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Efficacy and safety of apatinib in patients with advanced nonsmall cell lung cancer that failed prior chemotherapy or EGFR-TKIs

A pooled analysis

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Abstract

Background: Apatinib is a tyrosine kinase inhibitor (TKI) that selectively inhibits the vascular endothelial growth factor receptor-2. A weighted pooled analysis was performed to evaluate the clinical outcome, efficacy, and toxicity of apatinib in patients with advanced nonsmall cell lung cancer (NSCLC) that failed prior treatment with chemotherapy or epidermal growth factor receptor-TKIs (EGFR-TKIs).

Methods: The literature published in PubMed, Embase, and Cochrane Library databases was searched (from inception to November 30, 2017) for eligible trials using the following search terms: apatinib AND (lung cancer OR NSCLC). Meeting abstracts were also reviewed to identify appropriate studies. Inclusion criteria were as follows: prospective or retrospective studies that evaluated efficacy and/or safety of apatinib in patients with advanced NSCLC that failed prior chemotherapy or EGFR-TKIs; primary outcome included one of these endpoints, progression-free survival (PFS), overall survival (OS), objective response rate (ORR), disease control rate (DCR), or adverse events (AEs); English language; and number of cases in the study ≥10 cases.

Results: A total of 457 patients with advanced NSCLC were treated with apatinib in 14 studies (10 retrospective and 4 prospective studies) and were included in this pooled analysis. The pooled median PFS was 4.77 months [95% confidence interval (CI), 4.11–5.00] in all groups, 4.80 months (95% CI, 4.65–4.95) in the 750 mg apatinib (high-dose) group, and 3.88 months (95% CI, 3.11–4.65) in the 250 to 500 mg apatinib (low-dose) group. Median PFS stratified by single apatinib therapy or apatinib combined with continuous EGFR-TKIs was 4.76 months (95% CI, 3.66–5.06) and 5.20 months (95% CI, 3.66–6.74), respectively. The pooled median OS, ORR, and DCR values were 6.85 months, 18%, and 72%, respectively; pooled median ORR and DCR were 15% and 72% in the 750 mg apatinib group versus 20% and 72% in the 250 to 500 mg apatinib group. ORR and DCR stratified by therapeutic regimens were 14% and 70% for single-agent apatinib, 29% and 88% for apatinib combined with continuous EGFR-TKIs, and 26% and 63% for apatinib combined with chemotherapy, respectively. The pooled AE rates of grade 3/4 were hypertension (7%), proteinuria (3%), hand-foot-skin reaction (6%), fatigue (4%), decreased appetite (1.1%), oral mucositis (3%), and thrombocytopenia (3%).

Conclusion: Apatinib has promising antitumor activity and manageable toxicity profile in patients with advanced NSCLC that failed prior chemotherapy or EGFR-TKIs. This result needs to be confirmed through the ongoing Phase III clinical trial.

Abbreviations: AE = adverse event, ALK = anaplastic lymphoma kinase, ASCO = American Society of Clinical Oncology, CFDA = China Food And Drug Administration, CTC AE v = Common Terminology Criteria for Adverse Events version, DCR = disease control rate, EGFR = epidermal growth factor receptor, HFSR = hand foot skin reaction, MDR = multidrug resistance, NSCLC = nonsmall cell lung cancer, ORR = objective response rate, OS = overall survival, PD-1/PD-L1 = programmed cell death protein 1 or ligand 1, PFS = progression-free survival, ROS-1 = ROS Proto-Oncogene 1, TKI = tyrosine kinase inhibitor, VEGF = vascular endothelial growth factor, VEGFR-2 = vascular endothelial growth factor receptor-2, WCLC = World Conference on Lung Cancer.

Keywords: apatinib, epidermal growth factor receptor, nonsmall cell lung cancer (NSCLC), toxicity, vascular endothelial growth factor receptor

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1. Introduction

Recent advances in multidisciplinary comprehensive treatment for advanced nonsmall lung cancer (NSCLC) have been achieved, especially in therapies targeting driver genes and immunotherapies targeting immune checkpoints such as programmed cell death protein 1 or ligand 1 (PD-1/PD-L1). Driver genes have an important role in tumor initiation and progression, and driver gene variation is commonly required to develop lethal malignancies and advanced stages for most solid tumors.[1] NSCLC driver genes include epidermal growth factor receptor (*EGFR*), anaplastic lymphoma kinase (*ALK*), and ROS proto-oncogene 1 (ROS1), etc. Receptor tyrosine kinase inhibitors (TKIs) of EGFR, ALK, and ROS1 have become the first-line treatment for patients with advanced NSCLC who are positive for EGFR mutation or ALK/ROS1 rearrangement.[2–5] Platinum combined chemotherapy is still the standard care for patients with driver gene negative NSCLC or those who failed to respond to prior EGFR-TKIs and had no secondary T790M-positive NSCLC.[6] Patients who fail to respond to first-line chemotherapy are now routinely treated with immunotherapy as the standard second-line therapy, with approximately 20% of objective response rate (ORR) and median overall survival (OS) of 1 year.[7,8] However, immunotherapy is still in the process of being approved for patients with cancer in China.

Angiogenesis is required for tumors to spread to other tissues, or metastasis. Tumors induce angiogenesis by secreting growth factors such as vascular endothelial growth factor (VEGF).[9] Unlike normal blood vessels, tumor blood vessels are commonly dilated with an irregular shape. Thus, normalization of the vasculature by antiangiogenic therapy is an important approach for remodeling the tumor microenvironment.[10] Apatinib is an oral small molecule TKI that selectively targets VEGF receptor-2 (VEGFR-2) and inhibits VEGF-mediated vascular endothelial cell migration and proliferation, thereby blocking tumor neovascularization.[11] A Phase III placebo-controlled clinical trial showed that apatinib confers a significant survival advantage over placebo in third-line treatment of gastric cancer.[12] On the basis of this study, apatinib has been approved by China Food and Drug Administration (CFDA) for third-line treatment of advanced gastric cancer. A Phase II placebo-controlled trial investigating the efficacy and safety of apatinib in the third-line treatment of nonsquamous NSCLC, which was first reported at the American Society of Clinical Oncology meeting in 2012 (abstract 7548), indicated that apatinib had a promising antitumor activity in advanced NSCLC.[13] A series of exploratory clinical studies of apatinib in the subsequent line treatment of advanced NSCLC have reported ORRs of 6% to 51% and hypertension of any grade of 10% to 72%. However, the treatment regimens in those studies were not completely consistent, and included single-agent apatinib, apatinib and EGFR-TKI, and apatinib and chemotherapy. Furthermore, the dosage of apatinib varied from 250 to 750 mg. A Phase III clinical study (NCT02332512) comparing the efficacy and safety of apatinib and placebo as a third-line treatment of EGFR mutation negative advanced NSCLC is ongoing, and the results have not been reported. Here, we conducted a pooled analysis to evaluate the clinical efficacy and safety of apatinib in advanced NSCLC after failure of prior treatment.

2. Methods

2.1. Literature selection criteria

All eligible studies were included in the pooled analysis if they met the following inclusion criteria: prospective or retrospective studies (including single-arm studies) that evaluated efficacy and/or toxicity of apatinib in patients with advanced NSCLC that failed prior treatment of chemotherapy or TKIs; primary outcome of each study reported at least one of these endpoints, progression-free survival (PFS), OS, ORR, disease control rate (DCR), or adverse events (AEs) as per Common Terminology Criteria for Adverse Events version (CTC AE v) 3.0 or 4.0; English language; and number of cases in the study ≥10 cases.

2.2. Search strategy

PubMed, Embase, and Cochrane's Library databases were searched for relevant studies using the following search string: apatinib AND (lung cancer OR NSCLC). Relevant literature was reviewed to identify appropriate clinical studies for pooled analysis. Titles of abstracts from the websites of the American Society of Clinical Oncology, European Society of Medical Oncology, and International Association of Lung Cancer were searched using the keyword "apatinib" to include the most relevant and current literature in the analysis. Reference lists of the enrolled studies were manually scanned to ensure that all relevant literature was retrieved. The final literature search was performed on November 30, 2017.

2.3. Data extraction and synthesis

After finishing the literature search according to the inclusion criteria, 2 authors checked authorship, institutions, and abstracts to exclude duplicate papers. Then, 2 authors independently extracted data from all eligible studies, including first authors and the publication year; baseline information of the study, including patient characteristics, therapy methods, and apatinib doses; median PFS (mPFS) and median OS (mOS); ORR and DCR; and rate of AE.

2.4. Statistical methods

Statistical analyses were performed with Stata 12 (StataCorp, College Station, Texas). All effect sizes were pooled under the assumption of random effects model (DerSimonian–Laird method) or fixed-effects model (Mantel–Haenszel method). The effect sizes were the main outcomes of each study, including mPFS and mOS, ORR and DCR, and rate of AE. Subgroup analyses were performed on studies that reported apatinib dose and treatment methods. Test of study heterogeneity was assessed using the I^2 statistic, which describes the proportion of total variation across studies that was the result of heterogeneity rather than chance. Statistical heterogeneity was detected, defined as $P \leq .05$ or $I^2 > 50\%$.

2.5. Sensitivity analysis and publication bias

Sensitivity analyses were performed for the result of mPFS based on the leave-one-out approach. The potential for publication bias in reported mPFS values was assessed using funnel plots, with the appropriate accuracy intervals.

3. Results

3.1. Study population

We reviewed the full text of 22 published studies and meeting abstracts. A total of 14 studies met the inclusion and exclusion criteria.[13–26] In these studies, a total of 476 patients with

Table 1

Study characteristics.

Study	Publication year	Therapy line	Patient number	Histology	Status of driver gene	Apatinib dosage, mg	Therapy regime	ORR	DCR	PFS, mo	OS, mo
Zhang L	2012	3	91	NSCC	Any type	750 (H)	A	12.20%	61.10%	4.7 (2.14–5.86)	NR
Zhou Y	2016	2/3	20	NSCLC	*EGFR* wild-type	500 (L)	A	30.00%	85.00%	NR	4 (1–6)
Zhou C	2017	≥2	40	NSCLC	Any type	500 (L)	A	21.10%	76.30%	3.22 (2.37–4.86)	9.26 (5.37-nr)
Shi Y	2017	2	25	NSCLC	Unknown	500 (L)	A	8%	68%	5.17 (0.76–9.57)	NR
Wang S	2017	≥2	33	NSCLC	Any type	250 (L)	A	9.09%	51.52%	4 (0–8.2)	NR
Liang L	2017	2	16	NSCLC	Any type	250–500 (L)	AT	28.60%	100%	4.60 (2.23–12.52)	NR
Chai Y	2017	NR	33	NSCLC	Unknown	250 (L)	AT	51.50%	90.90%	NR	NR
Song Y	2017	3/4	72	NSCLC	Any type	750 (H)	A	13.89%	83.33%	4.8 (4.7–5)	NR
Wu Z	2017	≥3	15	NSCLC	Unknown	250 (L)	AC	50%	83%	NR	NR
Shi Q	2017	2/3	30	SCC	Unknown	250–500 (L)	AC	6.25%	43.75%	NR	NR
Zeng D	2017	2–4	16	ADC	*EGFR* wild-type	250–500 (L)	A	18.75%	68.75%	4.4 (2–10)	6 (3.9–8)
Song Z	2017	≥3	42	NSCLC	Any type	500 (L)	A	9.50%	61.50%	4.2 (1–9.5)	NR
Xu J	2017	2/3	27	NSCLC	Any type	500 (L)	AT	11.10%	81.50%	5.33 (3.63–7.03)	NR
Li F	2017	≥2	16	NSCLC	Any type	250 (L)	AT	28.60%	100%	4.6 (2.23–12.52)	NR

A = apatinib alone, AC = apatinib combined with chemotherapy, ADC = adenocarcinoma, AT = apatinib combined with EGFR-TKIs, DCR = disease control rate, H = high-dose group, L = low-dose group, NR = not reported, nr = not reached, NSCC = nonsquamous cell carcinoma, NSCLC = nonsmall cell lung cancer, ORR = overall response rate, OS = overall survival, PFS = progression-free survival, SCC = squamous cell carcinoma.

advanced NSCLC received a minimum of second-line treatment. Of these 14 studies, 5 were prospective studies and 9 were single-arm retrospective studies. The pooled analysis assigned patients with respect to therapeutic regimen into 3 groups: single apatinib (A) treatment in 8 studies with 339 patients; apatinib and EGFR-TKI (AT) treatment in 4 studies with 92 patients; and apatinib and chemotherapy (AC) treatment in 2 studies with 45 patients. Patients were further subgrouped according to the dosage of apatinib: the high-dose (750 mg) apatinib group (H group) appeared in 2 studies; the low-dose (250 or 500 mg) apatinib group (L group) appeared in 12 studies (Table 1).

3.2. Objective response rate and disease control rate

The overall pooled ORR for apatinib from 14 studies was 18% [95% confidence interval (95% CI), 12–24]. The pooled DCR from 12 studies was 72% (95% CI, 64–80). ORR and DCR stratified by dosage were 15% (95% CI, 10–21) and 72% (95% CI, 51–94), respectively, in the H group, and 20% (95% CI, 12–27) and 72% (95% CI, 62–82), respectively, in the L group. ORR and DCR stratified by therapeutic regimen were 29% (95% CI, 10–49) and 88% (95% CI, 79–96), respectively, in the AT group, 26% (95% CI 0–69) and 63% (95% CI 25–100), respectively, in the AC group, and 14% (95% CI, 10−18) and 70% (95% CI, 61–79), respectively, in the A group (Figs. 1 and 2, Tables 2 and 3).

3.3. Patient survival

Ten studies recorded PFS value and 95% CI. The overall mPFS was 4.77 months (95% CI, 4.62–4.91), with 4.80 months (95% CI, 4.65–4.95) in the H group and 3.88 months (95% CI, 3.11–4.65) in the L group. The mPFS stratified by therapeutic regimen was 4.76 months (95% CI, 4.61–4.91) in the A group and 5.20 months (95% CI, 3.66–6.74) in the AT group, respectively (Fig. 3, Table 4).

Only 3 studies reported OS data, but the 95% CI upper limit was not reached in 1 study, so the pooled median OS was calculated by a weighted average of the single study medians.[27] Median OS estimates computed with $\hat{U}_j$ ($\hat{U}_1$, $\hat{U}_2$, $\hat{U}_3$) were obtained in 3 eligible studies, with group sizes computed with N_j (N_1, N_2, N_3); these were summed to yield N_{all}. The pooled median OS was then estimated as the group-size weighted average as follows: $\hat{U}_{all} = (1/N_{all}) \sum N_j \times \hat{U}_j$. The last estimated pooled median OS was 6.85 months.

3.4. Apatinib safety

The most common AEs documented in the enrolled studies were hypertension, proteinuria, and hand foot skin reaction (HFSR) (Table 5). The pooled frequencies of any grade and grade ≥3 hypertension were 34% (95% CI, 22–46) and 7% (95% CI, 3–10), respectively, with 35% and 5% for the H group, 34% and 9% for the L group, 36% and 6% for the A group, 44% and 31% for the AT group, and 24% and 17% for the AC group, respectively. The pooled frequencies of any grade and grade ≥3 proteinuria were 18% and 3%, with 27% and 3% in the H group, 14% and 4% in the L group, 22% and 3% in the A group, and 3% of any grade in the AC group. There were no records of any grade proteinuria in the AT group or grade ≥3 proteinuria in the AC group. The incidences of any grade and grade ≥3 HFSR in all groups were 22% and 6%, respectively. The H group had a higher rate of any grade HFSR than the L group (34% vs 18%). Any grade of HFSR in A, AT, and AC groups was 25%, 19%, and 16%, respectively. Grade ≥3 HFSR in the H and L group was 6% and 7%, respectively, and in the A and AT groups was 6% and 6%, respectively.

Several other toxicities including fatigue, anepithymia/decreased appetite, oral mucositis, and thrombocytopenia were reported (Table 5). The incidences of any grade and grade ≥3 fatigue in all groups were 19% and 4%, respectively, with 18% and 3%, respectively, in the H group, and 20% and 5%, respectively, in the L group. Any grade fatigue in the AT group was higher than in the A or AC group (37% vs 19%, 16%), whereas grade ≥3 fatigue was 8% and 3%, respectively, in the AC and A groups. Oral mucositis occurred in 19% of patients; however, grade ≥3 oral mucositis was only observed in 4% of patients. The L group had a higher rate of any grade oral mucositis than the H group (28% vs 17%). The incidences of any grade and grade ≥3 oral mucositis in the AC group (50% and 8%, respectively) were higher than in the A group (18% and 3%, respectively). Four studies documented anepithymia and the final pooled rate was 14%; however, only 1 study recorded grade 3 anepithymia with an incidence rate of 1.1%. Thrombocytopenia occurred in 14% patients, with 19% and 9%, respectively, in H and L groups. Grade 3 thrombocytopenia was only 3% (Table 5).

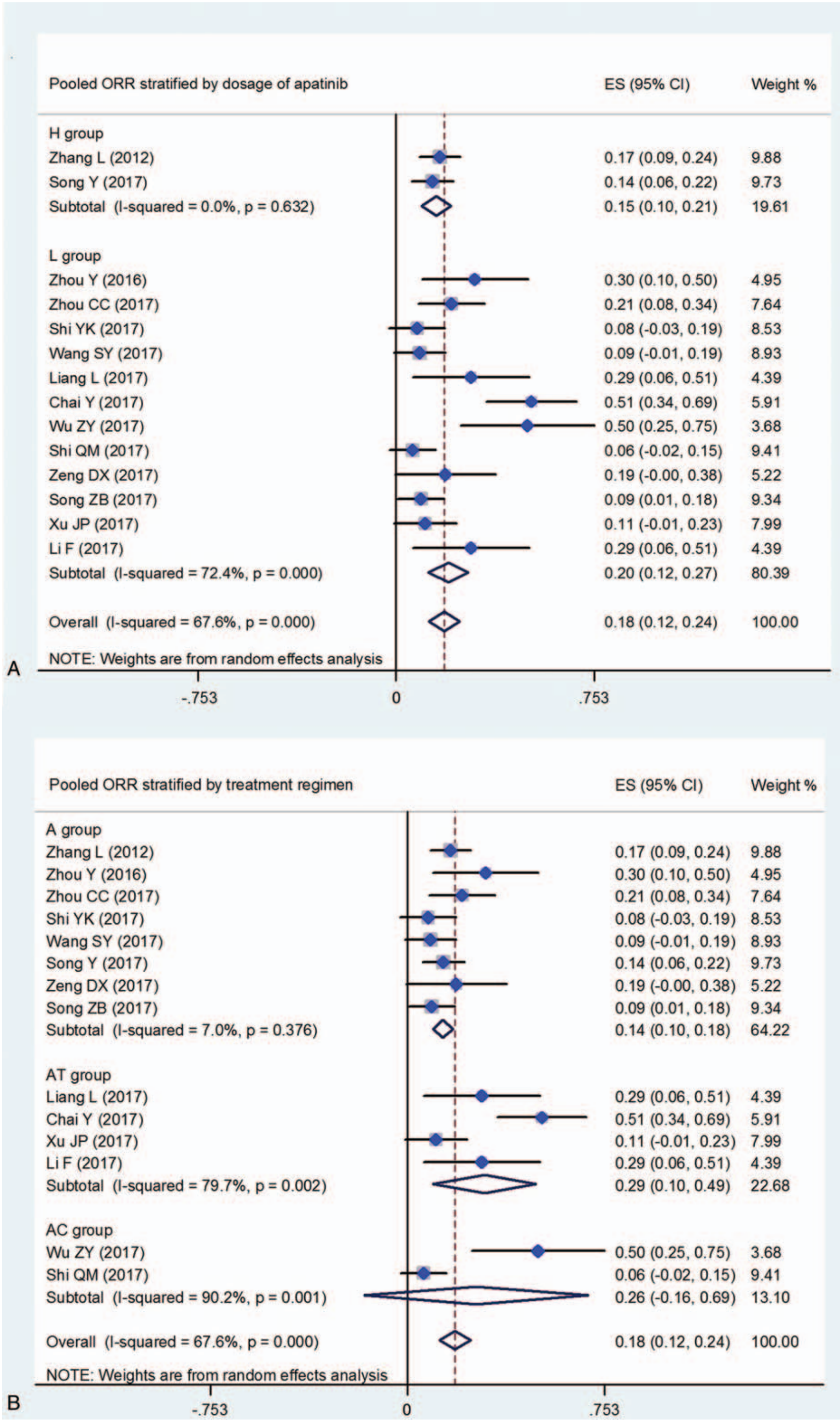

Figure 1. Pooled overall response rate (ORR) stratified by dosage (A) and treatment regimen (B). H group, high-dose apatinib group (750 mg); L group, low-dose apatinib group (250–500 mg); A group, single apatinib group; AT group, apatinib combined with EGFR-TKIs; AC group, apatinib combined with chemotherapy.

3.5. Sensitivity analysis

The results of leave-one-out sensitivity analyses for mPFS are summarized in Fig. 4. The estimated mPFS of each study was similar to the pooled mPFS value and 95% CI, except for the studies of Zhou et al[15] and Song et al.[20] The estimated pooled mPFS was 4.8 months (95% CI, 4.65–4.95) when the study of Zhou et al[15] was omitted, and 4.11 months (95% CI, 3.47–4.77) when the study of Song et al.[20]

3.6. Publication bias

Potential publication bias was assessed using funnel plots with PFS as the outcome. The funnel plots were symmetrical

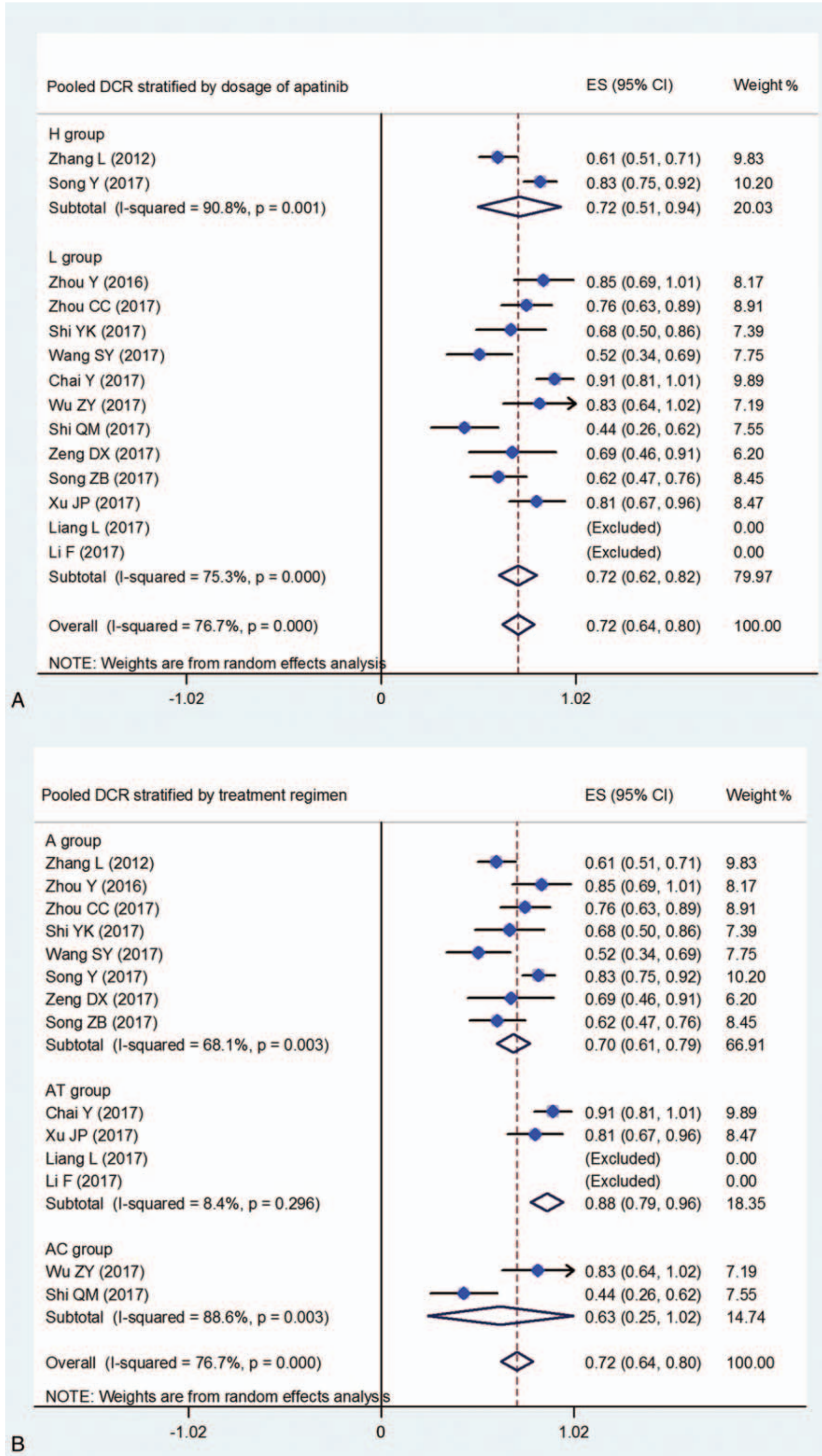

Figure 2. Pooled disease control rate (DCR) stratified by dosage (A) and treatment regimen (B). H group, high-dose apatinib group (750 mg); L group, low-dose apatinib group (250–500 mg); A group, single apatinib group; AT group, apatinib combined with EGFR-TKIs; AC group, apatinib combined with chemotherapy.

for each of the treatment groups, indicating no publication bias (Fig. 5).

4. Discussion

Treatment of solid tumors with angiogenesis inhibitors has been shown to be effective because it confers tumor vascular normalization, reduces microvascular permeability, and improves the hypoxic and immunosuppressive tumor microenvironment.[28–30] Although data from a prospective Phase III randomized control study evaluating the efficacy and toxicity of apatinib for patients with advanced NSCLC are lacking, our pooled analysis indicates that apatinib is a potent small molecule TKI in the second- and third-line treatments of patients with

Table 2

Overall response rate (ORR) of apatinib for advanced nonsmall cell lung cancer.

Subgroup	Study	Dose, mg/therapy regimen	N	ORR (%)	95% CI		Weight (%)	Heterogeneity	Significance	Heterogeneity between subgroups
H group	Zhang L (2012)	750	90	16.6	9	24.2	9.88	I^2=0%, P=.632	z=5.43, P=.000	NC
	Song Y (2017)	750	72	13.9	5.9	21.9	9.73			
	Pooled ORR	750	162	15.3	9.8	20.8	19.61			
L group	Zhou Y (2016)	500	20	30	9.9	50.1	4.95	I^2=72.4%, P=.00	z=5.16, P=.000	
	Zhou CC (2017)	500	40	21.1	8.5	33.7	7.64			
	Shi YK (2017)	500	25	5.17	−2.6	18.6	8.53			
	Wang SY (2017)	250	33	9	−0.8	18.8	8.93			
	Liang L (2017)	250–500	14	28.6	6.5	50.7	4.39			
	Chai Y (2017)	250	33	51.5	34.4	68.6	5.91			
	Wu ZY (2017)	250	15	50	24.7	75.3	3.68			
	Shi QM (2017)	250–500	30	6.3	−2.4	15	9.41			
	Zeng DX (2017)	250–500	16	18.8	−0.3	37.9	5.22			
	Song ZB (2017)	500	42	9.5	0.6	18.4	9.34			
	XU JP (2017)	500	27	11.1	−0.7	22.9	7.99			
	Li F (2017)	250	16	28.6	6.5	50.7	4.39			
	Pooled ORR	250–500	311	19.9	12.3	27.4	80.39			
A group	Zhang L (2012)	Apatinib	90	16.6	9	24.2	9.88	I^2=7.0%, P=.376	z=7.09, P=.000	NC
	Zhou Y (2016)	Apatinib	20	30	9.9	50.1	4.95			
	Zhou CC (2017)	Apatinib	40	21.1	8.5	33.7	7.64			
	Shi YK (2017)	Apatinib	25	8	−2.6	18.6	8.53			
	Wang SY (2017)	Apatinib	33	9	−0.8	18.8	8.93			
	Song Y (2017)	Apatinib	72	13.9	5.9	21.9	9.73			
	Zeng DX (2017)	Apatinib	16	18.8	−0.3	37.9	5.22			
	Song ZB (2017)	Apatinib	42	9.5	0.6	18.4	9.34			
	Pooled ORR	13.7	9.9	17.5	64.22					
AT group	Liang L (2017)	Apatinib+EGFR-TKIs	14	28.6	6.5	50.7	4.39	I^2=79.7%, P=.002	z=2.95, P=.003	
	Chai Y (2017)	Apatinib+EGFR-TKIs	33	51.5	34.4	68.6	5.91			
	Xu JP (2017)	Apatinib+Icotinib	27	11.1	−0.7	22.9	7.99			
	Li F (2017)	Apatinib+EGFR-TKIs	16	28.6	6.5	50.7	4.39			
	Pooled ORR	Apatinib+EGFR-TKIs	90	29.5	9.9	49.1	22.68			
AC group	Wu ZY (2017)	Apatinib+S1	15	50	24.7	75.3	3.68	I^2=90.2%, P=.001	z=1.21, P=.224	
	Shi QM (2017)	Apatinib+S1	30	6.3	−2.4	15	9.41			
	Pooled ORR	Apatinib+S1	45	26.5	−16.2	69.2	13.1			
All group	Overall pooled ORR		473	18.3	12.5	24.2	100	I^2=67.6%, P=.000	z=6.14, P=.000	

95% CI=95% confidence interval, A group=single apatinib group, AC group=apatinib combined with chemotherapy, AT group=apatinib combined with EGFR-TKIs, H group=high-dose apatinib group (750 mg), L group=low-dose apatinib group (250–500 mg), NC=not calculated.

advanced NSCLC that did not respond to prior chemotherapy or EGFR-TKIs. Apatinib has manageable toxicity and lower grade ≥3 AEs.

The addition of bevacizumab (anti-VEGF monoclonal antibody) to first-line chemotherapy significantly improves survival and is an accepted standard of care for advanced nonsquamous NSCLC.[31–33] By contrast, the addition of ramucirumab (anti-VEGF receptor 2 IgG1 monoclonal antibody) or nintedanib (a triple angiokinase inhibitor) to second-line docetaxel therapy improved OS by only 1 to 1.4 months compared with docetaxel alone.[34,35] The limited efficacy and poor tolerance for subsequent-line therapy reduced the long-term benefit for NSCLC patients to receive further treatment. In recent years, many clinical trials have been conducted to evaluate the efficacy and safety of novel multitarget antiangiogenic TKIs such as sorafenib, sunitinib, pazopanib, and vandetanib in first-line or higher treatment of advanced NSCLC. However, most of these studies failed to significantly improve survival, even in combination with chemotherapy.[36–45]

Apatinib is a novel small molecule oral TKI targeting VEGFR-2, PDGFRb, c-Kit, and Src.[45,46] A Phase II, placebo-controlled trial investigating the efficacy and safety of apatinib in the third-line treatment of nonsquamous NSCLC showed that apatinib (750 mg QD p.o.) significantly improved ORR (12.2% vs 0%), DCR (69% vs 24%), and PFS (4.7 vs 1.9 months) compared with placebo.[13] Our pooled analysis indicated that the pooled mPFS and OS in all groups were 4.77 and 6.85 months, respectively, and the ORR and DCR were 18% and 72%, respectively. Patients treated with 750 mg apatinib had a relatively longer PFS than those treated with 250 to 500 mg (4.80 vs 3.88 months). A total of 3 studies recorded OS data,[17,18,27] in which single-agent apatinib was administrated to patients with advanced NSCLC in second-line and higher treatment. Zhou et al[15] reported that median OS reached up to 9.26 months. By contrast, the survival data of our pooled analyses were similar to that of anlotinib, another oral TKI targeting VEGFR, PDGFR, FGFR, and c-Kit.[47] The ALTER 0303 study[48] (a randomized, placebo-controlled, Phase III trial), which was first reported at the 2017 American Society of Clinical Oncology (ASCO) meeting, evaluated the efficacy and safety of anlotinib in third-line treatment of patients with advanced NSCLC. The findings indicated that anlotinib significantly increased ORR (9.7%) and DCR (81%), and improved mPFS (5.37 months) and OS (9.63 months) compared with placebo.

Table 3

disease control rate (DCR) of apatinib for advanced nonsmall cell lung cancer.

Subgroup	Study	Dose, mg/therapy regimen	N	DCR (%)	95% CI		Weight (%)	Heterogeneity	Significance	Heterogeneity between subgroups
H group	Zhang L (2012)	750	90	61.1	51.1	71.1	9.83	I^2=90.8%, P=.001	z=6.52, P=.000	NC
	Song Y (2017)	750	72	83.3	74.4	91.9	10.2			
	Pooled DCR	750	162	72.4	50.6	94.1	20.03			
L group	Zhou Y (2016)	500	20	85	69.4	100.6	8.17	I^2=75.3%, P=.000	z=14.19, P=.000	
	Zhou CC (2017)	500	40	76.3	63.1	89.5	8.91			
	Shi YK (2017)	500	25	68	49.7	86.3	7.39			
	Wang SY (2017)	250	33	51.5	34.5	68.6	7.75			
	Chai Y (2017)	250	33	90.9	81.1	100.7	9.89			
	Wu ZY (2017)	250	15	83	64	102	7.19			
	Shi QM (2017)	250–500	30	43.8	26	61.5	7.55			
	Zeng DX (2017)	250–500	16	68.8	46	91.5	6.2			
	Song ZB (2017)	500	42	61.5	46.8	76.2	8.45			
	XU JP (2017)	500	27	81.5	66.9	96.1	8.47			
	Liang L (2017)	250–500	14	100 (excluded)						
	Li F (2017)	250	16	100 (excluded)						
	Pooled DCR	250–500	311	71.7	61.8	81.6	79.97			
A group	Zhang L (2012)	Apatinib	90	61.1	51.1	71.1	9.83	I^2=68.1%, P=.003	z=15.70, P=.000	NC
	Zhou Y (2016)	Apatinib	20	85	69.4	100.6	8.17			
	Zhou CC (2017)	Apatinib	40	76.3	63.1	89.5	8.91			
	Shi YK (2017)	Apatinib	25	68	49.7	86.3	7.39			
	Wang SY (2017)	Apatinib	33	51.5	34.5	68.6	7.75			
	Song Y (2017)	Apatinib	72	83.3	74.7	91.9	10.2			
	Zeng DX (2017)	Apatinib	16	68.8	46	91.5	6.2			
	Song ZB (2017)	Apatinib	42	61.5	46.8	76.2	8.45			
	Pooled DCR	Apatinib	338	70	61.3	78.7	66.91			
AT group	Chai Y (2017)	Apatinib+EGFR-TKIs	33	90.9	81.1	100.7	9.89	I^2=8.4%, P=.296	z=19.94, P=.000	
	Xu JP (2017)	Apatinib+Icotinib	27	81.5	66.9	96.1	8.47			
	Liang L (2017)	apatinib+EGFR-TKIs	14	100 (excluded)						
	Li F (2017)	Apatinib+ EGFR-TKIs	16	100 (excluded)						
	Pooled DCR	Apatinib+EGFR-TKIs	90	87.8	79.2	96.5	18.35			
AC group	Wu ZY (2017)	Apatinib+S1	15	83	64	102	7.19	I^2=88.6%, P=.003	z=3.22, P=.001	
	Shi QM (2017)	Apatinib+S1	30	43.8	26	61.5	7.55			
	Pooled DCR	Apatinib+S1	45	63.2	24.8	101.7	14.74			
All groups	Overall pooled DCR		473	71.9	63.5	80.2	100	I^2=76.7% P=.000	z=16.86, P=.000	

95% CI=95% confidence interval, A group=single apatinib group, AC group=apatinib combined with chemotherapy, AT group=apatinib combined with EGFR-TKIs, H group=high-dose apatinib group (750 mg), L group=low-dose apatinib group (250–500 mg), NC=not calculated.

Apatinib combined with chemotherapy or targeted therapy may further improve the clinical efficacy. Previous studies showed apatinib can reverse multidrug resistance (MDR) mediated by P-glycoprotein (P-gp, ABCB1) and breast cancer resistance protein (BCRP, ABCG2) by directly inhibiting ABCB1 and ABCG2 function, resulting in elevated intracellular concentrations of chemotherapeutic drugs. Confirmation of MDR reversal by apatinib in a tumor xenograft model further supports the potential usefulness of combining apatinib with other anticancer drugs in overcoming clinical resistance in cancer chemotherapy.[45] In our pooled analyses, 8 studies reported ORR and DCR results of single-agent apatinib (group A), with a pooled ORR of 14% (range, 8–30%) and DCR of 70% (range, 52–85%). Stratification analysis showed that apatinib combined with chemotherapy achieved improved ORR of 26%. Only 2 studies[21,22] used apatinib combined chemotherapy [both were Tegafur Gimeracil (S1)] in second-line and higher treatment for advanced NSCLC. The retrospective study by Wu et al[21] analyzed the efficacy and safety of apatinib and S1 among 15 patients with advanced NSCLC after failure of the second- and third-line chemotherapies, and achieved a 50% ORR and 83% DCR. Another study[22] enrolled only 12 patients with advanced squamous cell lung carcinoma who experienced progression with one or more lines of chemotherapy; the study reported that apatinib combined with S1 conferred only 6% ORR and 44% DCR. Both of these studies examined a small-sample AC group. Currently, we do not know whether differences between squamous carcinoma or adenocarcinoma histologies affect apatinib efficacy, because patients were not strictly grouped according to pathological type. At the 2017 World Conference on Lung Cancer (WCLC), 1 small prospective study[49] reported an ORR of 10% and DCR of 90% in 10 patients with SCLC treated with 3 lines or higher of single-agent apatinib. Further studies should stratify patient groups by histological type of lung cancer.

Combining EGFR-TKIs with VEGF/VEGFR inhibitors might overcome drug resistance for patients with EGFR mutation positive NSCLC because EGFR and VEGFR share parallel and reciprocal downstream signaling pathways, particularly during angiogenesis.[50] Dual inhibition of both VEGFR and EGFR effectively delays drug resistance in many preclinical and clinical studies.[50,51] A retrospective study[52] showed that combining EGFR-TKI with additional bevacizumab achieved higher DCR of 88% and a modest

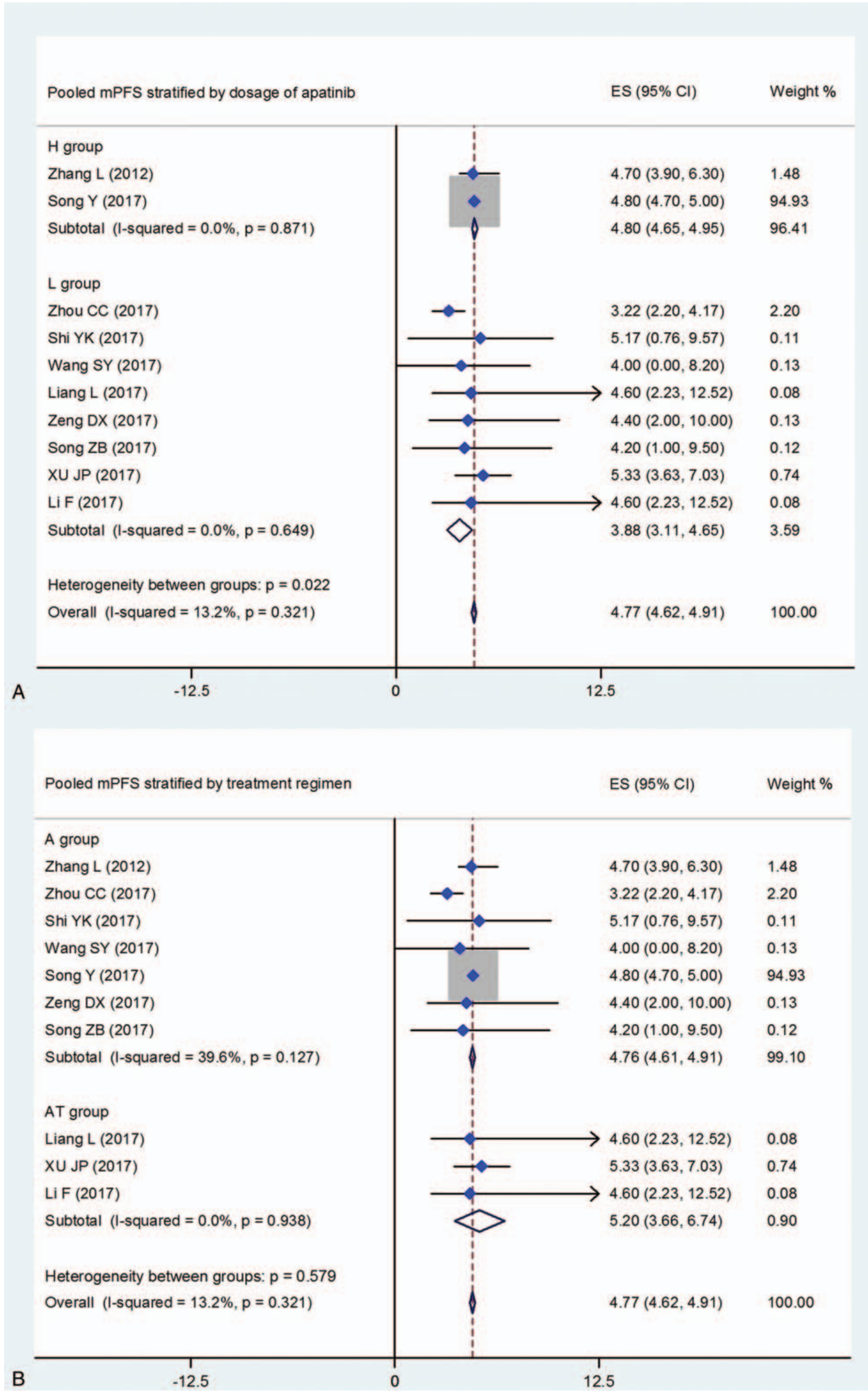

Figure 3. Pooled median progression-free survival (mPFS) stratified by dosage (A) and treatment regimen (B). H group, high-dose apatinib group (750 mg); L group, low-dose apatinib group (250–500 mg); A group, single apatinib group; AT group, apatinib combined with EGFR-TKIs.

PFS of 4.1 months in advanced NSCLC. Our pooled analysis showed that combining apatinib with continuous EGFR-TKIs achieved an impressive efficacy with an ORR of 29% and mPFS of 5.20 months. Four studies reported the efficacy of combining apatinib with continuous EGFR-TKIs; the study of Chai et al[19] included 33 patients with resistance to EGFR-TKIs, and their results showed a robust ORR of 51.5% and DCR of 91%. These results suggest that apatinib partly reverses MDR when combined with EGFR-TKIs (even with prior resistance) or chemotherapeutic drugs.

The Phase I dose-escalation clinical trial[11] studied the maximum tolerated dose and safety of apatinib in metastatic cancer, and confirmed the recommended daily dose of 750 mg for

Table 4

Median progression-free survival (mPFS) of apatinib for advanced nonsmall cell lung cancer.

Subgroup	Study	Dose, mg/therapy regimen	N	mPFS, m	95% CI		Weight (%)	Heterogeneity	Significance	Heterogeneity between subgroups
H group	Zhang L (2012)	750	90	4.7	3.9	6.3	1.48	I^2=0%, P=.871	z=63.19, P=.000	P=.022
	Song Y (2017)	750	72	4.8	4.7	5	94.93			
	Pooled data	750	162	4.8	4.65	4.95	96.41			
L group	Zhou CC (2017)	500	40	3.22	2.2	4.17	2.2	I^2=0%, P=.649	z=9.86, P=.000	
	Shi YK (2017)	500	25	5.17	0.76	9.57	0.11			
	Wang SY (2017)	250	33	4	0	8.2	0.13			
	Liang L (2017)	250–500	14	4.6	2.23	12.52	0.08			
	Zeng DX (2017)	250–500	16	4.4	2	10	0.13			
	Song ZB (2017)	500	42	4.2	1	9.5	0.12			
	XU JP (2017)	500	27	5.33	3.63	7.03	0.74			
	Li F (2017)	250	16	4.6	2.23	12.52	0.08			
	Pooled data	250–500	213	3.88	3.11	4.65	3.59			
A group	Zhang L (2012)	Apatinib	90	4.7	3.9	6.3	1.48	I^2=39.6%, P=.127	z=63.57, P=.000	P=.579
	Zhou CC (2017)	Apatinib	40	3.22	2.2	4.17	2.2			
	Shi YK (2017)	Apatinib	25	5.17	0.76	9.57	0.11			
	Wang SY (2017)	Apatinib	33	4	0	8.2	0.13			
	Song Y (2017)	Apatinib	72	4.8	4.7	5	94.93			
	Zeng DX (2017)	apatinib	16	4.4	2	10	0.13			
	Song ZB (2017)	apatinib	42	4.2	1	9.5	0.12			
	Pooled data	apatinib	318	4.76	4.62	4.91	99.1			
AT group	Liang L (2017)	apatinib+EGFR-TKIs	14	4.6	2.23	12.52	0.08	I^2=0%, P=.938	z=6.62, P=.000	
	XU JP (2017)	apatinib+Icotinib	27	5.33	3.63	7.03	0.74			
	Li F (2017)	apatinib+ EGFR-TKIs	16	4.6	2.23	12.52	0.08			
	Pooled data	apatinib+EGFR-TKIs	57	5.2	3.66	6.74	0.9			
All groups	Overall pooled mPFS		375	4.77	4.62	4.91	100	I^2=13.2%, P=.321	z=63.91, P=.000	

95% CI=95% confidence interval, A group=single apatinib group, AT group=apatinib combined with EGFR-TKIs, H group=high-dose apatinib group (750 mg), L group=low-dose apatinib group (250–500 mg).

the Phase II trial. The subsequent Phase II clinical trial[53] showed that the most common apatinib-related AEs were hypertension, proteinuria, and HFSR. In the present study, the pooled frequencies of any grade (≥10% AEs) and grade 3/4 AEs were, respectively, 34% and 7% for hypertension, 18% and 3% for proteinuria, 22% and 6% for HFSR, 19% and 4% for fatigue, 14% and 1.1% for decreased appetite, 19% and 3% for oral mucositis, and 14% and 3% for thrombocytopenia. No grade ≥3 AEs were more than 10% (Table 5). Another Phase II trial of apatinib treating metastatic TNBC[54] reported toxicities of 11.9, 13.6, and 17% for grade 3/4 hypertension, proteinuria, and HFSR, respectively. A prospective Phase III study[12] of apatinib to treat chemotherapy-refractory advanced gastric cancer reported that the leading grade 3/4 AE was hypertension, which occurred in 8.51% and 10.86% of patients treated with 850 mg once daily and 425 mg twice daily apatinib, respectively. There is a great difference in the safety profiles of apatinib and anlotinib. Grade 3/4 AEs of anlotinib in the ALTER 0303 trial[48] were

Table 5

Adverse events.

Events	Grade	Percent of patients with adverse event					
		Overall rate	H group	L group	A group	AT group	AC group
Hypertension	Any grade	34%	35%	34%	36%	44%	24%
	Grade ≥ 3	7%	5%	9%	6%	31%	17%
Proteinuria	Any grade	18%	27%	14%	22%	NR	3%
	Grade ≥ 3	3%	3%	4%	3%	NR	NR
HFSR	Any grade	22%	34%	18%	25%	19%	16%
	Grade ≥ 3	6%	6%	7%	6%	6%	NR
Fatigue	Any grade	19%	18%	20%	19%	37%	16%
	Grade ≥ 3	4%	3%	5%	4%	NR	8%
Decreased appetite	Any grade	14%	14%	22%	14%	22%	NR
	Grade ≥ 3	1.1%	1.1%	NR	NR	NR	NR
Oral mucositis	Any grade	19%	17%	28%	18%	NR	50%
	Grade ≥ 3	3%	NR	3%	3%	NR	8%
Thrombocytopenia	Any grade	14%	19%	9%	14%	NR	NR
	Grade ≥ 3	3%	3%	5%	4%	NR	NR

A=apatinib alone, AC=apatinib combined with chemotherapy, AT=apatinib combined with EGFR-TKIs, H group=high-dose group, HFSR=hand foot skin reaction, L group=low-dose group, NR=not reported.

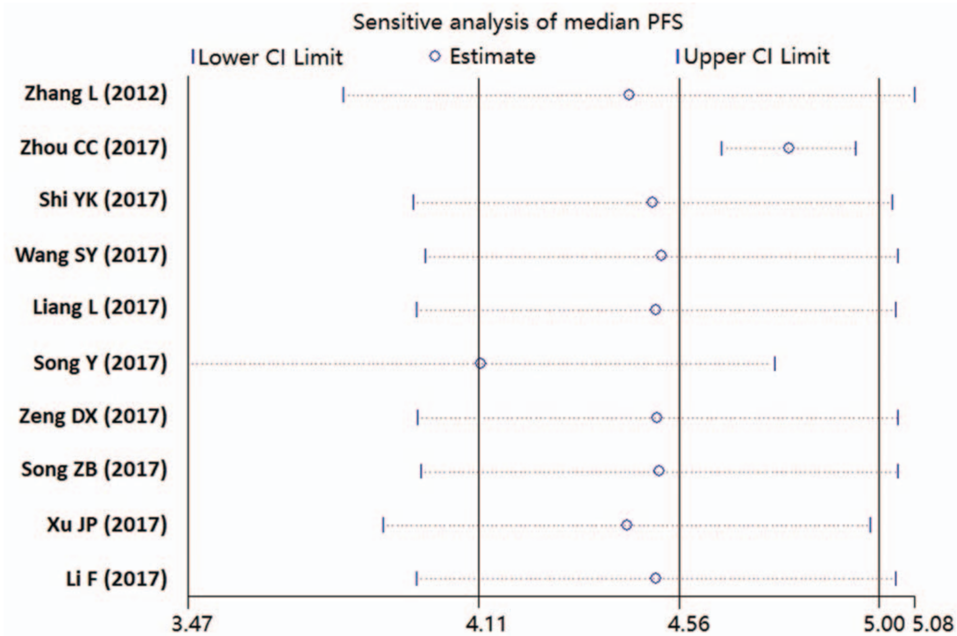

Figure 4. Sensitivity analyses for median progression-free survival (mPFS).

mainly hypertension (13.61%), dermal toxicity (3.74%), and hypertriglyceridemia (3.06%).

We found that the incidences of any grade and grade ≥3 hypertension were similar between high-dose and low-dose apatinib groups. However, the combination of apatinib with EGFR-TKI or chemotherapy led to more grade ≥3 hypertension than single-agent apatinib (6, 17, and 31% for A, AC, and AT groups, respectively). Only 1 study was included in the AT group and 2 studies were included in the AC group, so a study with a larger sample size is needed to confirm this.

Treatment-related fatigue often influences quality of life assessments. Fatigue occurred more frequently in the AT group than in the A or AC groups (37% vs 19%, 16%), although data for grade 3/4 fatigue in the AT group were not reported. We also observed that the high-dose group had a higher incidences of any grade HFSR (34% vs 18%) compared with the low-dose group. However, the incidences of grade 3/4 proteinuria (3%) and HFSR (6%) were not increased by dose escalation or changing therapy modes (Table 5). Our findings are consistent with a previous Phase III trial, which reported that only 4% of patients developed

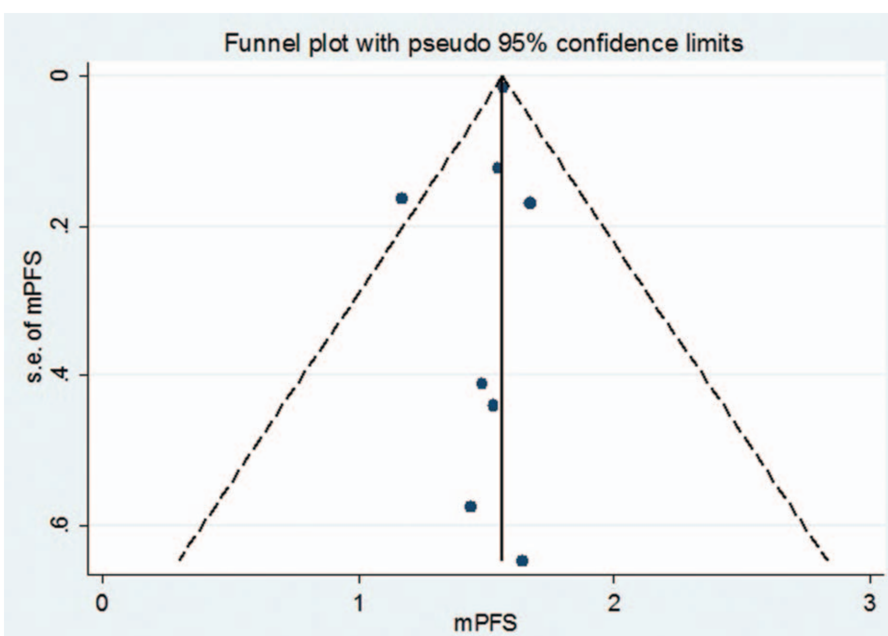

Figure 5. Funnel plot of included studies.

grade 3 proteinuria and none of them developed glomerulonephritis secondary to apatinib treatment.[12]

The combination of apatinib with EGFR-TKI led to grade 3/4 incidences of hypertension and any grade of fatigue. This may be due to the combined blockage of the EGFR and VEGF/VEGFR signaling pathways. Comparison of the JO25567 trial[55] using erlotinib and bevacizumab with erlotinib alone indicated that the combined therapy led to significantly increased grade 3 hypertension (60% vs 10%) and any grade of fatigue (13% vs 4%), respectively, in patients with EGFR mutation-positive advanced NSCLC. There are few studies reporting the safety of apatinib combined with EGFR-TKI. Therefore, results from the ongoing phase III clinical study (NCT02824458) of gefitinib with or without apatinib in the treatment of patients with advanced NSCLC harboring EGFR mutation are anticipated to provide crucial data. Chemotherapeutic drugs lead to mucositis and other adverse reactions, so apatinib combined with chemotherapy inevitably increases the number of adverse reactions observed with apatinib alone.

On the basis pf the present pooled data of efficacy and safety of apatinib in advance NSCLC, we recommend that 750 mg apatinib without other combination therapy is used for subsequent-line treatment of advanced NSCLC, and 250 to 500 mg apatinib is used when combined with EGFR-TKIs or chemotherapy.

There are some limitations to this pooled analysis. First, although no significant publication bias was found from the symmetrical funnel plot, only 1 Phase II, placebo-controlled trial is included in this pooled analysis, and most included studies belonged to single-arm retrospective trials lacking a comparative control group. Second, the results were pooled from heterogeneous studies with limited sample numbers, different treatment methods, and different treatment lines, thus resulting in unstable merged findings. Third, tumor pathology types were not stratified in this pooled study, so it remains to be determined whether apatinib efficacy differs between adenocarcinoma and squamous cell carcinoma. A well-designed randomized control trial that enrolls a large sample number is needed to further verify the efficacy of apatinib combined with or without other treatments for advanced NSCLC.

5. Conclusion

Apatinib is a novel small molecule TKI of VEGFR2 that is administered orally. Therapy with apatinib alone has shown promising efficacy and a tolerable safety profile in subsequent-line treatment of advanced NSCLC. Apatinib combination therapy with other drugs achieved improved outcomes but with higher AEs. Further research and investigation of apatinib in NSCLC are important.

Author contributions

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Investigation: Li Sun.
Methodology: Jietao Ma, ChengBo Han.
Resources: Jietao Ma, Li Sun, Shuling Zhang.
Software: Shuling Zhang.
Supervision: ChengBo Han.
Validation: Letian Huang.
Visualization: Letian Huang.
Writing – original draft: Jietao Ma.
Writing – review & editing: ChengBo Han.

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