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ORIGINAL ARTICLE

Low dosage of apatinib monotherapy as rescue treatment in advanced lung squamous cell carcinoma

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Abstract

Purpose Platinum-based doublet chemotherapy and radiotherapy are the standard treatment option in advanced squamous cell carcinoma patients. However, few agents could be selected for subsequent post-second-line treatment. As a small molecule inhibitor of vascular endothelial growth factor receptor-2 tyrosine kinase, apatinib had been proved in advanced gastric cancer. Here, we showed its efficacy and safety in lung squamous cell carcinoma.

Methods In this retrospective study, 13 advanced lung squamous cell carcinoma patients were enrolled. They received doublet chemotherapy or docetaxel as the first-line treatment. After disease progressed, all patients were administrated apatinib monotherapy (250–425 mg/day) for second-line or fourth-line therapy.

Results After apatinib monotherapy, two patients achieved partial response, four patients achieved stable disease, and seven patients achieved progression disease. The medium PFS was 3.1 months. The median OS had not yet been reached. The objective remission rate was 15.4% (2/13). The total disease control rate was 46.2% (6/13). The main advert effects were vomiting and hypertension.

Conclusion Apatinib might be an option as rescue treatment in advanced lung squamous cell carcinoma.

Keywords Squamous cell carcinoma · VEGFR-2 · Apatinib

Introduction

Non-small-cell lung cancer (NSCLC) accounts for more than 70% of lung cancer. In Asia, epidermal growth factor receptor (EGFR) mutation and anaplastic lymphoma kinase (ALK) rearrangements were common in lung adenocarcinoma patients [1]. However, few lung squamous cell carcinoma patients harbored these genetic driver mutations [2]. The majority of squamous cell carcinoma (SCC) patients are wild type and they cannot be treated with targeted based agents. Therefore, platinum-based doublet chemotherapy and radiotherapy are the standard treatment option in advanced SCC patients [2]. When disease progressed after first-line or second-line chemotherapy, few agents could be selected for subsequent treatment.

Angiogenesis is important tumor growth, development, and metastasis, and represents a key target in lung cancer treatment [3]. Vascular endothelial growth factor (VEGF) signaling, activated VEGF receptor (VEGFR) and then promoted tumor angiogenesis [4]. Recently, drugs targeting VEGF/VEGFR signaling have shown encouraging efficiency in several solid tumors. For example, the antibody against VEGF or VEGFR (bevacizumab or ramucirumab) exhibited encouraging improvement in progression-free survival (PFS) and overall survival (OS) when adding to chemotherapy in advanced nonsquamous NSCLC [5, 6]. Bevacizumab also significantly improved in ovarian cancer and colon cancer patients [7, 8]. However, adenocarcinoma and squamous carcinoma responded differently to anti-angiogenic drugs. Anti-vascular endothelial growth factor (VEGF) treatment might result in life-threatening side effects, often pulmonary hemorrhage in SCC. Up to date, only one kind of VEGF/VEGFR antibody (ramucirumab, a fully human IgG1 monoclonal against VEGFR-2) was approved in SCC treatment, which showing an improvement of 1.3 months of PFS as

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first-line treatment [6]. However, there was little evidence for anti-angiogenesis drugs monotherapy as post-first-line therapy in advanced lung SCC.

Apatinib is an oral small molecule inhibitor of vascular endothelial growth factor receptor-2 (VEGFR-2) tyrosine kinase. Apatinib has been proved the efficiency and safety in breast and gastric cancer therapy [9, 10]. Some recent reports had proved the efficiency of a high-dosage (500–850 mg/day) apatinib in NSCLC patients without driver mutation [11–16]. Our previous studies have proved the efficacy of a lower dosage of apatinib in (250 mg/day) adenocarcinoma patients without driver gene [14, 15]. However, there was no evidence about low dosage of apatinib in SCC patients. In this retrospective study, we showed the efficacy and safety of apatinib at a lower dosage (250–425 mg/day) in 13 advanced lung squamous carcinoma patients.

Materials and methods

All experiments were carried out according to the guidelines set by the the Science Council of China and approved by the research ethics committee of Soochow University Committee. Informed consent was obtained from all participants. A total of 13 patients were enrolled in this retrospective study. All patients were diagnosed pathologically advanced lung squamous carcinoma (IIIb–IV stage) via CT-Guided Percutaneous Lung Biopsy or transbronchial lung biopsy. Only one patients experienced docetaxel as first-line treatment due to poor PS score (PS = 2), and all other patients received doublet chemotherapy (Gemcitabine or Paclitaxel + Platinum) as the first-line treatment. All patients were administrated apatinib monotherapy (250–425 mg/day) as rescue therapy in second-line or fourth-line treatment.

Tumor responses were evaluated every 4 weeks or were assessed when significant signs of progression appeared, according to the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) using Chest imaging (CT scan). Objective tumor responses included complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). All the advert effects were recorded.

Results

The characteristics of all patients are shown in Tables 1 and 2. All patients were male except for one female. One month after apatinib monotherapy, two patients achieved partial response (PR), four patients achieved stable disease (SD), and seven patients achieved progression disease (PD) (as shown in Table 2, Fig. 1). The longest PFS is 4.5 months, the shortest PFS is 2.5 months, and the medium PFS was 3.1 months. The median OS had not yet been reached. The objective remission rate (ORR) was 15.4% (2/13). The total disease control rate (DCR) was 46.2% (6/13). 6 patients showed 1–2 grade advert effects, mainly hypertension, vomiting, and hand–foot reaction. All advert effects were manageable.

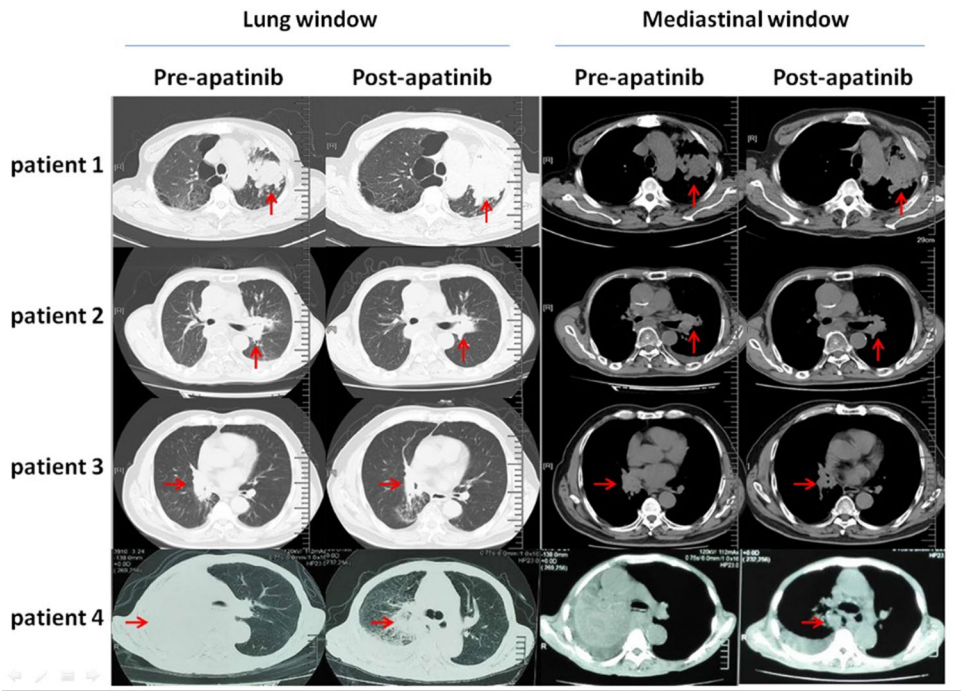

Fig. 1 Representative CT images (lung windows and mediastinal windows) of four patients before or after apatinib monotherapy. The CT images of patient 1 showed partial response. CT images of patient 2 and patient 3 showed stable disease response. CT images of patient 4 showed progress disease response

Table 1 Characteristics of 13 advanced lung squamous carcinoma patients

Patients	Sex	Age (years)	Stage	First-line	Second-line
1	70	M	IV ($T_2N_3M_1$)	Gem + Plat	Docetaxel
2	69	M	IIIb ($T_2N_3M_0$)	Pacl + Plat	Docetaxel
3	62	M	IIIb ($T_4N_2M_0$)	Gem + Plat	Docetaxel
4	69	M	IIIc ($T_3N_3M_0$)	Docetaxel	Apatinib
5	70	M	IV ($T_4N_3M_1$)	Gem + Plat	Docetaxel
6	68	M	IV ($T_4N_0M_1$)	Gem + Plat	Docetaxel
7	60	M	IV ($T_4N_2M_1$)	Doce + Plat	Apatinib
8	56	M	IV ($T_4N_1M_1$)	Gem + Plat	Docetaxel
9	64	F	IV ($T_4N_0M_1$)	Gem + Plat	Docetaxel
10	60	M	IIIb ($T_4N_2M_0$)	Doce + Plat	Apatinib
11	71	M	IVa (T2N1M1a)	Gem + Plat	Docetaxel
12	66	M	IVa (T4N3M1)	Doce + Plat	Gem
13	59	M	IVa (T2N2M1)	Gem + Plat	Apatinib

Discussion

As there were few driver mutations in advanced lung SCC, chemotherapy of two drugs based on platinum is the standard first-line treatment. When diseases progressed after second-line therapy, few drugs could be selected. Although adding anti-VEGF agents to chemotherapy significantly improved PFS and overall survival (OS) in several kinds of advanced solid cancer [5–8], this method showed little efficiency in advanced lung SCC. In our report, all patients have experienced standard chemotherapy as first-line treatment. We did not select anti-VEGF drugs in first-line treatment, because anti-VEGF treatment might result in life-threatening side effects, such as pulmonary hemorrhage in SCC.

As monoclonal antibody against VEGF or VEGFR, both bevacizumab and ramucirumab significantly improved PFS and OS in advanced nonsquamous NSCLC patients when adding to chemotherapy [5, 6]. Ramucirumab, combined with chemotherapy, is also suggested as first-line treatment in SCC [6]. However, few reports investigated anti-VEGF or anti-VEGFR agents monotherapy in cancer patients, especially in SCC. Some recent studies demonstrated the encouraging efficiency of apatinib in metastatic breast cancer and gastric cancer patients [9, 10]. Up to date, there remains no randomized controlled trial focused on apatinib monotherapy in lung cancer treatment. A few recent cases report showed the efficiency of a high-dose apatinib (500–850 mg/day) as post-second-line therapy in advanced NSCLC patients, including our two previous reports about EGFR wild-type adenocarcinoma [11–16]. In this report, we showed the efficiency of a lower dose of apatinib (250–425 mg/day) monotherapy in 13 advanced SCC patients. Two studies reported the efficacy of apatinib in SCC patients with a medium PFS of 1.9 months [12, 13], which was significantly less than PFS of our patients (3.1 months). These results in SCC were similar to the previous reports in adenocarcinoma patients. The underlying mechanism might be related to the suppression of endothelial cells' proliferation, migration, and inhibiting of the efflux function of multiple ATP-binding cassette transporters [17]. Nevertheless, further study remains needed to uncover the precise mechanism.

In our study, there are some points different from the above two cases report. First, we used a lower dosage of apatinib than the previous reports (250–425 mg/day vs. 500–850 mg/day) in SCC or adenocarcinoma patients. The lower dosage not only resulted in fewer economic burdens,

Table 2 Apatinib monotherapy and evaluation

Case	Apatinib and dosage	Evaluation	PFS (months)	Advert effects
1	Third-line, 250 mg/day	PD	–	Hemoptysis
2	Third-line, 250 mg/day	SD	3	–
3	Third-line, 250 mg/day	SD	4.5	Hand–foot syndrome
4	Second-line, 250 mg/day	PR	2.5	–
5	Third-line, 250 mg/day	PR	2.5	Vomiting, hypertension
6	Third-line, 425 mg/day	PD	–	Vomiting, hemoptysis
7	Second-line, 425 mg/day	SD	3	Vomiting
8	Third-line, 250 mg/day	PD	–	–
9	Third-line, 250 mg/day	PD	–	–
10	Second-line, 425 mg/day	PD	–	–
11	Fourth-line, 250 mg/day	PD	–	Hypertension
12	Third-line, 250 mg/day	SD	3	Vomiting
13	Second-line, 425 mg/day	PD	–	Hypertension

but also brought longer PFS (3.1 m vs. 1.9 m). The lower dosage also showed a well DCR (46.2%, 6/13). In our previous reports, a lower dosage of apatinib (250 mg/day) also showed a well diseases control rate (DCR, 68.75%) and PFS (4.4 months). Therefore, reduction of apatinib dosage might mean a better efficacy. However, the suitable doses remain unclear before more large scale RCTs were performed. Second, a lower dose of apatinib (250 mg/day) in our study showed a lower rate of advert effects. High dose of apatinib (850 mg/day) was often followed by high rate of toxicity, such as hypertension (40.43%), proteinuria (27.66%), and hand–foot syndrome (25.53%) [10]. In two cases report of NSCLC, high dose of apatinib (500–850 mg/day) also showed obvious side effects [16, 17]. However, it remain unclear the most suitable dosage of apatinib in SCC patients. In addition, apatinib was used monotherapy as post-first-line therapy in both our study and several previous reports. There were no data about the efficacy of apatinib, with or without chemotherapy, as first-line treatment in NSCLC.

In conclusion, this report revealed that apatinib might be a potential select as rescue treatment in lung SCC patients. Although lower dosage of apatinib showed a longer medium PFS and less advert effects, the most suitable dose remain need further investigation. Moreover, it was still unknown whether apatinib combination with chemotherapy showed more efficient or not.

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Compliance with ethical standards

Conflict of interest No conflict of interest.

References

1. Gridelli C, de Marinis F, Cappuzzo F et al (2014) Treatment of advanced non-small-cell lung cancer with epidermal growth factor receptor (EGFR) mutation or ALK gene rearrangement: results of an international expert panel meeting of the Italian Association of Thoracic Oncology. Clin Lung Cancer 15:173–181
2. Janku F, Garrido-Laguna I, Petruzelka LB et al (2011) Novel therapeutic targets in non-small cell lung cancer. J Thorac Oncol 6:1601–1612
3. Herbst RS, Onn A, Sandler A (2005) Angiogenesis and lung cancer: prognostic and therapeutic implications. J Clin Oncol 23:3243–3256
4. Goel HL, Mercurio AM (2013) VEGF targets the tumour cell. Nat Rev Cancer 13:871–882
5. Sandler A, Gray R, Perry MC et al (2006) Paclitaxel–carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med 355:2542–2550
6. Garon EB, Ciuleanu TE, Arrieta O et al (2014) Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. Lancet 384:665–673
7. de Gramont A, Van Cutsem E, Schmoll HJ et al (2012) Bevacizumab plus oxaliplatin-based chemotherapy as adjuvant treatment for colon cancer (AVANT): a phase 3 randomised controlled trial. Lancet Oncol 13:1225–1233
8. Pujade-Lauraine E, Hilpert F, Weber B et al (2014) Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: the AURELIA open-label randomized phase III trial. J Clin Oncol 32:1302–1308
9. Hu X, Zhang J, Xu B et al (2014) Multicenter phase II study of apatinib, a novel VEGFR inhibitor in heavily pretreated patients with metastatic triple-negative breast cancer. Int J Cancer 135:1961–1969
10. Li J, Qin S, Xu J et al (2013) Apatinib for chemotherapy-refractory advanced metastatic gastriccancer: results from a randomized, placebo-controlled, parallel-arm, phase II trial. J Clin Oncol 31:3219–3225
11. Ding L, Li QJ, You KY et al (2016) The use of apatinib in treating nonsmall-cell lung cancer: case report and review of literature. Medicine (Baltimore) 95:e3598
12. Song Z, Yu X, Lou G et al (2017) Salvage treatment with apatinib for advanced non-small-cell lung cancer. Onco Targets Ther 10:1821–1825
13. Xu J, Liu X, Yang S et al (2018) Clinical response to apatinib monotherapy in advanced non-small cell lung cancer. Asia Pac J Clin Oncol 14:264–269
14. Zeng DX, Wang CG, Lei W et al (2017) Efficiency of low dosage apatinib in post-first-line treatment of advanced lung adenocarcinoma. Oncotarget 8:66248–66253
15. Zeng DX, Wang CG, Huang JA et al (2017) Apatinib in the treatment of advanced lung adenocarcinoma with KRAS mutation. Onco Targets Ther 10:4269–4272
16. Fang SC, Zhang HT, Zhang YM et al (2017) Apatinib as post second-line therapy in EGFR wild-type and ALK-negative advanced lung adenocarcinoma. Onco Targets Ther 10:447–452
17. Mi YJ, Liang YJ, Huang HB et al (2010) Apatinib (YN968D1) reverses multidrug resistance by inhibiting the efflux function of multiple ATP-binding cassette transporters. Cancer Res 70:7981–7991