Original Article

Evaluation of safety and efficacy of apatinib combination with chemotherapy for ovarian cancer treatment: a systematic review and meta-analysis

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Background: Apatinib in combination with chemotherapy (CT) has been used in the treatment of ovarian cancer (OC), however, the safety and efficacy are unclear. The study aims at systematic evaluation of the safety and efficacy of the apatinib targeted therapy in combination with CT for the treatment of patients with advanced OC.

Methods: Literature about randomized controlled clinical trials was searched using search engines such as PubMed, EMBASE, Web of Science, CNKI, the Cochrane Library, CBM, VIP and the Wanfang. We collected the related clinical studies of apatinib in combination with CT in the treatment of OC. The duration of the data retrieval related to clinical studies was from the database establishment to September 2020. Adverse reactions (ADRs) due to treatment, disease control rate (DCR), and that of objective response rate (ORR), were collected as indicators to show treatment outcomes. The literature was independently screened by two researchers. They extracted the data and evaluated the risk of biases of the included studies. Then, Revman 5.4 software was employed for performing the meta-analysis.

Results: Twelve randomized controlled clinical trials with 698 patients having an advanced stage of OC were included. The results revealed that in comparison with the treatment with only CT, apatinib targeted therapy combination with CT showed significant improvement in the patients' ORR [OR =3.19, 95% CI: (2.06, 4.94), P<0.00001] and DCR [OR =4.97, 95% CI: (2.90, 8.52), P<0.00001]. The group that was treated with a combined therapy had shown proteinuria in higher amount (OR =3.08, 95% CI: 51.13–8.42, P<0.00001), while the analyses of other ADRs, such nausea and vomiting (OR =1.10, 95% CI: 0.67–1.79, P=0.71), hand-foot syndrome (OR =1.73, 95% CI: 0.97–3.10, P=0.06), hypertension (OR =1.18, 95% CI: 0.73–1.91, P=0.0.51), diarrhea (OR =1.05, 95% CI: 0.56–1.97, P=0.87), leucopenia (OR =1.22, 95% CI: 0.70–2.12, P=0.48), and myelosuppression (OR =1.00, 95% CI: 0.28–3.62, P=1.00), did not show any significant difference (P>0.05).

Discussion: The effects of apatinib combination with CT for the treatment of OC are significantly better than the CT used alone in ORR and DCR, despite with a relative low incidence of adverse effects. However, due to the very low number of studies available, the results need to be further verified using a high-quality, large sample and long-term studies.

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Keywords: Apatinib; chemotherapy (CT); combination; ovarian cancer (OC); meta-analysis

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Introduction

Ovarian cancer (OC) is a major reason for mortality in patients having gynecological malignant tumor (1), the mortality rate is second only to cervical cancer and uterine body cancer, ranking the third highest. Epidemiological survey shows that the annual incidence of new cases worldwide is 255 thousand, and the incidence rate is increasing by 0.1%/year in recent years (2). In 2018, more than 295,000 women worldwide developed epithelial ovarian cancer (EOC), of which more than 184,000 died (3). There is also a heterogenous group of rare ovarian tumours that affect mainly young patients—the non-EOCs. They are histologically and clinically distinct tumours, uncommon but not rare. Approximately 10% of the OC patients present with non-epithelial histology and those include germ cell tumours and sex-cord stromal tumours, each of which is subdivided into several histological subtypes (4). The treatment of OC includes surgery and postoperative platinum chemotherapy (CT) (5). Three or more cycles of neoadjuvant CT prior to debulking surgery and adjuvant CT is an alternative option for selected patients. Neoadjuvant CT offers the opportunity to test upfront chemosensitivity and to identify patients at higher risk of relapse. CT can effectively prevent the proliferation, invasion, and metastasis of tumor cells, but CT drugs can damage normal cells while killing tumor cells (6). This not only reduces the tolerance of patients to CT but also disturbs the survival time of patients and affects the quality of life (7). About 80% of OC patients will relapse and metastasize after standard treatment (8). The mean survival time was about 2 years (9). Therefore, there is an urgent need to explore new and effective treatment methods. The molecular advances have identified that defective DNA damage response is a defining hallmark of high grade EOC which led to specific interest in BRCA genes, which are involved in the repair of DNA double strand breaks via the homologous recombination (HR) repair pathway. Poly (ADP-ribose) polymerase (PARP) inhibition in BRCA mutant tumor cells could induce "synthetic lethality", based on the simultaneous targeting of two DNA repair pathways. Pharmacologic PARP inhibition in HR deficient tumors exploits this vulnerability. Moreover, a separate spectrum of genetic abnormalities related to the HR pathway sensitizes BRCA wild-type cancers to PARP inhibition. This molecular basis includes mutations in certain genes beyond BRCA1/2, homozygous somatic loss, and whole genome properties such as genomic scarring. Olaparib, rucaparib, and niraparib have been already commercialized in different settings in OC. Veliparib does not yet have an approved label, and its use is being investigated mostly in combination with CT or targeted agents (10).

In recent years, small molecule targeted therapy has revealed broad prospects. Using as a small molecule, the apatinib targeted therapy can suppress the proliferation and migration process of endothelial cells, induced by a vascular endothelial growth factor (VEGF) via specific binding to a VEGF receptor 2 (VEGFR-2), and hence reduces the tumor microvessels' density (11). Some studies have confirmed that it can't only be used as a sensitizer of CT drugs but also can be used in the initial or maintenance treatment of recurrent tumors (12). Chen *et al.* found that the patients with liver cancer treated by TACE combined with apatinib, the objective response rate (ORR) was higher than that of TACE alone (66.7% and 39.6%, P=0.020; 45.8% and 17.6%, P=0.021) (13). Zeng *et al.* found that low-dose apatinib has significant effect on lung squamous cell carcinoma, the MPFs was 3.1 months, and the disease control rate (DCR) was 46.2% (14). Lan *et al.* found that the ORR for apatinib mesylate in combination with etoposide used for the treatment of OC can reach more than 60% under the condition of controllable toxicity (1). Therefore, it is of great significance to evaluate clinically the safety, and efficacy of apatinib in combination with CT in the treatment of OC.

Evidence-based medicine emphasizes clinical decisions to be made based on the best available evidence on the basis of attaching importance to the clinical experience of doctors and respecting the values of patients (15). Based on high-quality clinical randomized controlled trials, systematic review/meta-analysis with rigorous methodology and clear report is the highest level of evidence recognized in the

Table 1 The search words and strategy of the PubMed database

No.	Search strategies
#1	"Apatinib"[Mesh]
#2	"rivoceranib mesylate"[Title/Abstract] OR"YN968D1"[Title/Abstract] OR"Rivoceranib"[Title/Abstract] OR"apatinib mesylate"[Title/Abstract]
#3	"Drug Therapies"[Mesh]
#4	"chemotherapy"[Title/Abstract] OR"chemotherapies"[Title/Abstract] OR"pharmacotherapy"[Title/Abstract] OR"Pharmacotherapies"[Title/Abstract]
#5	"Ovarian Neoplasm"[Mesh]
#6	"ovarian cancer"[Title/Abstract] OR"ovarian cancers"[Title/Abstract] OR"ovary neoplasm"[Title/Abstract] OR"ovary neoplasms"[Title/Abstract] OR"ovary Cancer"[Title/Abstract] OR"ovary cancers"[Title/Abstract] OR"cancer of ovary"[Title/Abstract] OR"cancer of the ovary"[Title/Abstract]
#7	#1OR#2
#8	#3OR#4
#9	#5OR#6
#10	#7AND#8AND#9

current health care field (16). In this study, the Cochrane system evaluation method was used to analyze and evaluate the clinical trials of apatinib in combination with CT for the treatment of OC, and to further study and analyze whether it could be a safe and effective treatment for OC, to provide the basis for clinical decision-makers.

We present the following article in accordance with the PRISMA 2020 reporting checklist (available at https://dx.doi.org/10.21037/apm-21-1662).

Methods

Search strategy

Related literature was extensively searched, using search engines such as PubMed, the Web of Science, EMBASE, CNKI, Cochrane Library, CBM, VIP, and the Wanfang database. Clinical studies, related to the use of a combination of apatinib and CT for the treatment of OC, was searched by using the aforementioned databases. The initial search was performed from the establishment of the database to September 2020. At the same time, the references of the studies included were traced to supplement the potential studies that met the inclusion criteria. Keywords used to search the literature were included "Apatinib", "rivoceranibmesylate", "YN968D1", "Rivoceranib", "apatinib mesylate", "Drug Therapies", "chemotherapy", "Chemotherapies", "Pharmacotherapy", "Pharmacotherapies", "ovarian cancer", "Ovarian Neoplasm", "Ovary Neoplasms", "Ovary Cancer", "Cancer of Ovary", "Cancer of the Ovary". No language limits were applied. Free words and subject words are used in the retrieval (*Table 1*).

Selection criteria

(I) Many participants were recruited for a clinical comparative study and received either apatinib plus CT or CT alone, regardless of randomization, assignment concealment, or blinding. (II) Participants: the subjects included must be patients diagnosed with OC. (III) Intervention measures: the experimental group was given apatinib based on the treatment criteria designed for the control group, while the control group received only basic CT. The dosage, dosage form, method, and time of the two groups were not limited. (IV) The outcomes consisted of tumor response, adverse reactions (ADRs) due to treatment, and SR. The modified response evaluation criteria in solid tumors (RECIST) criteria, categorized as partial remission (PR), complete remission (CR), progressive disease (PD), and stable disease (SD) was used to evaluate the treatment efficacy against tumor (17,18). DCR is represented by CR + PR + SD and the ORR is represented by CR + PR.

Exclusion criteria

Exclusion of the studies was carried out if any of the following criteria were met: (I) non-Chinese and Non-English literature. (II) Information in their original form could not be achieved upon contacting the author in case the original data were not extracted. (III) The literature was comprising multiple publications, duplicate records, animal experiments, clinical case studies, or similar type studies, (IV) and Literature with inconsistent outcome indicators.

Extraction of data and evaluation of the literature quality

The literature was searched by two researchers independently. They extracted the data and the results were also cross-checked by using different sources. In the case of disagreement, it was settled down through negotiation or

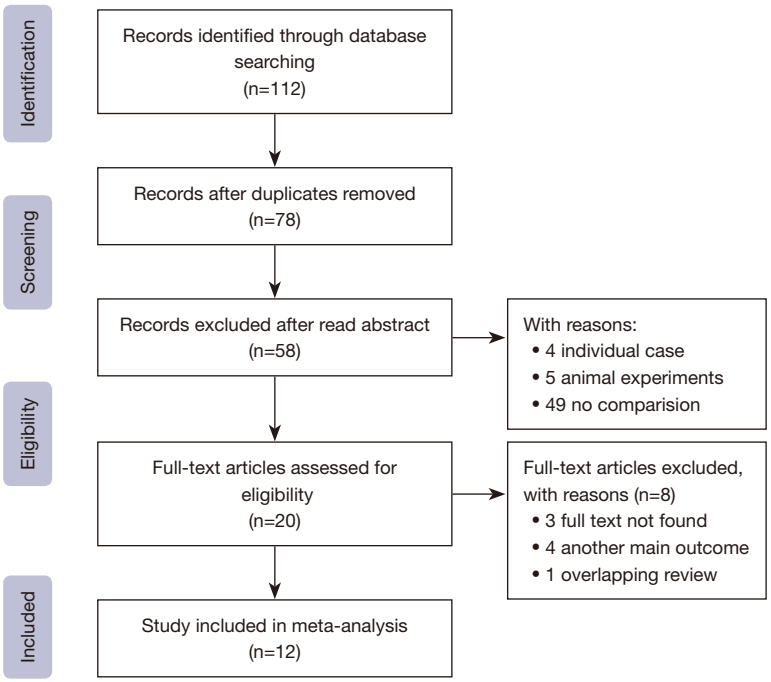

Figure 1 Flow diagram of the selection process.

discussion with a third party. While searching the literature, the title and abstract of a paper or article were read followed by reading the full text of the paper to identify whether the article should be included or not. The criteria for data to be extracted consisted of (I) basic information of the included study such as the title of publication, first author, year in which article was published, etc.; (II) basic characteristics and intervention measures of control and experimental group; (III) key information of bias risk assessment; (IV) outcome indicators. The risk of deviation for each qualified study was evaluated following Cochrane reviewer's manual 5.1.0 (19).

Statistical analysis

The analyses of the current study were performed using Revman 5.4 software (Cochrane; London, UK). Risk ratio (OR) was used as a statistic in counting the data, weighted mean difference (WMD) was used as a statistic in the data measurement, and 95% confidence interval (CI) was provided for statistical results. Analysis of the heterogeneity among the included research results was performed using the chi-square test (the test level was α=0.1), and the size of heterogeneity was quantitatively judged by combining it with I^2. If no significant statistical heterogeneity was observed ($I^2 \leq 50\%$, $P \geq 0.1$), then for merging the results, the fixed-effect model was used. If there is a significant statistical heterogeneity found ($I^2 > 50\%$, $P < 0.1$), then for merging the results, the random effect model was used. The sensitivity analysis method was performed to explore the source of heterogeneity. The publication bias test was conducted to identify any asymmetry among studies.

Results

Search results

A total of 112 related literatures were obtained from the initial examination, after review the title and authors, 34 literatures were excluded with the reason of duplications. After read the abstracts, 4 individual cases, 5 animal experiments and 49 no comparision studies were excluded. After review the full-text articles, 8 literatures were excluded because 3 full texts were not found, 4 studies have another main outcome and 1 overlapping review. Finally, 12 literatures were finally included after layer-by-layer screening (20-31). All the literatures included 698 patients, including 340 cases in the experimental group and 358 cases in the control group. The specific screening process is shown in *Figure 1*.

Table 2 Main characteristics of the 12 studies included in the meta-analysis

Authors, year	Nation	Line	Age, Exp/con	Therapeutic regimen, Exp/con	Patients, Exp/con	Enrollment period	Outcomes
Feng *et al.* (20), 2019	China	I–IV	45.80±5.70/46.20±6.10	Apatinib + DDP/DDP	30/30	2017.1–2019.1	①②③
Liu *et al.* (21), 2020	China	II	36.90±5.10/45.10±4.90	Apatinib + taxane/taxane	22/22	2017.2–2019.3	①②③
Li *et al.* (22), 2017	China	II	55.00±14.00/52.00±13.00	Apatinib + taxane/taxane	10/20	2016.2–2016.11	①②③
Li (23), 2018	China	III–IV	26–70/30–74	Apatinib + taxane/taxane	21/25	2016.2–2017.11	①②③
Quan *et al.* (24), 2020	China	III–IV	55.89±7.76/55.21±7.71	Apatinib + taxane/taxane	50/50	2016.1–2018.1	①②③
Ran *et al.* (25), 2020	China	III–IV	52.10±12.19/51.37±12.53	Apatinib + GEMOX/GEMOX	41/41	2013.2–2017.2	①②③
Shao *et al.* (26), 2019	China	No	64.28±1.63/58.55±1.45	Apatinib + TP/TP	14/14	2018.7–2019.3	①②③
Wang *et al.* (27), 2019	China	No	50.93±13.72/50.42±13.85	Apatinib + DP/DP	39/39	2016.1–2018.1	①②③
Zhao *et al.* (28), 2019	China	II	54.29±6.87/54.76±6.72	Apatinib + taxane/taxane	19/19	2018.9–2019.3	①②③
Zheng *et al.* (29), 2019	China	II	60.50±5.10/60.10±4.90	Apatinib + PH/PH	40/40	2018.9–2019.1	①②③
Yang *et al.* (30), 2019	China	I–IV	35–79/35–79	Apatinib + CT/CT	9/13	2016.4–2018.10	①②③
Qiu *et al.* (31), 2020	China	III–IV	47.39±4.87/47.39±4.87	Apatinib + paclitaxel/paclitaxel	45/45	2014.7–2016.3	①②③

Outcome: ① ORR, ② DCR, ③ adverse events; Con, control group (CT alone group); Exp, experimental group (apatinib targeted therapy plus CT). DDP, docetaxel l + cisplatin chemotherapy; GEMOX, gemcitabine + oxaliplatin; TP, paclitaxel + cisplatin; DP, docetaxel + cisplatin; PH, pirarubicin hydrochloride + paclitaxel liposome; CT, chemotherapy; ORR, objective response rate; DCR, disease control rate.

Patient characteristics

The trials included in this study were conducted in China. Collectively, 343 patients with an advanced stage of OC received apatinib-cum-CT as a treatment, and around 361 patients received only CT. Detailed information regarding trials and patients included in this study is presented in *Table 2*.

Quality assessment

The assessment of the bias risk is shown in *Figure 2*. Among the included studies, one was found to be having a low risk, and the rest of the 5 were not true randomized controlled trials. None of the included studies provided clear details of the risk detection and performance. The attrition risks of the included trials were found to be low; and due to selective reporting, five trials were found with unclear risk.

Meta-analysis results

ORR

In six included (22,23,25,27,28,31) studies involving 364 patients, the meta-analysis showed that the difference was statistically significant (OR =3.19, 95% CI: 2.06–4.94, P<0.00001), as shown in *Figure 3*.

DCR

In six included (22,23,25,28,30,31) studies involving 308 patients, the meta-analysis showed that the difference was statistically significant (OR =4.97, 95% CI: 2.90–8.52, P<0.00001), as shown in *Figure 4*.

Therapeutic efficacy assessments

As presented in *Table 3*, the results in pooled form revealed that the patients who received a combined therapy showed significantly improved CR, PR, ORR, and DCR (CR: OR =3.17, 95% CI: 1.87–5.38, P<0.00001; PR: OR =2.00, 95% CI: 1.45c2.75, P<0.00001; ORR: OR =3.19, 95% CI: 2.06–4.94, P<0.00001; DCR: OR =4.97, 95% CI: 2.90–8.52, P<0.00001) and PD was found to be significantly decreased (OR =0.29, 95% CI: 0.20–0.43, P<0.00001), while the SD was observed not significantly different from the group of patients receiving only CT (OR =0.75, 95% CI: 0.54–1.05, P=0.09). The OR rate was analyzed by using fixed effect models because of low heterogeneity.

AEs assessment

This meta-analysis also evaluated the safety of apatinib targeted therapy. As shown in the *Table 4*, group of patients treated with a combination therapy of apatinib and CT revealed higher rate of proteinuria (OR =0.17, 95% CI:

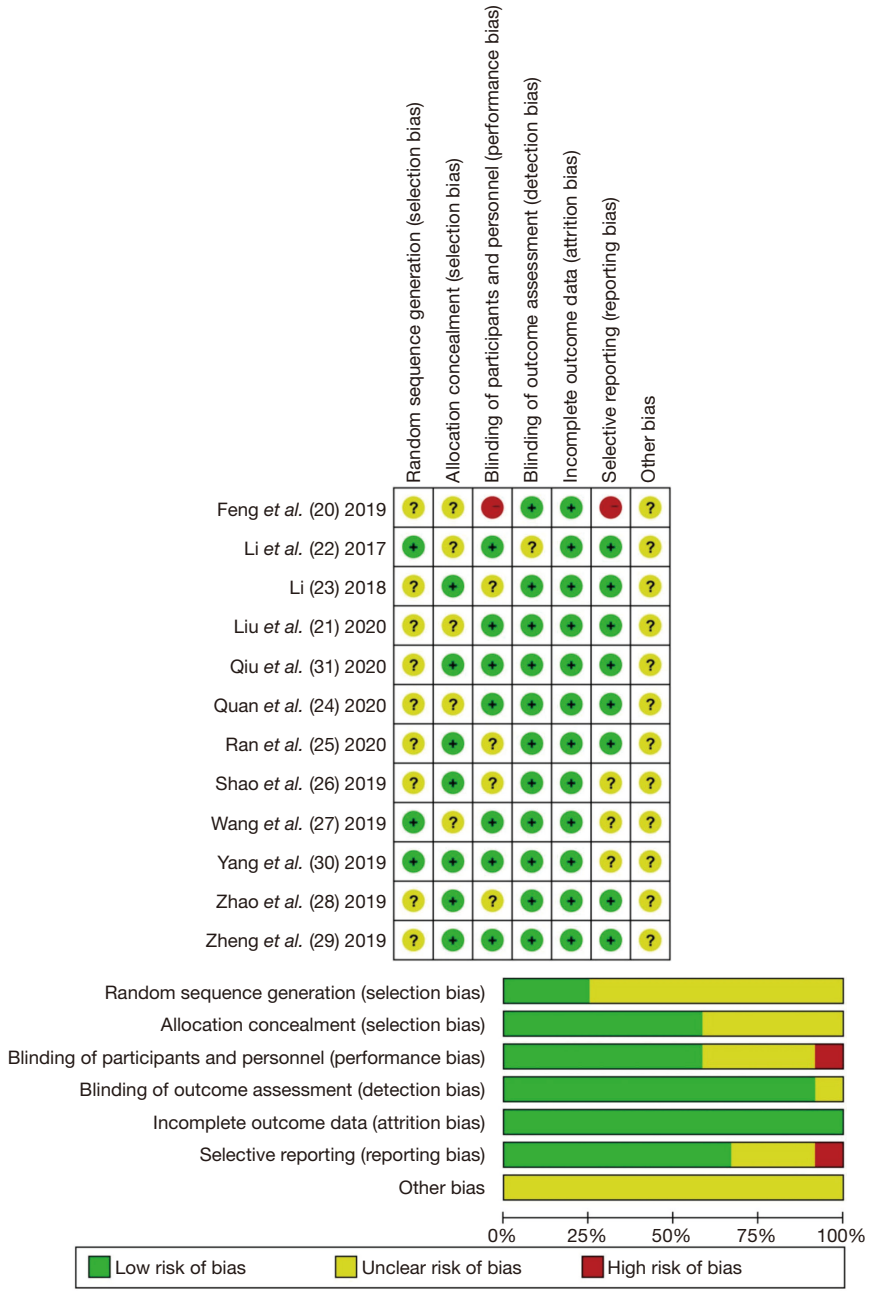

Figure 2 (A) Risk of bias summary: review of the authors' judgments about each risk of bias item for the included studies, (B) risk of bias graph: review of the authors' judgments about each risk of bias item presented as percentages across all included studies. Each color represents a different level of bias: red for high risk, green for low risk, and yellow for unclear risk of bias (20-31).

0.04–0.68, P=0.01), whereas analyses of the symptoms such as nausea and vomiting ,hand foot syndrome, hypertension, diarrhea, myelosuppression and leucopenia did not reveal any significant differences (Nausea and vomiting: OR =1.10, 95% CI: 0.67–1.79, P=0.71; hand foot syndrome: OR =1.73, 95% CI: 0.97–3.10, P=0.06; hypertension: OR =1.18, 95% CI: 0.73–1.91, P=0.51; diarrhea: OR =1.05, 95% CI: 0.56–1.97, P=0.87; leucopenia: OR =1.22, 95% CI: 0.70–2.12, P=0.48; myelosuppression: OR =0.82, 95% CI: 0.24–2.83, P=0.62)

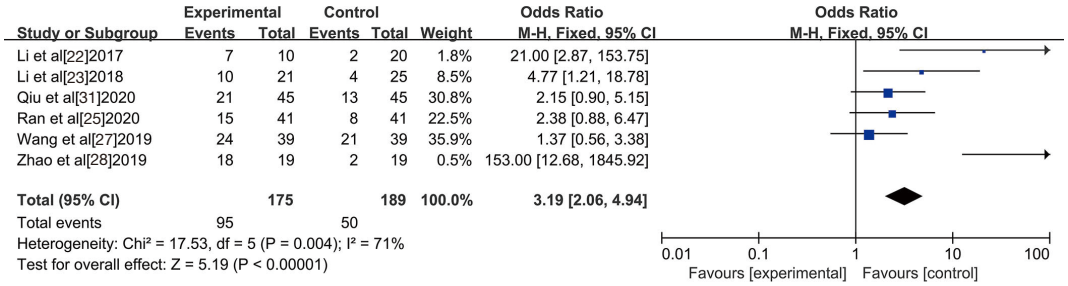

Figure 3 Forest plot of the comparison of the ORR between the experimental and control group (22,23,25,27,28,31). Control group, CT alone group; experimental group, apatinib targeted therapy plus CT. The fixed effects meta-analysis model (Mantel–Haenszel method) was used. CI, confidence interval; CT, chemotherapy; OR, odds ratio; ORR, overall response rate.

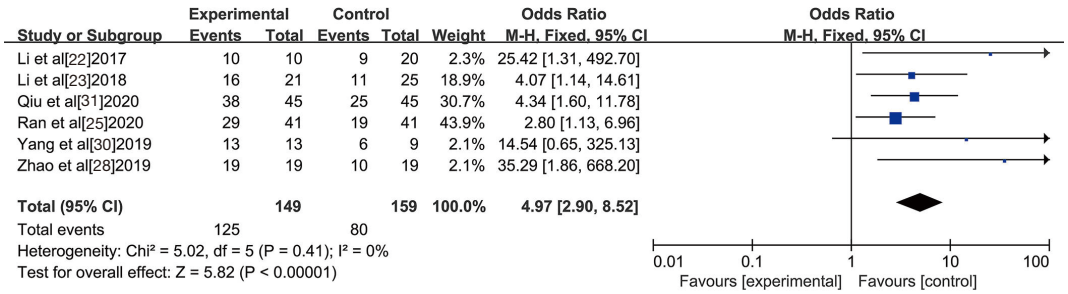

Figure 4 Forest plot of the comparison of the DCR between the experimental and control group (22,23,25,28,30,31). Control group, CT alone group; experimental group, apatinib targeted therapy plus CT. The fixed effects meta-analysis model (Mantel-Haenszel method) was used. CI, confidence interval; CT, chemotherapy; OR, odds ratio; ORR, overall response rate.

Table 3 Comparison of CR, PR, SD, PD, ORR, and DCR between the experimental and control groups

Parameter	Studies	Exp		Con		Heterogeneity		Pooled effect	
		Events	Total	Events	Total	I^2(%)	P value	OR (95% CI)	P value
CR	12	67	344	32	354	0	0.65	3.17 (1.87, 5.38)	<0.00001
PR	12	140	344	90	354	59	0.005	2.00 (1.45, 2.75)	<0.00001
SD	12	87	344	109	354	41	0.07	0.75 (0.54, 1.05)	0.09
PD	12	46	344	119	354	26	0.19	0.29 (0.20, 0.43)	<0.00001
ORR	6	95	175	50	189	72	0.004	3.19 (2.06, 4.94)	<0.00001
DCR	6	125	149	80	159	0	0.41	4.97 (2.90, 8.52)	<0.00001

Con, control group (CT alone group); Exp, experimental group (apatinib targeted therapy plus CT). CR, complete response rates; CT, chemotherapy; PR, partial response rates; SD, stable disease rates. PD, progressive disease rates; ORR, overall response rate; DCR, disease control rate; OR, odds ratio; CI, confidence intervals.

Table 4 Comparison of AEs between the experimental and control groups

Outcome	Studies	Exp		Con		Heterogeneity		Pooled effect	
		Events	Total	Events	Total	I^2(%)	P value	OR (95% CI)	P value
Nausea and vomiting	10	87	248	98	262	0	0.83	1.10 (0.67, 1.79)	0.71
Hand foot syndrome	7	73	187	83	197	66	0.02	1.73 (0.97, 3.10)	0.06
Hypertension	10	96	286	103	296	0	0.49	1.18 (0.73, 1.91)	0.51
Diarrhea	5	35	167	44	167	0	0.82	1.05 (0.56, 1.97)	0.87
Leukopenia	8	76	196	84	206	0	0.93	1.22 (0.70, 2.12)	0.48
Myelosuppression	2	5	79	6	79	0	0.75	0.82 (0.24, 2.83)	0.62
Proteinuria	4	23	105	37	109	0	0.11	0.17 (0.04, 0.68)	0.01

Con, control group (CT alone group); Exp, experimental group (apatinib targeted therapy plus CT). OR, odds ratio; CI, confidence intervals.

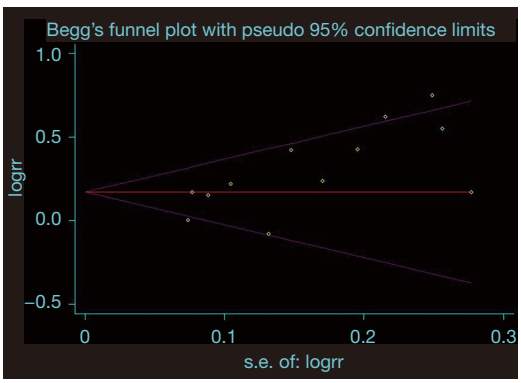

Figure 5 Funnel plot of percentage of ORR. ORR, overall response rate.

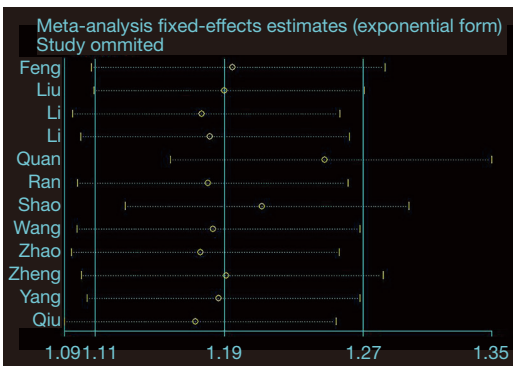

Figure 6 Sensitivity analysis of ORR. ORR, overall response rate.

Publication bias

drawn for the studies on outcome of ORR, but without complete symmetry, as presented in *Figure 5*.

Sensitivity analysis

We conducted a sensitivity analysis to explore the sources of heterogeneity in treatment regimens, apatinib dose, sample size, and related study types in ORR. As shown in *Figure 6*, our analysis showed that no significant differences were found between different treatment regimens, apatinib doses, sample sizes, and study types.

Discussion

The clinical symptoms of early OC are difficult to be detected, thus leading to its high rate of mortality rate. In most cases, cancer has progressed to an advanced stage at the time of its diagnosis. In the past 20 years, paclitaxel combined with platinum has been the global first-line CT program for OC patients (32). However, when cytotoxic drugs kill cancer cells, they also mediate adverse events to the body. As a result, CT is either stopped or its dose is reduced, thus affecting the efficacy of surgery and the patients' quality of life (33). Therefore, there is an urgent need to develop new targeted therapeutic drugs for the effective treatment of OC (34,35). In recent times, with the progress in the molecular biology of tumor and epigenetics, more and more drugs such as erlotinib, gefitinib, and apatinib against different targets are being used to treat patients with malignant tumors (36-38). Therefore, apatinib combined with conventional CT may be a new option to inhibit the growth of OC, especially for patients who have received multiple CT routes or are resistant to CT.

Basic research has confirmed that tumor neovascularization is a major factor involved in the occurrence and process of

the development of malignancy of tumors (39). Abnormal activation of the VEGF/VEGFR-2 signaling pathway is the key factor of neovascularization (40,41). In a variety of malignant tumors, its abnormal activation can promote the vascular endothelial cells proliferation and migration, inhibit the endothelial cells apoptosis and reorganization, thus it is closely related to the degree of malignancy and prognosis of the tumor (42). Apatinib is a new VEGFR-2 targeted blocker developed in China. It blocks VEGF/VEGFR-2 signal pathway with high selectivity and strong effect, thus inhibits the activation of mitogen-activated protein kinases (MAPKs), and hinders the vascular endothelial cells proliferation and migration. This in turn leads to the inhibition of tumor neovascularization and killing of cancer cells (43). At present, apatinib has been reported to treat the OC. Li Jing's (44) study showed that apatinib can effectively down-regulate the expression of CDK2 and p21 in A2780 cells, inhibit the cell proliferation in OC, and increase the sensitivity of OC towards paclitaxel. Despite the statistical analysis of many earlier published clinical trials, the exact therapeutic effects and safety have not been systematically determined so far, owing to the sample size variability in these clinical trials. In addition, in different clinical trials, different application schemes may lead to diverse therapeutic effects. In this study, an extensive online search was conducted followed by a rigorous comparison and combination for classification in order to present a clear, and systematic conclusion.

Results of the current meta-analysis show that apatinib targeted therapy in combination with CT is more effective than CT alone. Compared with the CT group, PR, PD, CR, ORR, and DCR were found to be significantly higher ($P<0.05$) for the group of combined treatment. The main adverse effects observed were nausea, pain in hand and foot, hypertension, leukopenia, and many more. These ADRs were from mild to a moderate level in terms of rampancy and can be overcome by appropriate treatment, including a temporary reduction in dose or other symptomatic treatment. It is worth mentioning that these studies did not report any disability or death related to treatment. Therefore, the combination of apatinib along with CT did not increase the ADRs, which means that the combination therapy can improve the efficacy of OC without increasing ADRs. These findings suggest that opioid targeted therapy improves the efficacy of CT through tumor angiogenesis inhibition, which in turn improves the quality of a patient's life.

However, some limitations also exist in our research. First of all, most of the studies were conducted for patients with OC in China. Probably because apatinib is an independently produced drug in China, mainly used in these areas. Secondly, there are only twelve articles available about the combination of apatinib and CT. This may be because combination therapy is a new treatment strategy, and further studies are currently being carried out, which is confirmed in literature search. We will continue to focus on the results and outcomes of subsequent studies and will update the current meta-analysis on time. Third, it is difficult to analyze the survival rate because the survival time in each study is inconsistent. Furthermore, the medication method and treatment course of apatinib, follow-up duration, and evaluation of adverse events after treatment were not completely consistent and reliable.

Conclusions

In summary, our study confirmed that apatinib in combination with CT for the treatment of patients with advanced OC is an effective treatment for advanced OC patients. Apatinib in combination with CT markedly enhances the ORR and DCR for advanced OC. However, this combined treatment could lead to greater rates of proteinuria, hypertension, albuminuria, and hand-foot syndrome and so on. Therefore, the benefits and risks should be considered before treatment.

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Footnote

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