Starting time	Ending time	Effect	PFS (m)
1st	Gemcitabine + cisplatinum	19th Jul 2012	25th Oct 2012	PR	4
2nd	Docetaxel	22th Nov 2012	12th Jan 2013	PD	2
3rd	Gefitinib	19th Jan 2013	8th Dec 2014	PR	23
4th	Vinorelbine	9th Dec 2014	10th Feb 2015	PD	2
5th	Pemetrexed	16th Feb 2015	3rd Apr 2015	PD	2
6th	S-1	7th Apr 2015	2nd Jun 2015	PD	2
7th	Osimertinib	18th Jun 2015	24th Oct 2015	PD	4
8th	Retrexed	3rd Nov 2015	14th Dec 2015	PD	2

PFS, progression-free survival; PR, partial response; PD, progressive disease.

decreased (15×10^9/L) after she took apatinib for 90 days. By stopping drug and treating with recombinant human thrombopoietin, the platelet count recovered. The patient also got proteinuria. The urine routine test showed the urinary protein was up to 3+ and the 24 hours total urine protein was 2.8 g. By taking calcium dobesilate capsules and Shenfukang capsules, the urinary protein fluctuated 1+ ~2+ and the 24 hours total urine protein fluctuated 0.6–2.0 g. Other adverse effects included grade 1 oral mucositis and grade 1 palmar-plantar erythrodysesthesia syndrome (*Figure 4*).

Discussion

Advanced non-small lung cancer (NSCLC) has poor progress. The median PFS is usually no more than one year. About 30–70% patients can receive more than second-line chemotherapy (3). But there are no standard recommendations for subsequent lines of therapy.

Tumor angiogenesis is a key link in the process of tumor growth and metastasis (7,8). Both vascular endothelial growth factor receptor (VEGFR) and vascular endothelial growth factor (VEGF) play an important role in the process of tumor angiogenesis (9). Bevacizumab combined with chemotherapy has been recommended as a standard treatment for advanced lung adenocarcinoma as first-line therapy. Many clinical trials attempt to evaluate the efficacy of antiangiogenic agent alone on second-line and subsequent lines of therapy in advanced NSCLC. But most of the results did not reach the positive end points (*Table 2*). In China, apatinib is a new small molecule TKI, it has been approved for the treatment for gastro-esophageal adenocarcinoma or advanced gastric adenocarcinoma as three lines or more than three lines choice. In phase I clinical trials, the maximum tolerated dose of apatinib was 850 mg/day and the recommended dose was 750 mg/day. In this case, the patient was treated with apatinib at 250 mg/d, but she still got 12 months PFS after several lines treatments

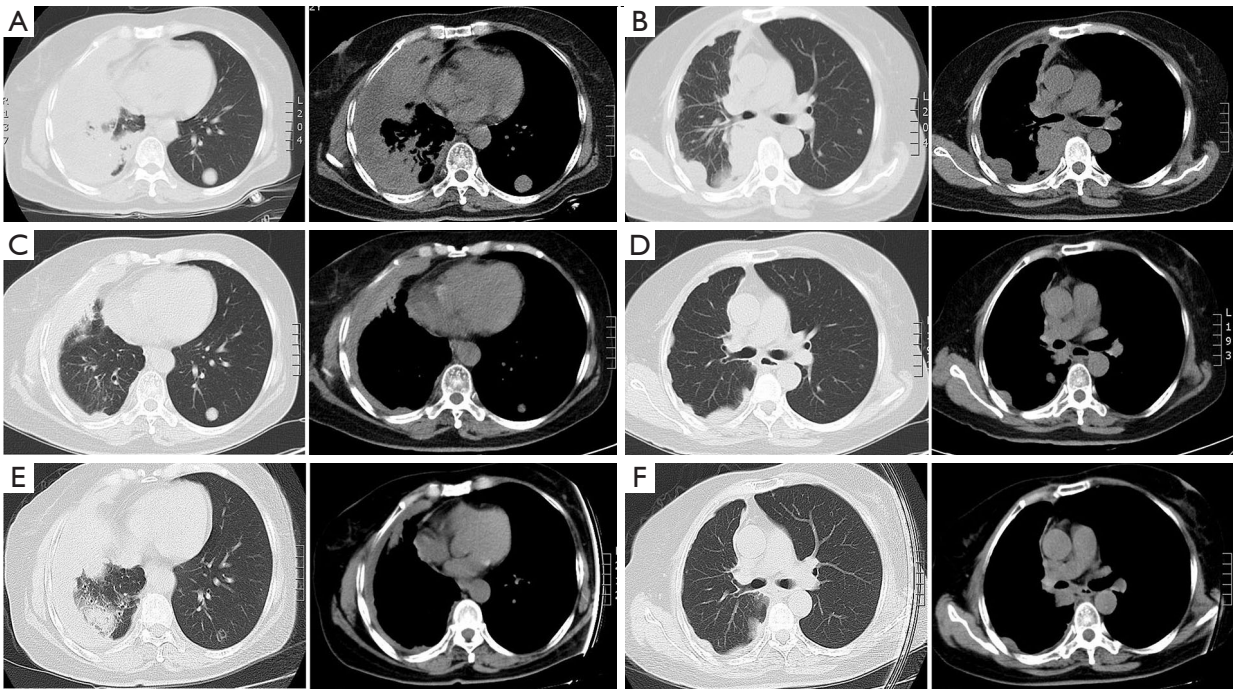

Figure 2 Sequence of the patient's anticancer treatment with apatinib before and after therapy. Chest CT baseline scan showed the right lung occupation and pleural metastasis on 3rd Nov 2015 (A,B, including lung window and mediastinal window). After treated with apatinib, chest CT scan showed PR on 31th March 2016 (C,D) and on 1st Sep 2016 (E,F).

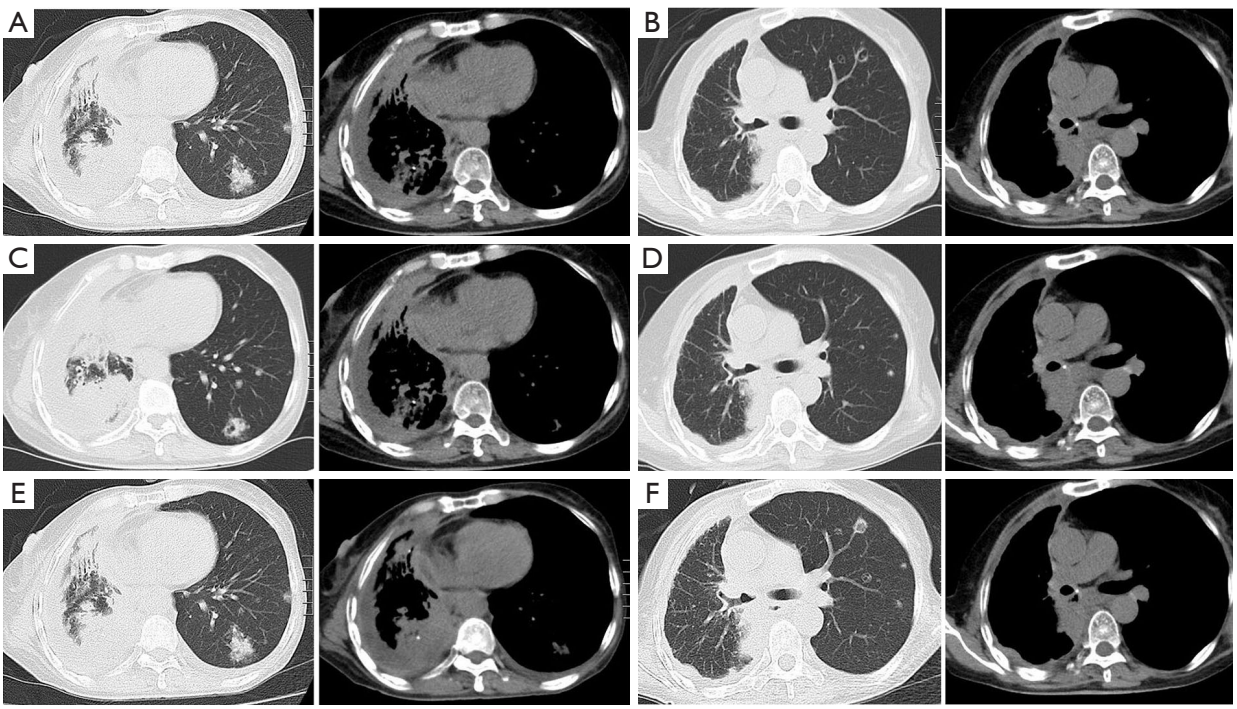

Figure 3 Sequence of the patient's anticancer treatment after PD of apatinib. Chest CT scan showed PD on 24th Dec 2016 (A,B). The patient continued taking apatinib. Chest CT showed lung occupation and pleural metastasis gradually progressed on 13th Mar 2017 (C,D) and on 14th Jul 2017 (E,F) which was three months before the patient died.

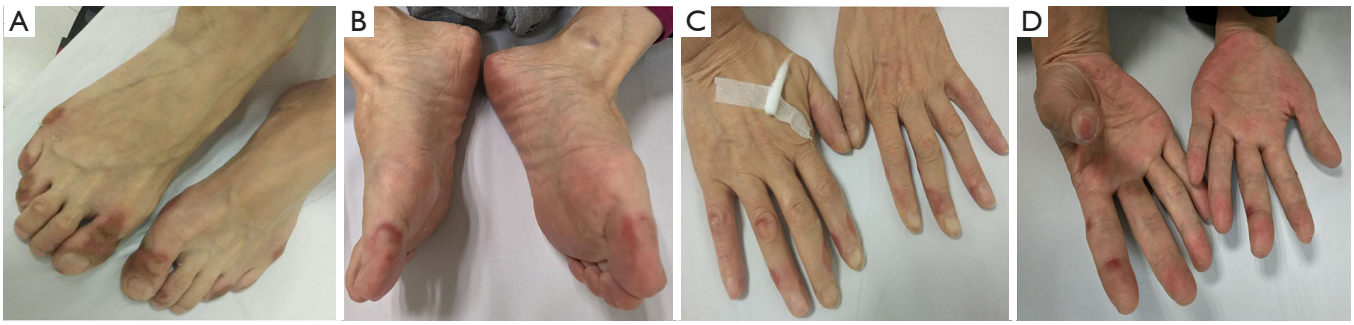

Figure 4 The patient had grade 1 palmar-plantar erythrodysesthesia syndrome: hands and feet scattered in the red spot accompanied by peeling but no pain.

Table 2 Clinical trials about antiangiogenic agent alone on second-line and subsequent lines of therapy in advanced NSCLC

Clinical Trials Identifier	Phase	Patient	Line	N	Experimental arm	Control arm	ORR/DCR	mPFS/ mTTP	mOS	PE, P value
NCT01270386 (6)	Phase II	NSCLC non-squamous	≥3	135	Apatinib	Placebo	68.9% *vs.* 24.45%	4.7 *vs.* 1.9 m	Results not yet	DFS, P<0.01
NCT01287962	Phase III	NSCLC non-squamous	≥3	480	Apatinib	Placebo	–	–	–	ORR
NCT03376191	Real word	NSCLC non-squamous	No limited	100	Apatinib	–	–	–	–	PFS
NCT00549328 (10)	Phase II	NSCLC	≥3	14	Pazopanib	–	–	No formal efficacy analyses	No formal efficacy analyses	DCR, 13%
NCT01049776	Phase II	NSCLC	≥3	32	Pazopanib	–	–	Results not yet reported	Results not yet reported	DCR, 38%
NCT01262820	Phase II	NSCLC	≥2	15	Pazopanib	–	0%	10.9 m	24.1 m	DCR, 13%
NCT00284141 (11)	Phase II	NSCLC	≥3	98	Aflibercept	–	–	2.7 m	6.2 m	ORR, 2%
NCT00404924 (12)	Phase III	NSCLC	≥2	924	Vandetanib	Placebo	3.6% *vs.* 0.7%	1.9 *vs.* 1.8 m	8.5 *vs.* 7.8 m	OS, P=0.527
NCT00364351 (13)	Phase III	NSCLC	≥2	1,240	Vandetanib	Erlotinib	12% *vs.* 12%	2.6 *vs.* 2.0 m	6.9 *vs.* 7.8 m	PFS, P=0.721
NCT00113516 (14)	Phase II	NSCLC	≥2	63	Sunitinib	–	11.10%	12 w	23.4 w	ORR, 11.1%
NCT00517790 (15)	Phase II	NSCLC	2	139	Linifanib	–	–	3.6 m	9 m	PFS, 33.1%
NCT00863746 (16)	Phase III	NSCLC	3,4	703	Sorafenib	Placebo	4.9% *vs.* 0.9%	2.8 *vs.* 1.4 m	8.2 *vs.* 8.3 m	PFS, P=0.47
NCT00922584 (17)	Phase II	NSCLC	≥2	65	Sorafenib	–	3.10%	3.7 m	7.4 m	ORR, 32.8%
NCT00101413 (18)	Phase II	NSCLC	≤3	52	Sorafenib	–	0%	2.7 m	6.7 m	ORR, 0%

NSCLC, non-small cell lung cancer; mPFS, median progression-free survival; mTTP, median time to progression; OS, overall survival; ORR, objective response rate; DCR, disease control rate; PE, primary endpoint; Plac, placebo; m, month; w, week.

including EGFR-TKI and chemotherapy. There were no serious adverse reactions to affect the treatment compliance of the patient. The patient received gene test for three times. On 24th Dec 2012, detection of EGFR gene by tissue showed 19 exon mutation. On 24th Sep 2015, after gefitinib and several lines of chemotherapy treatments failed, detection of EGFR gene by blood still showed 19 exon mutation but without T790 resistance gene mutation. On 5th Dec 2016, when the patient had disease progression of apatinib, she received multigene test by bood. The result showed no VEGFR-2 amplification and mutation. It showed EGFR-p.Glu746_Ser752 and EGFR-p. Gly724Ser mutations which were EGFR rare mutation genes and were sensitive to EGFR-TKI (19).

Another characteristic of the case was the patient took apatinib for another one year after progression. The lesions progressed slowly. It had reported that some patients could benefit from receiving an EGFR-TKI beyond progression (20). But there were no trials of continuing use of antiangiogenic drugs alone after progression. We consider apatinib may affect other pathways to inhibit the tumor progression. Recently, an *in vitro* study showed that apatinib inhibits cellular invasion and migration in lung cancer cells via suppressing RET/Src signaling pathway (21).

Conclusions

In conclusion, because of the high prices of ramucirumab and nintedanib in China, mono-apatinib might be an option as post second-line treatment in advanced lung adenocarcinoma even at low dose. We believe that with the publication of the results of clinical trials, more evidence will be provided for our clinical application.

Acknowledgements

Funding: This study was supported by National Science and Technology Major Project of the Ministry of Science and Technology of China (No. 2017ZX09304025), Clinical Capability Construction Project for Liaoning Provincial Hospitals (LNCCC-D07-2015), Science and Technology Plan Project of Liaoning Province (No. 2016007010), and the Key Research and Development Program of Shenyang (No. 17-230-9-01).

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Informed Consent: Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

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Cite this article as: Chen Y, Gong J, Zhou H, Qu X, Teng Y, Liu Y, Jin B. Apatinib for EGFR-TKI and chemotherapy refractory in an advanced lung cancer patient: a case report. J Thorac Dis 2018;10(7):E564-E569. doi: 10.21037/jtd.2018.06.136

