Efficacy and safety of antiangiogenic therapy (bevacizumab or apatinib) plus chemotherapy in patients with platinum-resistant recurrent ovarian cancer: A retrospective study

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Abstract. The majority of patients with ovarian cancer will relapse and subsequently develop platinum-resistant recurrent ovarian cancer (PRROC). Antiangiogenic therapy plus chemotherapy may be a potential treatment option in patients with PRROC. However, further evidence is required to facilitate clinical application. The present study aimed to investigate the efficacy and safety of antiangiogenic therapy (bevacizumab or apatinib) plus chemotherapy in patients with PRROC. Data from 86 patients with PRROC receiving antiangiogenic therapy (bevacizumab or apatinib) plus chemotherapy (pegylated liposomal doxorubicin, weekly-paclitaxel or gemcitabine) were reviewed retrospectively. Data for treatment response, progression-free survival (PFS), overall survival (OS) and adverse events were obtained. Complete response, partial response, stable disease and progressive disease rates were 0.0, 33.7, 44.2 and 22.1%, respectively. Objective response and disease control rates were 33.7 and 77.9%, respectively. Median (and 95% confidence intervals) PFS and OS values were 6.5 (4.7-8.2) and 20.3 (14.1-26.5) months, respectively. PFS (P=0.016) and OS (P=0.005) durations were longer in patients that received the antiangiogenic plus chemotherapy regimen as a second-line treatment vs. patients that received it as a third-line or above treatment. Ascites (yes vs. no) and current treatment lines (third or above vs. second) were independently associated with shorter PFS and OS (all P<0.05). The most frequent treatment-induced adverse events were leukopenia (34.9%), hypertension (30.2%) and fatigue (30.2%). All adverse events were considered acceptable and only previously reported adverse events were observed. The findings of the present study may provide further clinical evidence for the application of antiangiogenic therapy plus chemotherapy in patients with PRROC.

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Introduction

Ovarian cancer (OC) commonly occurs in postmenopausal women and accounts for more than two-thirds of gynaecological cancer-related mortalities (1-3). In 2020, a total of 313,959 new cases and 207,252 mortalities due to OC were recorded worldwide (4). Cytoreductive surgery followed by platinum-based chemotherapy is the standard treatment strategy for patients with OC (5,6). Notably, 70.0-80.0% of patients with OC suffer from disease recurrence and the majority of these patients will eventually develop platinum resistance through multiple recurrences (7-10). Currently, platinum resistance is a noteworthy obstacle that negatively affects the survival of patients with OC (11).

Previously, studies report that antiangiogenic therapy can inhibit neovascularisation and the supply of nutrients and oxygen to cancer cells, thus suppressing tumour proliferation, invasion and metastasis (12,13). Emerging evidence also suggests that antiangiogenic therapy, such as bevacizumab and apatinib, plus chemotherapy is a promising treatment approach for patients with platinum-resistant recurrent OC (PRROC) (14-16). For example, the randomised clinical trial APPROVE indicates that apatinib plus pegylated liposomal doxorubicin (PLD) increases progression-free survival (PFS) with tolerable adverse effects compared with PLD alone in patients with PRROC (14). Another study demonstrates that bevacizumab plus chemotherapy (PLD, weekly-paclitaxel or topotecan) increases the objective response rate (ORR) and PFS, but does not increase overall survival (OS) when compared with chemotherapy alone in patients with PRROC (15). Additionally, a study reveals that apatinib plus paclitaxel increases PFS and OS with acceptable toxicity compared with paclitaxel monotherapy in the same patients (16). Notably, the aforementioned studies include patients with PRROC who are only treated with one type of antiangiogenic drug, either apatinib or bevacizumab, plus chemotherapy. Therefore, evaluating the efficacy and safety of the different antiangiogenic drugs (bevacizumab or apatinib) plus chemotherapy could provide further clinical evidence for the application of this treatment modality.

The present study aimed to investigate the efficacy and safety profile of antiangiogenic therapy (bevacizumab or apatinib) plus chemotherapy in patients with PRROC.

Materials and methods

Patients. In the present retrospective study, a total of 86 female patients with PRROC that received antiangiogenic therapy plus chemotherapy between July 2019 and May 2023 at the People's Hospital of Zhongshan City (Zhongshan, China) were selected. Patient data from the hospital records were accessed from April 19, 2024 to April 29, 2024. The present study obtained permission from the Ethics Committee of People's Hospital of Zhongshan City (approval no. 2024-033; Zhongshan, China). The patients signed the informed consent form, or, if the patients were unable to sign, their family members signed it on their behalf.

Inclusion and exclusion criteria. Inclusion criteria were as follows: i) Patients diagnosed with epithelial ovarian, primary peritoneal or fallopian tube cancer (17); ii) aged ≥18 years; iii) treated with antiangiogenic therapy plus chemotherapy; iv) patients with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of ≤2; v) experienced disease progression within 6 months after receiving platinum-based chemotherapy; and vi) displayed at least one assessable lesion according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (18).

The exclusion criteria were as follows: i) Patients with uncontrolled hypertension; ii) patients with coagulation disorders; iii) patients with a history of bleeding; iv) patients with gastrointestinal perforation; and v) patients with no available follow-up data.

Treatment. Treatment data from patients with PRROC were collected from the electronic medical system. The treatment regimens were provided according to the National Comprehensive Cancer Network (NCCN) guideline and the condition and requests of the patient (19). The antiangiogenic drugs used were bevacizumab (10 mg/kg once every 2 weeks) or apatinib (250 mg once every day). The chemotherapy drugs were PLD (40 mg/m^2 once every 4 weeks), paclitaxel (80 mg/m^2 once every week) or gemcitabine (1,000 mg/m^2 on days 1 and 8 every 3 weeks). The dose of each drug was prescribed as recommended based on the NCCN guideline and was adjusted based on the condition of the patient (19). Every cycle was defined as 4 weeks of treatment with the aforementioned drugs.

Follow-up and assessment data. Follow-up data from patients with PRROC were obtained from the electronic medical system. Patients were followed up every two cycles of therapy and their condition was evaluated using magnetic resonance imaging or computed tomography (20). The median duration of follow-up was 13.7 months and the final follow-up date was August 2023. The treatment response of patients with PRROC was assessed based on RECIST version 1.1 and the best response was selected for evaluation. ORR and disease control rate (DCR) were also measured. PFS and OS were determined based on the follow-up data. Additionally, the adverse events were retrieved from the medical records of patients with PRROC.

Statistical analysis. All statistical analyses were performed using SPSS version 24.0 software (IBM Corp). For sample size calculation, an ORR of 0.3 and a confidence interval width of 0.2 was assumed. Assuming a dropout rate of 5%, the minimum sample size required was 86. The characteristics, treatment response and adverse events of patients with PRROC were assessed using descriptive statistics. The association between the current treatments, antiangiogenic drugs and chemotherapy drugs with PFS and OS was examined using Kaplan-Meier curves. All data were analysed using a log-rank test. Univariate and multivariate (stepwise forward) Cox regression analyses were performed to determine the factors that affect PFS and OS. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Baseline features of patients with PRROC. In the present study, the median age of patients with PRROC was 60.5 years [interquartile range (IQR), 51.0-67.0 years). A total of 32 (37.2%) patients presented with ascites. Moreover, 53 (61.6%) patients received antiangiogenic therapy plus chemotherapy as a second-line treatment and the remaining 33 (38.4%) patients received antiangiogenic therapy plus chemotherapy as a third-line or above treatment. Regarding the antiangiogenic drugs, 68 (79.1%) patients were treated with bevacizumab and 18 (20.9%) patients received apatinib. Finally, in terms of chemotherapy, 51 (59.3%) patients received PLD, 21 (24.4%) received weekly-paclitaxel and 14 (16.3%) received gemcitabine. The detailed data of patients with PRROC are presented in Table I.

Best response, ORR and DCR in patients with PRROC. In terms of the treatment response of patients with PRROC that received antiangiogenic therapy plus chemotherapy, no (0.0%) patients achieved a complete response (CR) and 29 (33.7%) patients achieved a partial response (PR). Furthermore, the ORR and DCR of patients with PRROC were 33.7 and 77.9%, respectively (Table II).

PFS and OS in patients with PRROC with different treatment information. Results of the present study revealed that the overall median PFS in patients with PRROC was 6.5 months [95% confidence interval (CI), 4.7-8.2 months; Fig. 1A]. The overall median OS was 20.3 months (95% CI, 14.1-26.5 months; Fig. 1B).

PFS was prolonged in patients with PRROC who received antiangiogenic therapy plus chemotherapy as a second-line treatment compared with patients who received the aforementioned regimen as a third-line or above treatment (P=0.016; Fig. 2A). However, no significant difference in PFS between patients with PRROC who received bevacizumab and patients who received apatinib was observed (P=0.678; Fig. 2B). Additionally, no significant difference in PFS was observed between patients who were treated with PLD, weekly-paclitaxel or gemcitabine (P=0.073; Fig. 2C).

OS was also increased in patients with PRROC who received antiangiogenic therapy plus chemotherapy as a second-line treatment vs. patients who received it as a third-line or above treatment (P=0.005; Fig. 2D). OS did not significantly differ between patients who received bevacizumab and patients who received apatinib (P=0.976;

Table I. Characteristics of patients with PRROC.

Characteristics	Patients with PRROC (n=86)
Age, years [median (IQR)]	60.5 (51.0-67.0)
Age, n (%)	
<65 years	57 (66.3)
≥65 years	29 (33.7)
Origin of cancer, n (%)	
Ovary	77 (89.5)
Fallopian tube	6 (7.0)
Peritoneum	3 (3.5)
Histology subtype, n (%)	
HGSC	66 (76.7)
LGSC	3 (3.5)
Endometrioid carcinoma	8 (9.3)
Clear cell carcinoma	9 (10.5)
ECOG PS, n (%)	
0	33 (38.3)
1	47 (54.7)
2	6 (7.0)
FIGO stage, n (%)	
I	4 (4.7)
II	7 (8.1)
III	64 (74.4)
IV	11 (12.8)
Platinum-free interval ≤3 months, n (%)	27 (31.4)
Ascites, n (%)	32 (37.2)
CA-125 ≥100 U/ml, n (%)	61 (70.9)
Prior chemotherapy, n (%)	86 (100.0)
Prior antiangiogenic therapy, n (%)	9 (10.5)
Current treatment lines, n (%)	
Second	53 (61.6)
Third or above	33 (38.4)
Antiangiogenic drugs, n (%)	
Bevacizumab	68 (79.1)
Apatinib	18 (20.9)
Chemotherapy drugs, n (%)	
PLD	51 (59.3)
Weekly-paclitaxel	21 (24.4)
Gemcitabine	14 (16.3)

PRROC, platinum-resistant recurrent ovarian cancer; IQR, interquartile range; HGSC, high-grade serous carcinoma; LGSC, low-grade serous carcinoma; ECOG, Eastern Cooperative Oncology Group; PS, performance status; FIGO, International Federation of Gynaecology and Obstetrics; CA-125, cancer antigen 125; PLD, pegylated liposomal doxorubicin.

Fig. 2E). Additionally, no significant difference in OS was observed between patients with PRROC who were treated with PLD, weekly-paclitaxel or gemcitabine (P=0.222; Fig. 2F).

Table II. Treatment response of patients with PRROC.

Treatment response	Patients with PRROC (n=86)
Best response, n (%)	
CR	0 (0.0)
PR	29 (33.7)
SD	38 (44.2)
PD	19 (22.1)
ORR, n (%)	
Yes	29 (33.7)
No	57 (66.3)
DCR, n (%)	
Yes	67 (77.9)
No	19 (22.1)

PRROC, platinum-resistant recurrent ovarian cancer; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate.

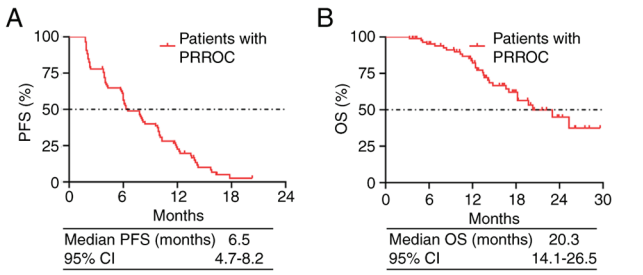

Figure 1. Kaplan-Meier curves for PFS and OS. (A) PFS and (B) OS in patients with PRROC that received antiangiogenic therapy plus chemotherapy. PFS, progression-free survival; OS, overall survival; PRROC, platinum-resistant recurrent ovarian cancer; CI, confidence interval.

Independent factors associated with PFS in patients with PRROC. Stepwise forward multivariate Cox regression model analysis revealed that ascites (yes vs. no) [hazard ratio (HR)=1.804; P=0.018] and current treatment lines (third or above vs. second) (HR=1.921; P=0.010) were independently associated with a reduced PFS in patients with PRROC (Table III).

Independent factors associated with OS in patients with PRROC. Stepwise forward multivariate Cox regression model analysis indicated that ascites (yes vs. no) (HR=2.439; P=0.026) and current treatment lines (third or above vs. second) (HR=2.991; P=0.003) were independently associated with a reduced OS in patients with PRROC (Table IV).

Adverse events in patients with PRROC. In the present cohort, the most common adverse events in patients with PRROC were leukopenia (34.9%), hypertension (30.2%), fatigue (30.2%), neutropenia (29.1%) as well as nausea and vomiting (27.9%). The specific adverse events are presented in Table V.

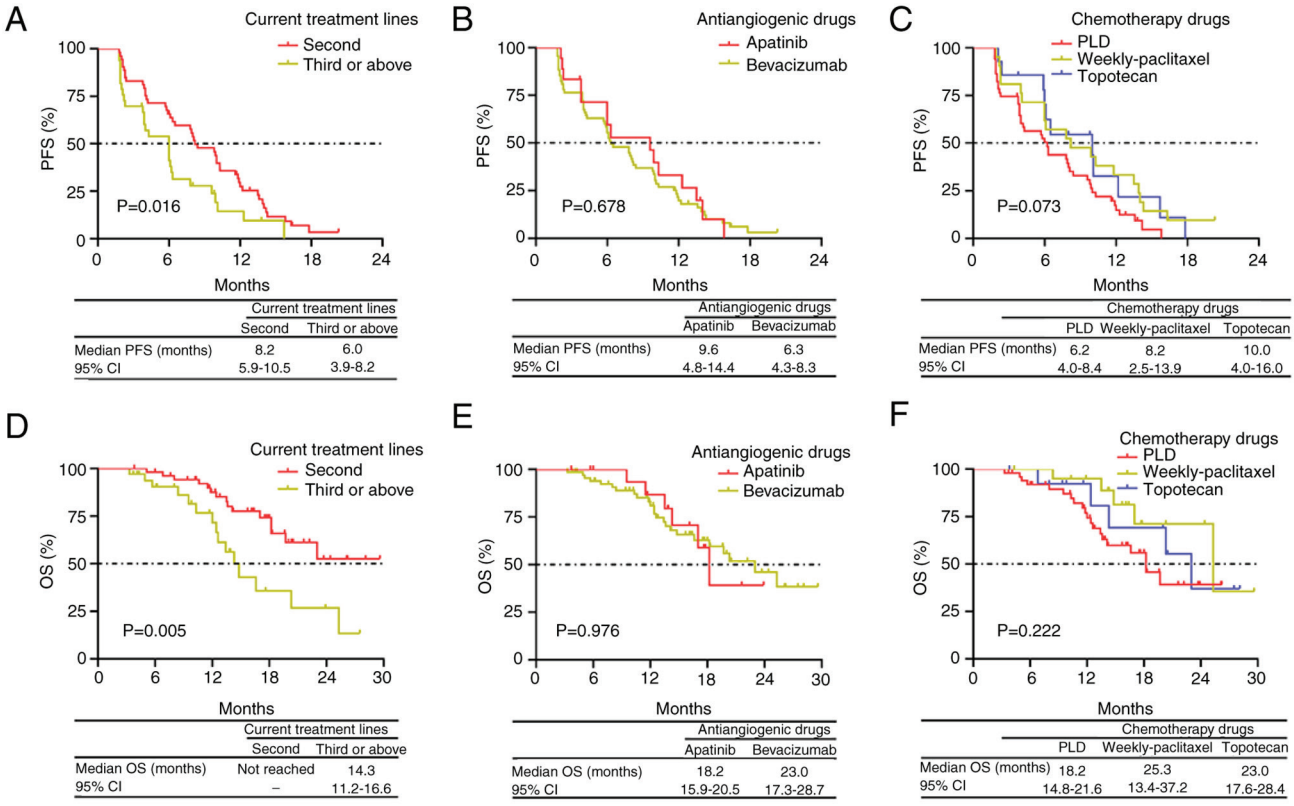

Figure 2. Kaplan-Meier curves for PFS and OS of patients with different treatment information. (A) Association of current treatment lines, (B) antiangiogenic drugs and (C) chemotherapy drugs with PFS in patients with PRROC that received antiangiogenic therapy plus chemotherapy. (D) Association of current treatment lines, (E) antiangiogenic drugs and (F) chemotherapy drugs with OS in patients with PRROC who received antiangiogenic therapy plus chemotherapy. PFS, progression-free survival; OS, overall survival; PRROC, platinum-resistant recurrent ovarian cancer; CI, confidence interval; PLD, pegylated liposomal doxorubicin.

Discussion

Platinum-based chemotherapy is the mainstay of OC treatment, but the occurrence of platinum resistance remains a challenge (9,10). Currently, single-agent non-platinum chemotherapy is one of the most commonly used treatment approaches for patients with PRROC (21). The efficacy of single-agent non-platinum chemotherapy in patients with PRROC has been investigated previously (14,22). For example, a previous study reveals that the median PFS and OS in patients with PRROC who received weekly-paclitaxel are 6.1 and 10.4 months, respectively (22). Another study demonstrates that patients with PRROC who are treated with PLD yield an ORR and DCR of 10.9 and 53.1%, respectively, with a median PFS and OS of 3.3 and 14.4 months, respectively (14). In the present study, the ORR and DCR of patients with PRROC who received antiangiogenic therapy plus chemotherapy were 33.7 and 77.9%, respectively, with a PFS of 6.5 months and an OS of 20.3 months. The aforementioned values were all increased compared with those reported in previous studies (14,22). A possible reason for this discrepancy might be that patients with PRROC in the present study received antiangiogenic therapy in addition to single-agent non-platinum chemotherapy, while the previous aforementioned studies only use single-agent non-platinum chemotherapy. Antiangiogenic drugs inhibit the vascular endothelial growth factor signalling pathway, which subsequently inhibits the delivery of nutrients and oxygen to tumour cells, suppressing tumour growth and metastasis (12,13). Additionally, antiangiogenic drugs normalise the abnormal tumour vasculature, increasing vascular perfusion and promoting the infiltration of immune effector cells into tumours, which may promote anticancer immunity (23). Previous studies also report that antiangiogenic drugs have synergistic effects with chemotherapy in killing tumour cells (24-27). In addition, a number of previous studies reveal that patients with PRROC who receive antiangiogenic therapy plus chemotherapy have ORRs and DCRs ranging from 27.3-43.1 and 57.1-84.4%, respectively. Furthermore, in these previous studies, the median PFS and OS range from 5.0-7.1 and 16.6-23.0 months, respectively (14-16,28,29). Therefore, the results of the present study were similar to those of the aforementioned studies, which suggested that the results of the present study were valid (14-16,28,29). Notably, the advantage of the present study was that it included patients with PRROC who received different antiangiogenic drugs (bevacizumab or apatinib) plus chemotherapy, while previous studies only included one type of antiangiogenic drug. The results of the present study may provide further comprehensive evidence for the application of antiangiogenic drugs plus chemotherapy in patients with PRROC.

The present study demonstrated that administering antiangiogenic therapy plus chemotherapy as a third-line or above therapy was independently associated with a reduced PFS and OS in patients with PRROC compared with patients who received the therapy as a second-line treatment. A possible explanation for this may be that patients with PRROC are

Table III. Univariate and stepwise forward multivariate COX regression models of PFS.

A, Univariate COX regression model		
Factors	HR (95% CI)	P-value
Age, ≥65 years vs. <65 years	1.371 (0.841-2.234)	0.205
Origin of cancer		
Ovary	Reference	
Fallopian tube	1.401 (0.601-3.265)	0.435
Peritoneum	1.078 (0.337-3.451)	0.899
Histology subtype		
HGSC	Reference	
LGSC	0.322 (0.045-2.335)	0.263
Endometrioid carcinoma	0.519 (0.223-1.207)	0.128
Clear cell carcinoma	0.684 (0.326-1.438)	0.317
ECOG PS	1.459 (0.997-2.135)	0.052
FIGO stage	1.592 (1.071-2.366)	0.021
Platinum-free interval, >3 months vs. ≤3 months	1.126 (0.686-1.847)	0.639
Ascites, yes vs. no	1.671 (1.033-2.702)	0.036
CA-125, ≥100 U/ml vs. <100 U/ml	0.945 (0.569-1.571)	0.828
Prior antiangiogenic therapy, yes vs. no	1.685 (0.801-3.542)	0.169
Current treatment lines, third or above vs. second	1.788 (1.100-2.905)	0.019
Antiangiogenic drugs, bevacizumab vs. apatinib	1.127 (0.638-1.991)	0.681
Chemotherapy drugs		
PLD	Reference	
Weekly-paclitaxel	0.569 (0.325-0.995)	0.048
Gemcitabine	0.585 (0.298-1.147)	0.119
B, Stepwise forward multivariate COX regression model		
Ascites, yes vs. no	1.804 (1.106-2.942)	0.018
Current treatment lines, third or above vs. second	1.921 (1.172-3.150)	0.010

PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; HGSC, high-grade serous carcinoma; LGSC, low-grade serous carcinoma; ECOG, Eastern Cooperative Oncology Group; PS, performance status; FIGO, International Federation of Gynaecology and Obstetrics; CA-125, cancer antigen 125; PLD, pegylated liposomal doxorubicin.

administered antiangiogenic drugs plus chemotherapy as a third-line or above therapy after their first- and second-line treatments fail; thus, these patients may be more resistant to multiple types of chemotherapy drugs compared with those who received the therapy as a second-line treatment. Additionally, in patients with PRROC who received antiangiogenic therapy plus chemotherapy, ascites also independently predicted reduced PFS and OS values compared with patients that did not have ascites. This may be explained as the ascites themselves represent the metastasis of malignant cells into the peritoneal cavity and thus indicate the aggravated progression of the tumour (30).

The safety of antiangiogenic therapy plus chemotherapy in treating patients with PRROC is also a noteworthy issue (31,32). A previous study discloses that the most common adverse events in patients with PRROC who receive apatinib plus PLD are decreased white blood cell count (60.8%), decreased neutrophil count (59.5%) and oral ulcers (28.4%) (14). Another study demonstrates that the most common adverse events in patients with PRROC who were treated with bevacizumab plus PLD are mucositis (including dysphagia; 64.0%), palmar-plantar erythroderma/ulceration (52.0%) and asthenia (52.0%) (33). In the present study, the most frequent adverse events were leukopenia (34.9%), hypertension (30.2%) and fatigue (30.2%). The incidences of the aforementioned adverse events were reduced compared with those reported in previous studies, which could be attributed to the underestimation of adverse events due to the retrospective nature of the present study. Moreover, only previously reported adverse events were observed. The findings of the present study support the safety of antiangiogenic therapy plus chemotherapy in patients with PRROC.

However, the present study had limitations. Firstly, the sample size in the present study was small. Therefore, studies with a larger sample size are required to verify the results of the present study. Secondly, the present study was a single-arm

Table IV. Univariate and stepwise forward multivariate COX regression models of OS.

A, Univariate COX regression model		
Factors	HR (95% CI)	P-value
Age, ≥65 years vs. <65 years	2.078 (1.012-4.267)	0.046
Origin of cancer		
Ovary	Reference	
Fallopian tube	0.886 (0.209-3.750)	0.869
Peritoneum	1.744 (0.411-7.403)	0.451
Histology subtype		
HGSC	Reference	
LGSC	1.949 (0.252-15.097)	0.523
Endometrioid carcinoma	0.220 (0.030-1.630)	0.138
Clear cell carcinoma	0.539 (0.162-1.794)	0.314
ECOG PS	1.475 (0.832-2.614)	0.183
FIGO stage	2.031 (1.016-4.063)	0.045
Platinum-free interval, >3 months vs. ≤3 months	1.363 (0.647-2.875)	0.415
Ascites, yes vs. no	2.133 (0.999-4.552)	0.050
CA-125, ≥100 U/ml vs. <100 U/ml	1.726 (0.704-4.231)	0.233
Prior antiangiogenic therapy, yes vs. no	2.185 (0.742-6.436)	0.156
Current treatment lines, third or above vs. second	2.729 (1.325-5.621)	0.006
Antiangiogenic drugs, bevacizumab vs. apatinib	1.014 (0.411-2.504)	0.976
Chemotherapy drugs		
PLD	Reference	
Weekly-paclitaxel	0.443 (0.166-1.185)	0.105
Gemcitabine	0.665 (0.246-1.793)	0.420
B, Stepwise forward multivariate COX regression model		
Ascites, yes vs. no	2.439 (1.115-5.333)	0.026
Current treatment lines, third or above vs. second	2.991 (1.436-6.232)	0.003

OR, overall survival; HR, hazard ratio; CI, confidence interval; HGSC, high-grade serous carcinoma; LGSC, low-grade serous carcinoma; ECOG, Eastern Cooperative Oncology Group; PS, performance status; FIGO, International Federation of Gynaecology and Obstetrics; CA-125, cancer antigen 125; PLD, pegylated liposomal doxorubicin.

Table V. Adverse events of patients with PRROC (n=86).

Adverse events	Patients with PRROC, n (%)
Leukopenia	30 (34.9)
Hypertension	26 (30.2)
Fatigue	26 (30.2)
Neutropenia	25 (29.1)
Nausea and vomiting	24 (27.9)
Anaemia	21 (24.4)
Hand-foot syndrome	17 (19.8)
Diarrhoea	14 (16.3)
Dysregulated liver function	14 (16.3)
Oral ulcer	14 (16.3)
Thrombocytopenia	13 (15.1)
Proteinuria	10 (11.6)
Bleeding	5 (5.8)
Gastrointestinal perforation	2 (2.3)

PRROC, platinum-resistant recurrent ovarian cancer.

study; therefore, the results should be further verified by randomised, controlled studies. Finally, the follow-up period of the present study was short. Therefore, further studies with a longer follow-up period should be carried out to investigate the efficacy and safety of antiangiogenic therapy plus chemotherapy in patients with PRROC.

In conclusion, antiangiogenic therapy plus chemotherapy achieved an ORR of 33.7%, a median PFS of 6.5 months and a median OS of 20.3 months with tolerable toxicity in patients with PRROC. Moreover, ascites and administering treatment as a third-line or above therapy independently predicted an unfavourable survival rate in these patients. Future studies should consider increasing the sample size, including a control group and extending the follow-up period to further investigate the long-term efficacy and safety of antiangiogenic therapy plus chemotherapy in patients with PRROC.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

HL contributed to the study conception and design. JX performed data collection and analysis. MT was responsible for the interpretation of data. All authors contributed to drafting the article. HL and MT confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The study obtained permission from the Ethics Committee of People's Hospital of Zhongshan City (approval no. 2024-033; Zhongshan, China). The patients signed the informed consent form, or if the patient were unable to sign, their family members signed the informed consent form on their behalf.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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