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ORIGINAL RESEARCH

Efficacy and safety assessment of apatinib in patients with advanced gastric cancer: a meta-analysis

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Aim: This meta-analysis was performed to evaluate the efficacy and safety of apatinib in patients with advanced gastric cancer (AGC).

Methods: After evaluating the inclusion and exclusion criteria, the data of eligible randomized clinical trials (RCTs) were extracted. Outcomes including objective response rate (ORR), disease control rate (DCR), and adverse events (AEs) were analyzed in the meta-analysis.

Results: Data of 1,069 patients from 13 RCTs were statistically analyzed. Pooled odds ratio (OR) for ORR and DCR was found to be 0.46 (95% confidence interval [CI]: 0.33, 0.64; P < 0.00001) and 0.23 (95% CI: 0.15, 0.36; P < 0.00001), respectively. Compared with placebo, apatinib showed statistical significance in AEs at any grade, including leucopenia, neutropenia, thrombocytopenia, diarrhea, hypertension, proteinuria, hand-foot syndrome, and fatigue (all P < 0.05).

Conclusion: The results of our meta-analysis revealed that apatinib shows short-term efficacy over no-apatinib regimens or placebo regardless of its use as first- or second-line chemotherapy or for further treatment in patients with AGC accompanied with apparent AEs of any grade. **Keywords:** objective response rate, disease control rate, adverse events

Introduction

Gastric cancer is one of the most common cancers worldwide with approximately 1 million new cases and more than 700,000 deaths reported globally each year.¹ Although the treatment of gastric cancer has been improved significantly with the development of surgery, chemotherapy, and radiotherapy, the overall survival (OS) of patients with advanced gastric cancer (AGC) or metastatic cancer still remains less than 1 year.² Fortunately, valuation of targeted therapy has been confirmed in recent years. Trastuzumab has demonstrated to extend the median OS of patients with human epidermal growth factor receptor-2-positive AGC or cancer of the gastroesophageal junction by 2.7 months (hazard ratio [HR]=0.74, 95% confidence interval (CI): 0.60, 0.91; P=0.0046).³ In terms of antiangiogenesis, bevacizumab demonstrated efficacy in AGC with a prolonged progression-free survival (PFS) compared to placebo (6.7 versus 5.3 months, HR=0.80, 95% CI: 0.68-0.93; P=0.0037).⁴ Another randomized, placebo-controlled, Phase III clinical trial on ramucirumab revealed that patients with pretreated AGC would benefit from ramucirumab with a prolonged PFS as well as OS;5 however, it causes significant adverse events (AEs) such as proteinuria and hypertension.⁵ Therefore, there is an urgent need to develop chemotherapeutic agents with higher efficacy and lower toxicities that can be used in the treatment of AGC.

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Apatinib, a small-molecule tyrosine kinase inhibitor, selectively binds to and strongly inhibits VEGFR-2, thereby decreasing VEGF-mediated endothelial cell migration, proliferation, and density of the tumor microvasculature. A randomized, double-blind, placebo-controlled Phase III trial demonstrated that apatinib treatment significantly improved OS (6.5 versus 4.7 months, HR=0.709, 95% CI: 0.537, 0.937; P=0.0156) and PFS (2.6 versus 1.8 months, HR=0.444, 95%) CI: 0.331, 0.595; P<0.001) with an acceptable safety profile in patients with AGC refractory to two or more lines of prior chemotherapy.6 In addition, numerous randomized clinical trials (RCTs) had been developed to evaluate the efficacy and safety in patients with AGC, especially in People's Republic of China in recent years. However, according to relative literatures (Table 1), the efficacy and safety assessment of apatinib for treatment in patients with AGC were presented with inconsistency.

Therefore, in this review, we aimed to provide a detailed evaluation of the efficacy and safety profile of apatinib as the first- and second-line chemotherapeutic agent or for further treatment in patients with AGC.

Materials and methods Search strategy

The following databases were searched for the publications in English and Chinese: PubMed, Google Scholar, Cochrane Library, EBSCO Publishing, ClinicalKey, Ovid, and China National Knowledge Infrastructure (CNKI). Meeting abstracts including American Society of Clinical Oncology (ASCO) and European Society of Medical Oncology (ESMO) were also reviewed. The date of the last search was July 4, 2017. The definite words applied for searching in English were "apatinib" and "gastric cancer" or "stomach cancer" in the titles, whereas the definite words for searching in Chinese (for CNKI) were "apatinib" or "Ai tan" and "Wei ai" included in the titles.

Selection criteria

Inclusion criteria

 RCTs including patients aged above 18 years with Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2 and having at least one measurable lesion as defined by RECIST version 1.1.⁷

References	Status of	Treatment arms	Cases	End points
	treatment			-
Li et al ⁶	Second-line	Apatinib	181	ORR/DCR/PFS/OS
	or further	Placebo	92	
Li et al ¹⁰	Second-line	Placebo	48	ORR/DCR/PFS/OS
	or further	Apatinib 850 mg Qd*	48	
		Apatinib 425 mg Bid**	48	
Zhu et al''	Second-line	PTX or 5-FU or CPT-11	39	ORR/DCR
	or further	Above+apatinib	32	
Gao et al ¹²	Second-line	Apatinib+S-I	16	ORR/DCR
	or further	S-1	15	
Gao and Fang ¹³	First-line	Apatinib+FOLFIRI	40	ORR/DCR
		FOLFIRI***	40	
Wen et al ¹⁴	First-line	Apatinib+SOX	45	ORR/DCR
		SOX****	45	
Chen et al ¹⁵	Second-line	Apatinib	50	ORR
	or further	S-1	49	
Ding et al ¹⁶	Second-line	Apatinib	30	ORR/DCR
	or further	S-1	30	
Lang et al ¹⁷	Second-line	Apatinib	14	ORR/DCR
	or further	Placebo	14	
Fan et al ¹⁸	First-line	Apatinib+S-I	15	ORR/DCR
		S-1	15	
Wang et al ¹⁹	First-line	Apatinib+PS	29	ORR
		PS****	29	
Wang et al ²⁰	Second-line	Apatinib	25	ORR
	or further	S-1	25	
Xue and Cui ²¹	Second-line	Apatinib	25	ORR
	or further	Placebo	30	

Table I The characteristics of included studies

Notes: *Qd: one time a day. ***Bid: two times a day. ***FOLFIRI: irinotecan+fluorouracil+leucovorin. ****SOX: oxaliplatin+S-1. *****PS: nedaplatin+S-1.

Abbreviations: 5-FU, 5-fluorouracil; CPT-11, irinotecan; DCR, disease control rate; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PTX, paclitaxel; S-1, tegafur gimeracil oteracil potassium capsule.

- Patients included in the original research should be histologically or cytologically diagnosed as having advanced (IIIB/IIIC/IV) GC, cancer staging performed according to the 7th edition of the American Joint Committee on Cancer (AJCC).⁸
- 3. Prospective Phase II/III RCTs that evaluated apatinib alone or apatinib-based regimens as the first- or second-line chemotherapy or used for further treatment in patients with AGC. Patients who received apatinib therapy as the second-line chemotherapy or for further treatment should have experienced failure of standard regimens such as 5-fluorouracil and/or platinum-based regimens. Treatment failure was defined as intolerable AEs or disease progression during treatment with chemotherapy.
- 4. The patients included should be randomized into two arms: one managed with apatinib and the other arm handled with standard chemotherapy regimens or placebo for the control.
- 5. One of the following results should be reported: objective response rate (ORR), disease control rate (DCR), or AEs.

Exclusion criteria

- 1. Non-RCTs, meta-analysis, reviews, case reports, and correspondings were excluded.
- 2. Not prospective Phase II/III RCTs.
- 3. Studies without the field of interest of this review.
- 4. If the language was not English or Chinese.

Data extraction

- 1. Basic characteristics of RCTs including first author's names, year of publication, status of treatment, treatment regimens, patients' indications, and end points.
- 2. End points in this meta-analysis were ORR (including rate of complete response plus partial response), DCR (including rate of complete response plus partial response plus stable disease), and any grade AEs including hematological toxicities, digestive events, and general events; ORR accounts for the primary end point. AEs were assessed with National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.⁹
- 3. The meta-analysis was executed with the guidelines by Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) report.

Statistical analysis

The data were analyzed with RevMan 5.3 software. For efficacy and safety evaluation, ORR, DCR, and AEs were

calculated with odds ratio (OR). A *P*-value <0.05 was considered statistically significant. Cochrane *Q* test and inconsistency statistic (*I*²) were used to evaluate the heterogeneity among the included RCTs. Fixed-effect model was adopted for the existence of heterogeneity, in which *P*>0.1 and *I*²<50% and developed with fixed-effect model, whereas in case of *P*<0.1 and *I*²>50%, random-effect model was adopted. Publication bias was assessed using funnel plots with primary end point.

Results

Search results

According to PRISMA diagram shown in Figure 1, 502 RCTs were obtained from PubMed (n=210) and other databases (n=292). After deleting the duplicates, 413 RCTs were left, of which 86 RCTs were selected by reading titles. With the limitation to RCTs of apatinib in gastric cancer, 13 studies were included for the final analysis. All included RCTs used apatinib as the first- or second-line chemotherapy or for further treatment in patients with AGC. Table 1 shows treatment regimens and group control settings. The studies included did not report any relationship between age, sex, and clinical outcomes (P>0.05).

A total of 1,069 patients were included in the analysis, all of whom received apatinib alone or apatinib-based regimens as treatment.

Efficacy results

The pooled OR for ORR was found to be 0.46 (95% CI: 0.33, 0.64; P < 0.00001). Results of ORR with the evaluation of heterogeneity between subgroups with I^2 test showed no statistically significant heterogeneity ($I^2=0\%$, P=0.77) (Figure 2A).

Results of DCR with the evaluation of heterogeneity between subgroups with I^2 test showed statistically significant heterogeneity (I^2 =76.5%, P=0.04) (Figure 2B). After switching to Mantel–Haenzel (M–H) random-effect model for analysis, the pooled OR for DCR was found to be 0.23 (95% CI: 0.15, 0.36; P<0.00001).

AEs

For analysis of hematological toxicities with M–H random model, the pooled OR for leukopenia of any grade was found to be 5.73 (95% CI: 2.90, 11.32; P<0.00001). The pooled ORs for neutropenia, anemia, and thrombocytopenia of any grade were found to be 3.38 (95% CI: 1.57, 7.29; P=0.002), 1.25 (95% CI: 0.83, 1.88; P=0.28), and 2.25 (95% CI: 1.30, 3.90; P=0.004), respectively (Figure 3A).

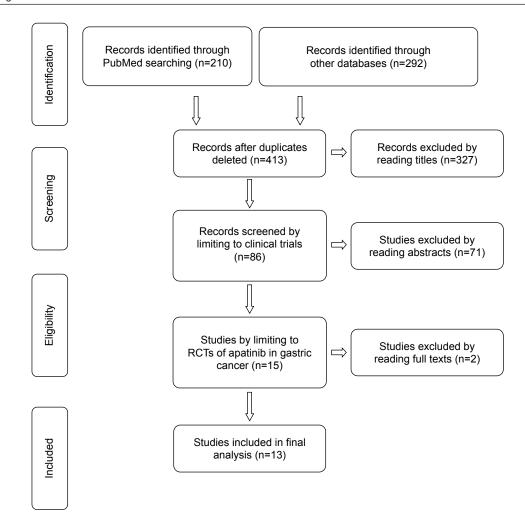


Figure I Study selection procedure with PRISMA flow diagram.

Abbreviations: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCTs, randomized controlled trials.

In terms of digestive events, the pooled ORs for diarrhea and nausea/vomiting of any grade were found to be 2.88 (95% CI: 1.46, 5.68; P=0.002) and 1.24 (95% CI: 0.74, 2.08; P=0.42), respectively (Figure 3B).

When referring to the general events, the pooled ORs for hypertension, proteinuria, hand-foot syndrome, and fatigue of any grade were found to be 10.76 (95% CI: 5.94, 17.49; P < 0.00001), 4.55 (95% CI: 2.78, 7.44; P < 0.00001), 5.15 (95% CI: 2.91, 9.11; P < 0.00001), and 1.67 (95% CI: 1.01, 2.76; P=0.04), respectively (Figure 3C1 and 2).

Publication bias

Funnel plot with ORR did not reveal any significant publication bias (Figure 4).

Discussion

To our knowledge, this is the first meta-analysis to evaluate the efficacy and safety of apatinib in patients with AGC. The results of this meta-analysis have demonstrated that apatinib shows short-term efficacy (ORR: 0.46, 95% CI: 0.33, 0.64; P < 0.00001; DCR: 0.23, 95% CI: 0.15, 0.36; P < 0.00001) over no-apatinib regimens or placebo regardless of apatinib being administered as first- or second-line chemotherapy or for further treatment in patients with AGC. In addition, apatinib has been accompanied with substantial AEs of any grade, including hematological toxicities, digestive events, and general events, such as hypertension, proteinuria, hand-foot syndrome, and fatigue compared to the control treatment.

Apatinib, was invented in People's Republic of China and approved by the China Food and Drug Administration (CFDA) for further treatment in patients with AGC or esophagogastric junction adenocarcinoma on October 17, 2014.²² This is the reason why majority of the relative clinical trials have been developed in the past 1 or 2 years in People's Republic of China. During our analysis of ORR, all included studies were pooled to gather statistics, three of which had been designed as comparative trials between apatinib and tegafur gimeracil oteracil potassium capsule (S-1) which had already

A	Study or subgroup	Apatinib Events	Total	No apatii Events	nib Total	Weight (%)	Odds ratio M–H, fixed, 95% Cl	Odds ratio M–H, fixed, 95% Cl	
	First-line								
	Fan et al ¹⁸	11	15	14	15	3.5	0.20 (0.02, 2.02)		
	Gao and Fang ¹³	21	40	26	40	11.6	0.60 (0.24, 1.46)		
	Wang et al19	6	29	10	29	7.4	0.50 (0.15, 1.61)		
	Wen et al14	27	45	34	45	12.7	0.49 (0.20, 1.20)		
	Subtotal (95% CI)		129		129	35.3	0.49 (0.29, 0.85)	•	
	Total events	65		84					
	Heterogeneity: $\chi^2=0$.77, df=3 (P	=0.86); /2	² =0%					
	Test for overall effect	t: Z=2.54 (P	=0.01)						
	Second-line or furt	her							
	Chen et al ¹⁵	16	50	17	49	10.9	0.89 (0.38, 2.04)		
	Ding et al ¹⁶	16	30	17	30	7.4	0.87 (0.32, 2.42)		
	Gao et al ¹²	9	16	11	15	4.7	0.47 (0.10, 2.12)		
	Lang et al ¹⁷	11	14	13	14	2.6	0.28 (0.03, 3.11)		
	Li et al ⁶	176	182	92	92	4.1	0.15 (0.01, 2.63)		
	Li et al ¹⁰	45	48	48	48	3.2	0.13 (0.01, 2.67)		
	Wang et al ²⁰	15	25	18	25	6.7	0.58 (0.18, 1.91)		
	Xue and Cui ²¹	11	25	24	30	11.5	0.20 (0.06, 0.65)		
	Zhu et al ¹¹	20	39	27	32	13.5	0.19 (0.06, 0.61)		
	Subtotal (95% CI)	20	429	2,	335	64.7	0.45 (0.30, 0.68)	•	
	Heterogeneity: $\chi^2=9$ Test for subgroup dif		=3.81 (<i>P</i> =						
	Total (95% CI)		558		464	100	0.46 (0.33, 0.64)	•	
	Total events	384		351			Ĩ		
	Heterogeneity: $\chi^2=1$						0.01	0.1 1	10
	Test for overall effect Test for subgroup dit				·)· 12-09/			Favors apatinib Favor	s no apatinib
	lest for subgroup an	lielences. χ	-0.00, u), 7 -0 %				-
3	Study or	Apatinib		No apat		Weight	Odds ratio M–H,	Odds ratio M–H,	
	subgroup	Events	Total	Events	Total	(%)	random, 95% Cl	random, 95% Cl	
	First-line Fan et al ¹⁸	1	15	5	15	3.7	0.14 (0.01, 1.42)		
	Gao and Fang ¹³	7	40	15	40	14.3	0.35 (0.13, 1.00)		
	Wen et al ¹⁴	, 10	45	16	45	16.7	0.52 (0.20, 1.31)		
	Subtotal (95% CI)		100		100	34.7	0.40 (0.20, 0.77)		
	Total events	18		36		•		•	
	Heterogeneity: $\tau^2=0$. Test for overall effect	.00; χ²=1.13			%				
	Second-line or furt	her							
	Ding et al ¹⁶	2	30	4	30	5.8	0.46 (0.08, 2.75)		
	Gao et al ¹²	3	16	5	15	6.7	0.46 (0.09, 2.41)		
	Lang et al ¹⁷	3	14	11	14	5.7	0.07 (0.01, 0.45) -		
	Liptal ⁶	105	181	84	02	21.0	0.13 (0.06, 0.29)		

Figure 2 Forest plot of ORR (A) and DCR (B) between apatinib-alone or apatinib-based regimens and no-apatinib groups.
Abbreviations: CI, confidence interval; DCR, disease control rate; M–H, Mantel–Haenzel; ORR, objective response rate.

been recommended for standard chemotherapy in People's Republic of China according to JCOG9912.²³ Owing to the second-line chemotherapeutic status of apatinib or S-1 in the three trials, they were considered for the final analysis.^{15,16,20}

105

24

6

143

161

Test for overall effect: Z=7.23 (P<0.00001)

Test for overall effect: Z=6.35 (P<0.00001)

Heterogeneity: τ²=0.00; χ²=4.64, df=5 (P=0.46); l²=0%

Heterogeneity: *r*²=0.10; *χ*²=10.05, *df*=8 (*P*=0.26); *I*²=20%

Test for subgroup differences: χ^2 =4.25, df=1 (P=0.04); I²=76.5%

181

48

39

328

428

84

43

14

161

197

92

48

32

231

331

21.0

133

12.8

65.3

100

0.13 (0.06, 0.29)

0.12 (0.04, 0.34)

0.23 (0.08, 0.71)

0.17 (0.10, 0.27)

0.23 (0.15, 0.36)

0.01

With the pooled analysis of short-term efficacy including ORR and DCR, it is evident that apatinib can shrink the size of the tumor with or without chemotherapy; its efficacy was found to be in accordance with another antiangiogenic agent,

0.1

Favors apatinib

1

Li et al6

Li et al10

Zhu et al11

Total events

Total (95% CI)

Total events

Subtotal (95% CI)

10

Favors no apatinib

100

ramucirumab. According to some Phase III studies, a significant ORR was observed in treatment group with ramucirumab compared to placebo group, including in patients with AGC or gastroesophageal junction adenocarcinoma,^{5,24} non-small-cell lung cancer (NSCLC),²⁵ and advanced hepatocellular carcinoma.²⁶ Meanwhile, ramucirumab has shown the benefits of improved OS in patients with solid carcinomas such as gastric cancer, NSCLC, and colorectal cancer.²⁷ However,

Α

Study or subgroup	Apatinib Events	Total	No apat Events	inib Total	Weight (%)	Odds ratio M–H, random, 95% Cl	Odds ratio M–H, random, 95% Cl
_eukopenia							
an et al ¹⁸	11	14	2	14	2.5	22.00 (3.08, 157.34)	
ao et al ¹²	14	16	12	15	2.5	1.75 (0.25, 12.28)	
ao and Fang ¹³	21	40	11	40	5.3	2.91 (1.15, 7.39)	
ang et al ¹⁷	11	14	2	14	2.5	22.00 (3.08, 157.34)	
et al6	71	176	8	91	5.8	7.02 (3.20, 15.39)	
et al ¹⁰	23	48	4	47	4.5	9.89 (3.07, 31.89)	
ue and Cui ²¹	2	25	2	30	2.4	1.22 (0.16, 9.33)	
ubtotal (95% CI)		333		251	25.5	5.73 (2.90, 11.32)	•
otal events	153		41				
eterogeneity: $\tau^2=0.33$	3; $\chi^2 = 10.37$,	df=6 (P=	=0.11); / ² =4	2%			
est for overall effect:			-				
eutropenia							
ao and Fang ¹³	11	40	7	40	4.8	1.79 (0.61, 5.22)	
ang et al ¹⁷	9	14	2	14	2.7	10.80 (1.69, 68.94)	
et al ⁶	66	176	9	91	5.9	5.47 (2.57, 11.61)	
et al ¹⁰	18	48	3	47	4.0	8.80 (2.38, 32.53)	
/en et al ¹⁴	5	45	4	45	3.8	1.28 (0.32, 5.12)	
ue and Cui ²¹	1	45 25	4	40 30	5.8 1.8	0.58 (0.05, 6.84)	
ubtotal (95% CI)	1	20 348	2	30 267	23.1	3.38 (1.57, 7.29)	
otal events	110	040	27	201	20.1	0.00 (1.01, 1.20)	-
eterogeneity: $\tau^2=0.44$		df=5 (D-		1%			
est for overall effect:			-0.07), 7 = 5	1 /0			
		,					
nemia an et al ¹⁸	10	15	4	15	3.3	5.50 (1.15, 26.41)	
ao et al ¹²	10	16	- 10	15	3.5	1.10 (0.24, 4.96)	
ao and Fang ¹³	19	40	16	40	5.4	1.36 (0.56, 3.29)	
et al ⁶	44	40 176	22	40 91	5.4 6.5	1.05 (0.58, 1.88)	
et al ¹⁰	9	48	9	47	0.5 4.9	0.97 (0.35, 2.72)	
ue and Cui ²¹	1	25 320	0	30 228	1.2 24 0	3.73 (0.15, 95.79) 1 25 (0 83, 1 88)	
ubtotal (95% CI)	04	320	61	238	24.9	1.25 (0.83, 1.88)	T
otal events	94		61	,			
eterogeneity: $\tau^2=0.00$ est for overall effect:			J.48); /*=0%	o			
hrombocytopenia	2-1.00 (7-1	0.20)					
an et al ¹⁸	4	15	3	15	3.0	1.45 (0.26, 8.01)	
ao et al ¹²	6	16	7	15	3.7	0.69 (0.16, 2.87)	
ao and Fang ¹³	7	40	2	40	3.2	4.03 (0.78, 20.76)	
et al ⁶	44	176	6	91	5.4	4.72 (1.93, 11.56)	
et al ¹⁰	14	48	6	47	4.8	2.81 (0.98, 8.11)	
en et al ¹⁴	4	45	3	45	4.0 3.4	1.37 (0.29, 6.48)	
ue and Cui ²¹	3	25	3	30	3.0	1.23 (0.23, 6.69)	
ubtotal (95% CI)	0	25 365	0	283	26.5	2.25 (1.30, 3.90)	
tal events	82	000	30	200	20.0	2.20 (1.00, 0.30)	-
		IF-6 (D-0		0/			
eterogeneity: $\tau^2=0.09$ est for overall effect:			J.ST), I ⁻ =15	/0			
	(,	,		1 0 2 0	100	2 75 (1 00 1 02)	
otal (95% CI) otal events	439	1,366	159	1,039	100	2.75 (1.88, 4.02)	•
leterogeneity: $\tau^2=0.48$		df=25 (E		12=57%		L	
est for overall effect:				-51/0		0.001	0.1 1 10
est for subgroup diffe		,			40/		vors apatinib Favors no apatinib

Figure 3 (Continued)

Study or subgroup	Apatinib Events) Total	No apati Events	inib Total	Weight (%)	Odds ratio M–H, fixed, 95% Cl			s ratio M–H, , 95% Cl		
Diarrhea											
Fan et al ¹⁸	3	15	2	15	4.4	1.63 (0.23, 11.46)				_	
Gao et al12	8	16	6	15	8.4	1.50 (0.36, 6.23)		_			
Lang et al ¹⁷	3	14	0	14	1.0	8.83 (0.41, 188.73	3)	-			\rightarrow
Li et al6	20	176	3	91	9.5	3.76 (1.09, 13.01)	'				
Li et al ¹⁰	8	48	2	47	4.6	4.50 (0.90, 22.44)					
Wen et al14	1	45	1	45	2.7	1.00 (0.06, 16.50)			_		
Subtotal (95% CI)		314		227	30.6	2.88 (1.46, 5.68)					
Total events	43		14								
Nausea/vomiting Fan et al ¹⁸ Gao et al ¹²	11 11	15 16	6 11	15 15	4.4 9.7	4.13 (0.88, 19.27) 0.80 (0.17, 3.80)	1				
Gao and Fang ¹³	16	40	11	40	9.7 18.0	1.76 (0.69, 4.50)					
Li et al ¹⁰	8	48	10	47	22.9	0.74 (0.26, 2.08)					
Wen et al ¹⁴	5	45	6	45	14.5	0.81 (0.23, 2.88)			-		
Subtotal (95% CI)	U	164	U	162	69.4	1.24 (0.74, 2.08)					
Total events	51	104	44	102	00.4	1.24 (0.74, 2.00)					
Heterogeneity: $\chi^2=4$ Test for overall effect			l ² =12%								
Total (95% CI)		478		389	100	1.74 (1.16, 2.61)			•		
Total events	94		58								
Heterogeneity: $\chi^2=1$		•									
Test for overall effect				05) 12 7	2.0%		0.01	0.1	1	10	
Test for subgroup di	inerences: ;	<i>τ</i> =3.73,	$\mu = 1 (P=0.)$	05); /=/:	3.∠%			Favors apatinib	Favors	no apatinil	D

Favors apatinib

C1

Hypertension Fan et all ¹⁸ 8 15 1 15 0.7 16.00 (1.66, 154.59) Gao et all ¹² 3 16 0 15 0.6 8.04 (0.38, 169.99) Gao and Fang ¹³ 17 40 3 40 2.7 9.12 (2.40, 34.58) Lang et all ¹⁷ 9 14 0 14 0.3 50.09 (2.47, 1.014.62) Li et al ⁶ 65 176 5 91 6.4 10.07 (3.89, 26.10) Li et al ¹⁰ 19 48 2 47 1.9 14.74 (3.19, 68.07) Wen et al ¹⁴ 5 4.5 1 4.5 5.00 (0.62, 49.11)	Study or	Apatinib		No apati		Weight	Odds ratio M–H,	Odds ratio M–H,
Fan et al ¹⁸ 8 15 1 15 0.7 16.00 (1.66, 154.59) Gao et al ¹² 3 16 0 15 0.6 8.04 (0.38, 169.99) Gao and Fang ¹³ 17 40 3 40 2.7 9.12 (2.40, 34.58) Lang et al ¹⁷ 9 14 0 14 0.3 50.09 (2.47, 1.014.62) Li et al ⁶ 65 176 5 91 6.4 10.07 (3.89, 26.10) Li et al ¹⁰ 19 48 2 47 1.9 14.74 (3.19, 68.07) Wen et al ¹⁴ 5 45 1 45 1.4 5.50 (0.62, 49.11) Xue and Cui ²¹ 1 25 0 30 0.7 3.73 (0.15, 95.79) Subtotal (95% Cl) 379 297 14.7 10.76 (5.94, 19.49) (5.94, 19.49) Total events 127 12 Heterogeneity: χ^2 =2.17, <i>df=7</i> (<i>P</i> =0.95); <i>I</i> ² =0% 7 3.00 (0.71, 69.49) (6.0, 256.66) (6.11, 75.50) (6.14, 6.2) (6.14, 6.2) (6.14, 6.2) (6.14, 6.2) (6.14, 6.2) (6.14, 6.2) (6.14, 6.2) (6.14, 6.2)	subgroup	Events	Total	Events	Total	(%)	fixed, 95% Cl	fixed, 95% Cl
Gao et al ¹² 3 16 0 15 0.6 8.04 (0.38, 169.99) Gao and Fang ¹³ 17 40 3 40 2.7 9.12 (2.40, 34.58) Lang et al ¹⁷ 9 14 0 14 0.3 50.09 (2.47, 1.014.62) Li et al ⁶ 65 176 5 91 6.4 10.07 (3.89, 26.10) Li et al ¹⁰ 19 48 2 47 1.9 14.74 (3.19, 68.07) Wen et al ¹⁴ 5 45 1 45 1.4 5.50 (0.62, 49.11) Xue and Cui ²¹ 1 25 0 30 0.7 3.73 (0.15, 95.79) Subtotal (95% Cl) 379 297 14.7 10.76 (5.94, 19.49) 4 Total events 127 12 12 12 12 Heterogeneity: $\chi^2=2.17, df=7$ ($P=0.95$); $l^2=0\%$ 7 3.00 (0.11, 79.50)	Hypertension							
Gao and Fang ¹³ 17 40 3 40 2.7 9.12 (2.40, 34.58) Lang et al ¹⁷ 9 14 0 14 0.3 50.09 (2.47, 1,014.62) Li et al ⁶ 65 176 5 91 6.4 10.07 (3.89, 26.10) Li et al ¹⁰ 19 48 2 47 1.9 14.74 (3.19, 68.07) Wen et al ¹⁴ 5 45 1 45 1.4 5.50 (0.62, 49.11) Xue and Cui ²¹ 1 25 0 30 0.7 3.73 (0.15, 95.79) Subtotal (95% CI) 379 297 14.7 10.76 (5.94, 19.49) (5.94, 19.49) Total events 127 12 Heterogeneity: χ^2 =2.17, df=7 (P=0.95); l ² =0% 7 3.00 (0.71, 69.49) (5.94, 19.49) Gao et al ¹² 1 16 0 15 0.7 3.00 (0.11, 79.50) (5.94, 19.49) Lang et al ¹⁷⁷ 4 14 0.5 12.43 (0.60, 256.66) (6.9, 10, 10, 10, 10, 10, 10, 10, 10, 10, 10	Fan et al ¹⁸	8	15	1	15	0.7	16.00 (1.66, 154.59)	
Lang et al ¹⁷ 9 14 0 14 0.3 $50.09 (2.47, 1,014.62)$ Li et al ⁶ 65 176 5 91 6.4 10.07 (3.89, 26.10) Li et al ¹⁰ 19 48 2 47 1.9 14.74 (3.19, 68.07) Wen et al ¹⁴ 5 45 1 45 1.4 5.50 (0.62, 49.11) Xue and Cui ²¹ 1 25 0 30 0.7 3.73 (0.15, 95.79) Subtotal (95% CI) 379 297 14.7 10.76 (5.94, 19.49) Total events 127 12 Heterogeneity: $\chi^2=2.17$, $df=7$ ($P=0.95$); $I^2=0\%$ Test for overall effect: $Z=7.84$ ($P<0.00001$) Proteinuria Fan et al ¹⁸ 5 15 1 15 1.0 7.00 (0.71, 69.49) Gao et al ¹² 1 16 0 15 0.7 3.00 (0.11, 79.50) Lang et al ¹⁷ 4 14 0 14 0.5 12.43 (0.60, 256.66) Li et al ⁶ 84 176 15 91 16.0 4.63 (2.47, 8.67) Li et al ¹⁶ 13 48 6 47 6.8 2.54 (0.87, 7.38) Wen et al ¹⁴ 3 45 0 45 0.7 7.49 (0.38, 149.40) Xue and Cui ²¹ 4 25 0 30 0.6 12.77 (0.65, 249.71) Subtotal (95% CI) 339 257 26.5 4.55 (2.78, 7.44)	Gao et al ¹²	3	16	0	15	0.6	8.04 (0.38, 169.99)	
Li et al ⁶ 65 176 5 91 6.4 10.07 (3.89, 26.10) Li et al ¹⁰ 19 48 2 47 1.9 14.74 (3.19, 68.07) Wen et al ¹⁴ 5 45 1 45 1.4 5.50 (0.62, 49.11) Xue and Cui ²¹ 1 25 0 30 0.7 3.73 (0.15, 95.79) Subtotal (95% CI) 379 297 14.7 10.76 (5.94, 19.49) Total events 127 12 Heterogeneity: χ^2 =2.17, df =7 (P =0.95); l^2 =0% Test for overall effect: Z =7.84 (P <0.00001) Proteinuria Fan et al ¹⁸ 5 15 1 15 1.0 7.00 (0.71, 69.49) Gao et al ¹² 1 16 0 15 0.7 3.00 (0.11, 79.50) Lang et al ¹⁷ 4 14 0 14 0.5 12.43 (0.60, 256.66) Li et al ⁶ 84 176 15 91 16.0 4.63 (2.47, 8.67) Li et al ¹⁶ 13 48 6 47 6.8 2.54 (0.87, 7.38) Wen et al ¹⁴ 3 45 0 45 0.7 7.49 (0.38, 149.40) Xue and Cui ²¹ 4 25 0 30 0.6 12.77 (0.65, 249.71) Subtotal (95% CI) 339 257 26.5 4.55 (2.78, 7.44)	Gao and Fang ¹³	17	40	3	40	2.7	9.12 (2.40, 34.58)	
Li et al ⁶ 65 176 5 91 6.4 10.07 (3.89, 26.10) Li et al ¹⁰ 19 48 2 47 1.9 14.74 (3.19, 68.07) Wen et al ¹⁴ 5 45 1 45 1.4 5.50 (0.62, 49.11) Xue and Cui ²¹ 1 25 0 30 0.7 3.73 (0.15, 95.79) Subtotal (95% CI) 379 297 14.7 10.76 (5.94, 19.49) Total events 127 12 Heterogeneity: χ^2 =2.17, df =7 (P =0.95); l^2 =0% Test for overall effect: Z =7.84 (P <0.00001) Proteinuria Fan et al ¹⁸ 5 15 1 15 1.0 7.00 (0.71, 69.49) Gao et al ¹² 1 16 0 15 0.7 3.00 (0.11, 79.50) Lang et al ¹⁷ 4 14 0 14 0.5 12.43 (0.60, 256.66) Li et al ⁶ 84 176 15 91 16.0 4.63 (2.47, 8.67) Li et al ¹⁰ 13 48 6 47 6.8 2.54 (0.87, 7.38) Wen et al ¹⁴ 3 45 0 45 0.7 7.49 (0.38, 149.40) Xue and Cui ²¹ 4 25 0 30 0.6 12.77 (0.65, 249.71) Subtotal (95% CI) 339 257 26.5 4.55 (2.78, 7.44)	Lang et al ¹⁷	9	14	0	14	0.3	50.09 (2.47, 1,014.62)	
Wen et al ¹⁴ 5 45 1 45 1.4 5.50 (0.62, 49.11) Xue and Cul ²¹ 1 25 0 30 0.7 3.73 (0.15, 95.79) Subtotal (95% Cl) 379 297 14.7 10.76 (5.94, 19.49) • Total events 127 12 Heterogeneity: $\chi^2=2.17$, $df=7$ ($P=0.95$); $l^2=0\%$ Test for overall effect: $Z=7.84$ ($P<0.00001$) • Proteinuria Fan et al ¹⁸ 5 15 1 15 0.7 3.00 (0.11, 79.50) Lang et al ¹⁷² 1 16 0 15 0.7 3.00 (0.11, 79.50) Li et al ¹⁶ 84 176 15 91 16.0 4.63 (2.47, 8.67) Li et al ¹⁶ 84 176 15 91 16.0 4.63 (2.47, 8.67) Li et al ¹⁰ 13 48 6 47 6.8 2.54 (0.87, 7.38) Wen et al ¹⁴ 3 45 0 30 0.6 12.77 (0.65, 249.71) Subtotal (95% Cl) 339 257 26.5 4.55 (2.78, 7.44) •		65	176	5	91	6.4	10.07 (3.89, 26.10)	
Xue and Cui^{21} 1 25 0 30 0.7 3.73 (0.15, 95.79) Subtotal (95% CI) 379 297 14.7 10.76 (5.94, 19.49) Total events 127 12 Heterogeneity: $\chi^2=2.17$, $df=7$ ($P=0.95$); $I^2=0\%$ 7 14.7 10.76 (5.94, 19.49) Test for overall effect: $Z=7.84$ ($P<0.00001$) - - - Proteinuria - - - - Gao et al ¹² 1 16 0 15 0.7 3.00 (0.11, 79.50) Lang et al ¹⁷⁷ 4 14 0 14 0.5 12.43 (0.60, 256.66) - Li et al ⁶ 84 176 15 91 16.0 4.63 (2.47, 8.67) - Li et al ⁶ 84 176 15 91 16.0 4.63 (2.47, 8.67) - - Li et al ¹⁰ 13 48 6 47 6.8 2.54 (0.87, 7.38) - - Wen et al ¹⁴ 3 45 0 30 0.6 12.77 (0.65, 249.71) - - - Subtotal (95% C	Li et al ¹⁰	19	48	2	47	1.9	14.74 (3.19, 68.07)	
Subtotal (95% Cl) 379 297 14.7 10.76 (5.94, 19.49) Total events 127 12 Heterogeneity: $\chi^2=2.17$, $df=7$ ($P=0.95$); $P=0\%$ Test for overall effect: $Z=7.84$ ($P<0.00001$) Proteinuria Fan et al ¹⁸ 5 15 1 15 0.7 3.00 (0.71, 69.49) Gao et al ¹² 1 16 0 15 0.7 3.00 (0.11, 79.50) Lang et al ¹⁷⁷ 4 14 0 14 0.5 12.43 (0.60, 256.66) Li et al ⁶ 84 176 15 91 16.0 4.63 (2.47, 8.67) Li et al ¹⁶ 13 48 6 47 6.8 2.54 (0.87, 7.38) Wen et al ¹⁴ 3 45 0 30 0.6 12.77 (0.65, 249.71) Subtotal (95% Cl) 339 257 26.5 4.55 (2.78, 7.44) \checkmark	Wen et al14	5	45	1	45	1.4	5.50 (0.62, 49.11)	
Total events 127 12 Heterogeneity: χ^2 =2.17, df=7 (P=0.95); I²=0% Test for overall effect: Z=7.84 (P<0.00001) Proteinuria Fan et al ¹⁸ 5 15 1 15 1.0 7.00 (0.71, 69.49) Gao et al ¹² 1 16 0 15 0.7 3.00 (0.11, 79.50) Lang et al ¹⁷ 4 14 0 14 0.5 12.43 (0.60, 256.66) Li et al ⁶ 84 176 15 91 16.0 4.63 (2.47, 8.67) Li et al ¹⁰ 13 48 6 47 6.8 2.54 (0.87, 7.38) Wen et al ¹⁴ 3 45 0 45 0.7 7.49 (0.38, 149.40) Xue and Cui ²¹ 4 25 0 30 0.6 12.77 (0.65, 249.71) Subtotal (95% CI) 339 257 26.5 4.55 (2.78, 7.44) \checkmark	Xue and Cui ²¹	1	25	0	30	0.7	3.73 (0.15, 95.79)	
Heterogeneity: $\chi^2=2.17$, $df=7$ (P=0.95); $P=0\%$ Test for overall effect: Z=7.84 (P<0.00001)	Subtotal (95% C	;1)	379		297	14.7	10.76 (5.94, 19.49)	•
Test for overall effect: $Z=7.84$ (P<0.00001)	Total events	127		12				
Fan et al5151151.0 $7.00 (0.71, 69.49)$ Gao et al12116015 0.7 $3.00 (0.11, 79.50)$ Lang et al140140.5 $12.43 (0.60, 256.66)$ Li et al84176159116.0 $4.63 (2.47, 8.67)$ Li et al13486476.8 $2.54 (0.87, 7.38)$ Wen et al345045 0.7 $7.49 (0.38, 149.40)$ Xue and Cul ²¹ 425030 0.6 $12.77 (0.65, 249.71)$ Subtotal (95% CI)33925726.5 $4.55 (2.78, 7.44)$ Total events11422 22 $4.55 (2.78, 7.44)$		11ECL 2-7.04	(F <0.00	001)				
Gao et al 12 1 16 0 15 0.7 3.00 (0.11, 79.50) Lang et al 17 4 14 0 14 0.5 12.43 (0.60, 256.66) Li et al 6 84 176 15 91 16.0 4.63 (2.47, 8.67) Li et al 10 13 48 6 47 6.8 2.54 (0.87, 7.38) Wen et al 14 3 45 0 45 0.7 7.49 (0.38, 149.40) Xue and Cul 21 4 25 0 30 0.6 12.77 (0.65, 249.71) Subtotal (95% Cl) 339 257 26.5 4.55 (2.78, 7.44) \checkmark								
Lang et al140140.512.43 (0.60, 256.66)Li et al84176159116.0 $4.63 (2.47, 8.67)$ Li et al13486476.8 $2.54 (0.87, 7.38)$ Wen et al3450450.7 $7.49 (0.38, 149.40)$ Xue and Cul ²¹ 4250300.612.77 (0.65, 249.71)Subtotal (95% CI)33925726.54.55 (2.78, 7.44)Total events11422 $4.55 (2.78, 7.44)$								
Li et al ⁶ 84 176 15 91 16.0 4.63 (2.47, 8.67) Li et al ¹⁰ 13 48 6 47 6.8 2.54 (0.87, 7.38) Wen et al ¹⁴ 3 45 0 45 0.7 7.49 (0.38, 149.40) Xue and Cul ²¹ 4 25 0 30 0.6 12.77 (0.65, 249.71) Subtotal (95% Cl) 339 257 26.5 4.55 (2.78, 7.44) \checkmark	Fan et al ¹⁸							
Li et al ¹⁰ 13 48 6 47 6.8 2.54 (0.87, 7.38) Wen et al ¹⁴ 3 45 0 45 0.7 7.49 (0.38, 149.40) Xue and Cul ²¹ 4 25 0 30 0.6 12.77 (0.65, 249.71) Subtotal (95% CI) 339 257 26.5 4.55 (2.78, 7.44)	Fan et al ¹⁸ Gao et al ¹²	1	16	0	15	0.7	3.00 (0.11, 79.50)	
Wen et al ¹⁴ 3 45 0 45 0.7 7.49 (0.38, 149.40) Xue and Cul ²¹ 4 25 0 30 0.6 12.77 (0.65, 249.71) Subtotal (95% Cl) 339 257 26.5 4.55 (2.78, 7.44)	Fan et al ¹⁸ Gao et al ¹² Lang et al ¹⁷	1 4	16 14	0 0	15 14	0.7 0.5	3.00 (0.11, 79.50) 12.43 (0.60, 256.66)	<u>·</u>
Xue and Cul ²¹ 4 25 0 30 0.6 12.77 (0.65, 249.71) Subtotal (95% Cl) 339 257 26.5 4.55 (2.78, 7.44) \checkmark Total events 114 22 257 26.5 4.55 (2.78, 7.44) \checkmark	Fan et al ¹⁸ Gao et al ¹² Lang et al ¹⁷ Li et al ⁶	1 4 84	16 14 176	0 0 15	15 14 91	0.7 0.5 16.0	3.00 (0.11, 79.50) 12.43 (0.60, 256.66) 4.63 (2.47, 8.67)	
Subtotal (95% CI) 339 257 26.5 4.55 (2.78, 7.44) Total events 114 22	Fan et al ¹⁸ Gao et al ¹² Lang et al ¹⁷ Li et al ⁶ Li et al ¹⁰	1 4 84 13	16 14 176 48	0 0 15 6	15 14 91 47	0.7 0.5 16.0 6.8	3.00 (0.11, 79.50) 12.43 (0.60, 256.66) 4.63 (2.47, 8.67) 2.54 (0.87, 7.38)	
Total events 114 22	Fan et al ¹⁸ Gao et al ¹² Lang et al ¹⁷ Li et al ⁶ Li et al ¹⁰ Wen et al ¹⁴	1 4 84 13 3	16 14 176 48 45	0 0 15 6	15 14 91 47 45	0.7 0.5 16.0 6.8 0.7	3.00 (0.11, 79.50) 12.43 (0.60, 256.66) 4.63 (2.47, 8.67) 2.54 (0.87, 7.38) 7.49 (0.38, 149.40)	
	Fan et al ¹⁸ Gao et al ¹² Lang et al ¹⁷ Li et al ⁶ Li et al ¹⁰ Wen et al ¹⁴ Xue and Cui ²¹	1 4 84 13 3 4	16 14 176 48 45 25	0 0 15 6 0	15 14 91 47 45 30	0.7 0.5 16.0 6.8 0.7 0.6	3.00 (0.11, 79.50) 12.43 (0.60, 256.66) 4.63 (2.47, 8.67) 2.54 (0.87, 7.38) 7.49 (0.38, 149.40) 12.77 (0.65, 249.71)	
	Fan et al ¹⁸ Gao et al ¹² Lang et al ¹⁷ Li et al ⁶ Li et al ¹⁰ Wen et al ¹⁴ Xue and Cui ²¹	1 4 84 13 3 4 1 3	16 14 176 48 45 25	0 0 15 6 0 0	15 14 91 47 45 30	0.7 0.5 16.0 6.8 0.7 0.6	3.00 (0.11, 79.50) 12.43 (0.60, 256.66) 4.63 (2.47, 8.67) 2.54 (0.87, 7.38) 7.49 (0.38, 149.40) 12.77 (0.65, 249.71)	
Test for overall effect: Z=6.04 (P<0.00001)	Fan et al ¹⁸ Gao et al ¹² Lang et al ¹⁷ Li et al ⁶ Li et al ¹⁰ Wen et al ¹⁴ Xue and Cui ²¹ Subtotal (95% C Total events Heterogeneity: χ	1 4 84 13 3 4 (1) 114 ² =2.34, <i>df</i> =6	16 14 176 48 45 25 339 (P=0.89	0 0 15 6 0 0 22); / ² =0%	15 14 91 47 45 30	0.7 0.5 16.0 6.8 0.7 0.6	3.00 (0.11, 79.50) 12.43 (0.60, 256.66) 4.63 (2.47, 8.67) 2.54 (0.87, 7.38) 7.49 (0.38, 149.40) 12.77 (0.65, 249.71)	

Figure 3 (Continued)

Apatinib

No apatinib

Weight

Dovepress

subgroup	Events	Total	Events	Total	(%)	fixed, 95% Cl		fixed,	95% CI	
Hand-foot syndi	rome									
Fan et al ¹⁸	7	15	5	15	4.1	1.75 (0.40, 7.66)			·	
Gao et al ¹²	5	16	0	15	0.5	14.83 (0.74, 295.97)		-		
Gao and Fang ¹³	8	40	5	40	6.2	1.75 (0.52, 5.90)		_		
Lang et al17	3	14	0	14	0.6	8.83 (0.41, 188.73)				
Li et al6	49	176	2	91	2.9	17.17 (4.07, 72.44)				_
Li et al ¹⁰	12	48	2	47	2.3	7.50 (1.58, 35.68)				
Wen et al14	2	45	2	45	3.0	1.00 (0.13, 7.43)				
Xue and Cui ²¹	1	25	0	30	0.7	3.73 (0.15, 95.79)			•	
Subtotal (95% C	;1)	379		297	20.4	5.15 (2.91, 9.11)				
Total events	87		16							
Heterogeneity: χ^2	² =11.19, <i>df=</i> 7	7 (P=0.13	3); /²=37%							
Test for overall ef	ffect: Z=5.63	(P<0.00	001)							
Fatigue	6	15	5	15	4.6	1 33 (0 30 5 91)				
Fan et al ¹⁸	6	15	5	15	4.6	1.33 (0.30, 5.91)				
Gao et al ¹²	10	16	8	15	4.8	1.46 (0.35, 6.11)				
Li et al ⁶	36	176	13	91	21.1	1.54 (0.77, 3.08)			+	
Li et al ¹⁰	8	48	5	47	6.5	1.68 (0.51, 5.57)		-		
Wen et al14	5	45	1	45	1.4	5.50 (0.62, 49.11)			· · ·	
Subtotal (95% C		300		213	38.5	1.67 (1.01, 2.76)			-	
Total events	65		32							
Heterogeneity: χ^2	,	•								
Test for overall ef	ffect: Z=2.02	(<i>P</i> =0.04))							
Total (95% CI)		1,397		1,064	100	4.48 (3.46, 5.80)			•	
Total events	393		82							
Heterogeneity: X2										
Test for overall ef	ffect: Z=11.34	4 (<i>P</i> <0.00	0001)				0.01	0.1	1 10	100

Figure 3 Forest plot of hematological toxicity (A), digestive events (B), and general events (CI and C2) between apatinib-alone or apatinib-based regimens and noapatinib groups.

Abbreviations: CI, confidence interval; M-H, Mantel-Haenzel.

long-term efficacy of apatinib in improving PFS or OS has not been evaluated in this analysis due to the data deficiencies. Outcomes such as PFS and OS have been reported for apatinib in only two RCTs,^{6,10} which might be due to the fact that the

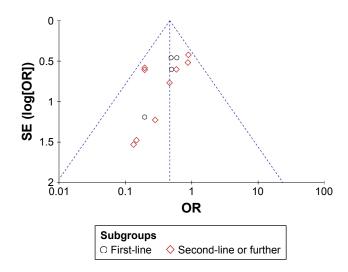


Figure 4 Funnel plot for publication bias with ORR.

Abbreviations: OR, odds ratio; ORR, objective response rate; SE, standard error.

majority of studies were conducted in years 2016 and 2017 with the immature outcomes of PFS and OS. According to the aforementioned two RCTs, apatinib shows long-term efficacy based on outcomes such as PFS and OS, which might indicate its promising role as an anticancer drug in the future.

Although majority of the trials report that the AEs of apatinib are tolerable,^{6,13,19} the pooled analysis outcomes of AEs, especially AEs of any grade, including hematological toxicities, digestive events, and general events, showed a significant difference (Figure 3). During the final analysis of AEs, the full-analysis set population was used instead of intent-to-treat population. In addition, three RCTs, which had been designed as the comparison of apatinib and S-1, had been excluded in the final analysis of AEs due to the probable bias caused by S-1 instead of placebo or other balanced regimens between apatinib groups and the control ones.^{15,16,20} As shown in Figure 3, AEs of any grade, including leucopenia, neutropenia, thrombocytopenia, diarrhea, hypertension, proteinuria, hand-foot syndrome, and fatigue had been deemed as statistically significant (P < 0.05). This might

have restricted the application of apatinib in patients with AGC, especially with poor performance status of 2 or 3. Ramucirumab has been reported to show AEs, including proteinuria,²⁸ stomatitis and gastrointestinal perforation,²⁹ hypertension,³⁰ and hematological toxicity.³¹ However, RCTs included in this meta-analysis did not report gastrointestinal perforation during the treatment with apatinib. The safety comparison between ramucirumab and apatinib is still controversial, which needs further and more direct assessment.

Other than AGC, the efficacy and safety of apatinib has been explored in more cancers, including NSCLC, osteosarcoma, advanced soft tissue sarcoma, metastatic breast cancer, prostate cancer, hepatocellular carcinoma, and colorectal cancer according to ASCO annual meeting 2017 (meeting. ascopubs.org). We believe that more promising results with regard to apatinib will be presented in the near future.

This meta-analysis has some limitations. First, all the RCTs included in the analysis were performed on Asian population (Chinese), because of the regional employment of apatinib in recent years. Missing data in Caucasian population might lead to a racial bias in the final analysis. Second, except for the two RCTs,^{6,10} the deficiency of long-term follow-up period makes us confused with the survival benefit of apatinib, which is supposed to be the paramount norm in the treatment in advanced cancers. Confirmatory prospective clinical studies in this regard are highly warranted.

Conclusion

This meta-analysis has revealed that apatinib has an advantage of short-term efficacy over no-apatinib regimens or placebo regardless of its use as first- or second-line chemotherapeutic agent or for further treatment in patients with AGC accompanied with apparent AEs of any grade.

Disclosure

The authors report no conflicts of interest in this work.

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