Am J Transl Res 2023;15(3):1973-1981
www.ajtr.org /ISSN:1943-8141/AJTR0147925

Original Article

Effectiveness and safety of mono-anlotinib mono therapy or in combination with chemotherapy in platinum-resistant recurrent ovarian cancer: a single-center retrospective study

Yue Wu[1,2*], Ping Li[1,2*], Yaodong Zhu[1,2], Fengli Zhang[1,2], Li Su[1,2], Yingquan Ye[1,2], Yi Huang[3], Mei Zhang[1,2]

[1]Oncology Department of Integrated Traditional and Western Medicine, The First Affiliated Hospital of Anhui Medical University, Hefei 230022, Anhui, China; [2]The Traditional and Western Medicine (TCM)-Integrated Cancer Center of Anhui Medical University, Hefei 230032, Anhui, China; [3]Anhui University of Traditional Chinese Medicine, Hefei 230038, Anhui, China. [*]Equal contributors.

Received November 21, 2022; Accepted February 9, 2023; Epub March 15, 2023; Published March 30, 2023

Abstract: Objective: To evaluate the clinical efficacy of mono-anlotinib therapy by itself or in combination with chemotherapy in platinum-resistant recurrent ovarian cancer (PROC). Methods: The clinical data of 35 patients with platinum-resistant recurrent ovarian cancer admitted to the First Affiliated Hospital of Anhui Medical University from March 2019 to July 2020 were retrospectively analyzed. All the patients received anlotinib mono- or combined chemotherapy. The effectiveness and adverse events (AEs) were analyzed by RECIST1.1 and CTCAE5.0. Results: In the 35 patients, the median follow-up was 9.80 (95% CI: 3.83-15.77) months. The median progression free survival (mPFS) achieved 6.50 (95% CI: 2.02-10.98) months, the objective response rate (ORR) achieved 17.14%, and disease control rate (DCR) achieved 60.00%. ORR and DCR were 12.50% and 25.0% for monotherapy, 18.52% and 70.37% for combined chemotherapy. The PFS of combined chemotherapy was longer than that of monotherapy (log-rank P = 0.003). thirty-four patients (97.14%) were in a third-line therapy or above, and their ORR and DCR were 14.71% and 58.82%, respectively. Two patients discontinued treatment because of intolerable AEs. No cases of grade 4-5 AEs have been reported. Conclusion: Anlotinib had promising effectiveness and tolerable safety in patients with PROC, even in patients who accepted anlotinib as a third-line or above therapy or with a history of other antiangiogenic drugs.

Keywords: Angiogenesis inhibitors, anlotinib, ovarian epithelial carcinoma, ovarian neoplasms, combination drug therapy

Introduction

Ovarian cancer (OC) is a highly malignant affliction of the female reproductive system, with considerable mortality, and a high incidence, ranking first among gynecological tumors [1]. In China, over 50,000 cases of OC are diagnosed every year, and more than 70% of them already are at an advanced stage at the initial diagnosis [2]. The treatment of OC mainly relies on cytoreductive surgery and platinum-based chemotherapy, however, resistance to chemotherapeutic drugs and recurrence are still high. According to the US NCCN guidelines, recurrent OC (ROC) is classified as platinum-sensitive, platinum-resistant, biochemically recurrent, and refractory. About 80% patients relapse within 1 to 2 years after initial treatment and gradually progress to platinum-resistance recurrent OC (PROC), accompanied by significantly shortened survival [2]. PROC shows poor response to chemotherapy, and non-platinum-based chemotherapy recommended in the above guidelines produces limited therapeutic benefit, with an effective rate of only 10%-25% [3]. Thus, it is vital to identify novel drugs that can help improve the prognosis of PROC patients.

One of the critical factors in the development of solid tumors is abnormal angiogenesis [4].

Vascular endothelial growth factor (VEGF) and its receptors have been targets for antitumor treatment [5], and anti-angiogenic drugs can exert beneficial effects in patients with PROC [6, 7]. Several anti-angiogenic drugs, such as bevacizumab, were ratified by the Food and Drug Administration (FDA) for the treatment of ROC, and combined therapy with antiangiogenic agents and non-platinum-based chemotherapy has gradually become the predominant mode of PROC treatment [7].

Such regimens may prolong the survival of the patients with PROC; however, the problems of drug resistance and adverse reactions remain. To improve the overall survival of OC patients, reducing the frequency of side effects of grade 3 or higher side effects is a priority. Anlotinib, a small-molecular multitargeted tyrosine kinase inhibitor, is an orally available antiangiogenic drug that was developed in the People's Republic China, and which can achieve good efficacy in the therapy of various solid tumors [8-10]. Currently, the FDA approves anlotinib as an orphan drug for the therapy of OC. Observational studies have indicated its effectiveness and safety in monotherapy or in combination chemotherapy in ROC [11-13], however, respective evidence for PROC is still insufficient.

The present retrospective study was conducted by analyzing clinical data to assess the effectiveness and security of anlotinib in patients with PROC.

Methods

Patients

We used data of patients who were diagnosed with PROC and received treatment with anlotinib in the First Affiliated Hospital of Anhui Medical University between March 2019 and July 2021. This retrospective study was approved by the ethics committee of the First Affiliated Hospital of Anhui Medical University (Ethical Review-Kuai-PJ2019-03-19).

Inclusion criteria were: (1) patients aged between 20-80 years old; (2) patients diagnosed with epithelial OC by histopathology and previous tumor cytoreductive surgery; (3) patients with platinum-based chemotherapy as first-line treatment; (4) patients with platinum-resistant recrudescence (disease progression within six months after platinum chemotherapy); (5) patients with at least two cycles of anlotinib treatment (monotherapy or combined therapy) after recurrence; (6) patients with Eastern Cooperative Oncology Group (ECOG) score of 0-2 points; (7) patients with presence of assessable lesions.

Exclusion criteria were: (1) patients combined with another tumor; (2) patients with severe acute or chronic diseases that may have a marked impact on antitumor therapy and prognosis, such as acute infection, immune deficiency diseases, infection with human immunodeficiency virus, and uncontrolled hypertension; (3) patients with incomplete data (such as lost to follow-up).

Treatment

All patients were administered 12 mg anlotinib once per day in addition to combination chemotherapy or as monotherapy for two consecutive weeks (21 days per treatment cycle). At the same time, based on the combined chemotherapy (albumin-binding taxol, irinotecan, gemcitabine, doxorubicin liposomes, cyclophosphamide tablets, etoposide soft capsules, capecitabine tablets, and tegio capsules, all of which are recommended non-platinum based chemotherapy agents without previous cross-resistance) in the 2019 or 2020 CSCO OC diagnosis and treatment guidelines.

Patients who were intolerant to chemotherapy received anlotinib monotherapy with individualized dosages. Doses were reduced to 8 mg anlotinib once per day when severe intolerable adverse reactions occurred.

Data compilation and definition

The compilation data included age, pathological type, International Federation of Gynecology and Obstetrics (FIGO) stage, Karnofsky performance scale (KPS), complicating diseases, ascites, size of recurrence, number of recurrent lesions, metastasis, previous treatment, therapy lines, treatment regimen, and anlotinib discontinuation.

The outcomes included: progression-free survival (PFS), objective response rate (ORR). Di-

Table 1. Demographic and baseline clinical characteristics of the patients

	Total (N = 35)
Age, years, median (range)	53 (29-77)
Histology, n (%)	
Serous	25 (71.43)
Mucinous	4 (11.42)
Clear-cell	5 (14.29)
Malignant mesodermal mixed tumor	1 (2.86)
International FIGO stage, n (%)	
IIIA	6 (17.14)
IIIC	8 (22.86)
IV	21 (60.00)
KPS, median (range), n (%)	80 (60-90)
Complicating disease, n (%)	6 (17.14)
Complicated with ascites, n (%)	8 (22.86)
Size of recurrence, n (%)	
≤ 5 cm	21 (60.00)
> 5 cm	14 (40.00)
Number of recurrent lesions, n (%)	
Multiple	28 (80.00)
Single	6 (17.14)
NE	1 (2.86)
Peritoneal metastasis, n (%)	20 (57.14)
Lymphatic metastasis, n (%)	23 (65.71)
Viscera metastasis, n (%)	25 (71.43)
Previous other anti-angiogenic therapy, n (%)	24 (68.57)
Current treatment lines, n (%)	
2	1 (2.86)
3	6 (17.14)
> 3	28 (80.00)
Therapeutic regimen, n (%)	
Anlotinib	8 (22.86)
Anlotinib + etoposide + cyclophosphamide	3 (8.57)
Anlotinib + capecitabine	3 (8.57)
Anlotinib + etoposide	4 (11.43)
Anlotinib + irinotecan	5 (14.29)
Anlotinib + liposomal doxorubicin	3 (8.57)
Anlotinib + cyclophosphamide	3 (8.57)
Anlotinib + nab-paclitaxel	3 (8.57)
Anlotinib + pemetrexed	3 (8.57)

Federation of Gynecology and Obstetrics (FIGO), Karnofsky performance scale (KPS).

sease control rate (DCR), and safety. The outcomes were evaluated by the investigators according to the Response Evaluation Criteria in Solid Tumors 1.1 (RECIST1.1), graded by the severity of toxic effects based on the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE5.0).

Follow-up

Imaging examination (CT or MRI) and clinical evaluation was performed every 2 cycles. The last follow-up was July 1, 2021.

Statistical analysis

Statistical analyses were conducted using SPSS 22.0 software (IBM Corp., Armronk, NY, USA). Survival curves were produced using GraphPad Prism7 (GraphPad Software, San Diego, CA, USA). Categorical data (case, %) were tested using a Chi-squared test or Fisher's exact test. Statistical significance was reported at $P < 0.05$.

Results

Baseline data

A total of 35 patients with PROC were included in this study, all of whom were diagnosed with terminal OC (6 at stage IIIA, 8 at stage IIIB, and 21 at stage IV). Twenty-seven (77.14%) patients received anlotinib in combination with chemotherapy, and 8 (22.86%) patients received anlotinib monotherapy due to chemotherapy intolerance. The median follow-up period was 9.80 months (95% CI: 3.83-15.77), as of July 1, 2021. Fifteen patients discontinued the treatment until the last follow-up.

The baseline characteristics of all the patients are described in **Table 1**. The median age was 53 (29-77) years old. The pathological subtypes included serous carcinoma (25 cases; 71.43%), mucinous carcinoma (4 cases; 11.42%), clear cell carcinoma (5 cases; 14.29%) and malignant mesodermal mixed tumor (1 case; 2.86%). Most patients (n = 34, 97.14%) received anlotinib as third-line therapy or higher, of whom 28 (80.00) was treated with above

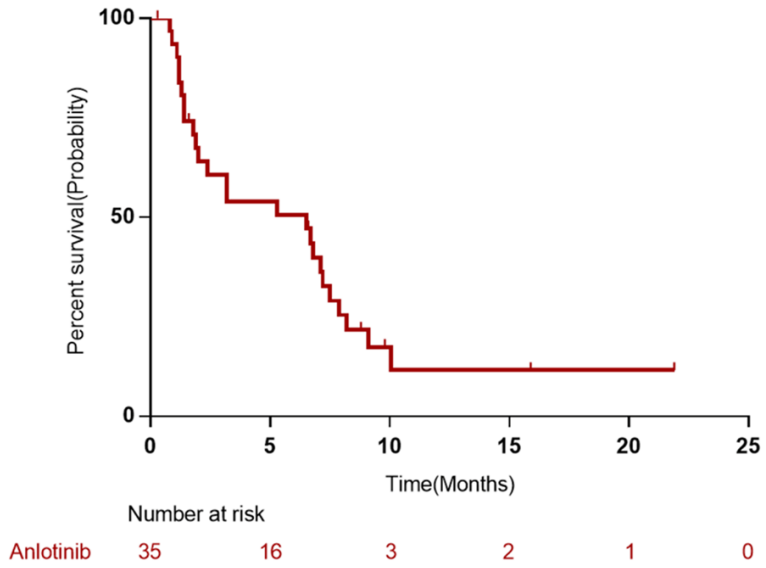

Figure 1. PFS of the patients with PROC. Progression-free survival (PFS), platinum-resistant recurrent ovarian cancer (PROC).

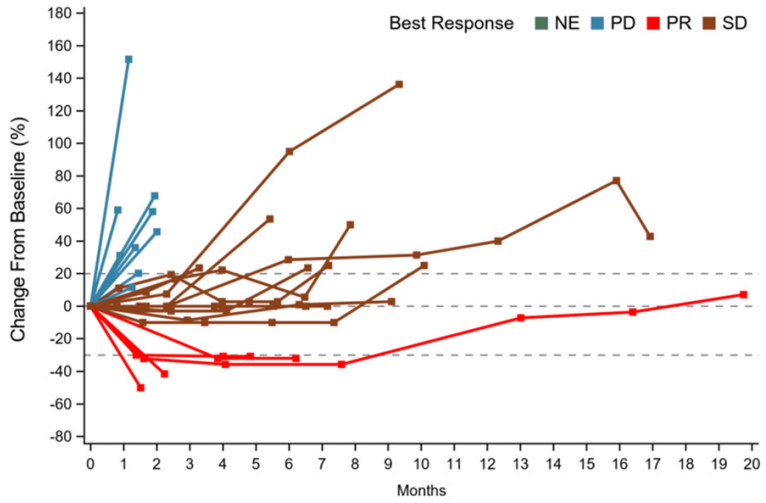

Figure 2. Short-term effectiveness of the patients who received assessment according RECIST1.1. Response Evaluation Criteria in Solid Tumors 1.1 (RECIST1.1).

Table 2. Short-term effectiveness of all the patients

	Anlotinib (N = 35)
PR, n (%)	6 (17.14)
SD, n (%)	15 (42.86)
PD, n (%)	10 (28.57)
NE, n (%)	4 (11.43)
ORR (%, 95% CI)	17.14 (6.56, 33.65)
DCR (%, 95% CI)	60.00 (42.11, 76.13)

Objective response rate (ORR), disease control rate (DCR), partial response (PR), stable disease (SD).

third-line therapy. Twenty-four patients (68.57%) had previously used other antiangiogenic agents (such as bevacizumab).

Effectiveness assessment

Among all patients, the median PFS (mPFS) was 6.50 months (95% CI: 2.02-10.98; **Figure 1**), and none of patients died until the last follow-up.

Regarding short-term effectiveness, 6 patients (17.14%) achieved partial response (PR), 15 patients (42.86%) reached a stable disease (SD) state, and 14 patients (40.00%) exhibited progressive disease (PD; **Figure 2** and **Table 2**). The ORR and DCR were 17.14% (95% CI: 6.56-33.65), and 60.00% (95% CI: 42.11-76.13; **Table 2**).

Effectiveness of anlotinib as monotherapy and in combination with chemotherapy

Among the 35 patients who were assessed for short-term effectiveness, 8 were treated with anlotinib monotherapy, of whom 1 (12.50%) achieved PR, 1 (12.50%) achieved SD, and 6 (75.0%) exhibited PD. The remaining 27 patients were treated with anlotinib in combination with chemotherapy, 5 of which (18.52%) achieved PR, 14 (51.85%) achieved SD state, and 8 (29.63%) exhibited PD. Thus, ORR was 12.50% and 18.52%, with DCR of 25.0% and 70.37% in those who received anlotinib monotherapy or anlotinib combined with chemotherapy, respectively (**Table 3**). The mPFS of monotherapy was 1.20 months (95% CI: 0.96-1.42), and the mPFS of combined therapy was 6.80 months (95% CI: 5.89-7.71). The PFS of combined therapy was longer than that of monotherapy (log-rank P = 0.003; **Figure 3**).

Table 3. Short-term effectiveness of mono-anlotinib therapy and in combination with chemotherapy (n = 35)

	Anlotinib monotherapy (n = 8)	Anlotinib + chemotherapy (n = 27)	P
CR, n (%)	0	0	
PR, n (%)	1 (12.50)	5 (18.52)	
SD, n (%)	1 (12.50)	14 (51.85)	
PD, n (%)	6 (75.00)	8 (29.63)	
ORR (%)	12.50%	18.52%	0.96433
DCR (%)	25.0%	70.37%	0.1473

Objective response rate (ORR), disease control rate (DCR), partial response (PR), stable disease (SD).

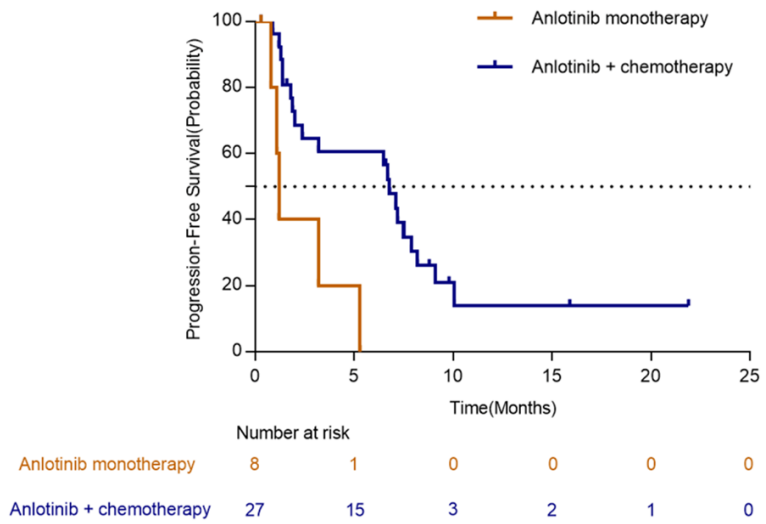

Figure 3. PFS of mono-anlotinib therapy and in combination with chemotherapy. Progression-free survival (PFS).

Effectiveness in various subgroups

Grouping the data according to previous use of anti-angiogenic agents (**Table 4**) showed that 11 patients had received no other anti-angiogenic therapy previously, 3 of whom (27.27%) achieved PR, 5 (45.45%) achieved SD, and 3 (27.27%) showed PD. Among those who previously received other anti-angiogenic therapy (n = 24), 5 (20.83%) achieved PR, 8 (33.33%) reached SD state, and 11 (45.83%) experienced PD. Thus, in patients who received anlotinib as the first anti-angiogenic agent or after previous administration of other anti-angiogenic agents, the ORR was 27.27% and 20.53%, with a DCR of 72.72% and 54.17%, respectively. Moreover, 34 patients used anlotinib as third-line or above therapy, of which 5 (14.71%) achieved PR, 15 (44.12%) reached SD, and 14 (41.18%) experienced PD. Thus, the ORR was 14.71% and the DCR was 58.82%. Histology, FIGO stage and previous treatment with other anti-angiogenic drugs were not associated with PFS (log-rank tests, P > 0.05).

Safety assessment

During follow-up, two patients aborted treatment due to intolerable adverse events, including one patient (2.86%) showing a grade-3 adverse reaction (oral mucositis) and one patient showing gross hematuria (grade-2). No grade-4 or 5 adverse reactions occurred.

The most commonly reported adverse reactions were decreased appetite (n = 12, 34.29%), fatigue (n = 10, 28.57%), nausea and vomiting (n = 8, 22.86%), hand and foot skin reaction (n = 5, 17.14%), and hypertension (n = 2, 11.43%).

Discussion

In patients with ROC, especially those with non-platinum chemotherapy intervals of < 6 months or those developing progression during chemotherapy, options for treatments are limited and their efficacy is mostly unsatisfactory. One of the main difficulties in current clinical practice is the insidious onset of OC in most cases, thus typically precluding early detection [14, 15]. According to statistical date from the China Cancer Center, the incidence of OC in China is increasing annually, and survival rates have not markedly improved [16], mostly because some patients show recurrence within a short time after initial treatment, and gradually developed into PROC [17]. High expression of VEGF predicts the median survival time of patients with OC [15, 18-20], and high expression of platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), and their receptors are similarly poor prognostic factors in OC [21, 22]. Thus,

Table 4. Short-term effectiveness of different subgroups

	Not use of other anti-angiogenic therapy previously (n = 11)	After use of ther anti-angiogenic therapy previously (n = 24)	Anlotinib used as third-line or above therapy (n = 34)
CR, n (%)	0	0	0
PR, n (%)	3 (27.27)	3 (12.50)	5 (14.71)
SD, n (%)	5 (45.45)	10 (41.67)	15 (44.12)
PD, n (%)	3 (27.27)	11 (45.83)	14 (41.18)
ORR	27.27%	12.50%	14.71%
DCR	72.72%	54.17%	58.82%

Objective response rate (ORR), disease control rate (DCR), partial response (PR), stable disease (SD).

preventing abnormal blood vessel formation and persistence and remodeling in the tumor microenvironment are new directions in the treatment of OC [15]. Anti-angiogen drugs can improve the survival of patients with advanced OC [23, 24]. The current recommended treatment for ROC is chemotherapy with or without targeted therapy [15, 25]. However, there are several drawbacks, e.g., the duration of recurrence is gradually shortened in repeated treatments, drug resistance may emerge, these drugs are expensive, and some patients experience intolerable adverse reactions [26, 27].

Anti-angiogenic drugs can also remarkably improve the prognosis of patients with PROC [6, 20, 27]. For example, in a massive phase-III study of chemotherapy in combination with bevacizumab versus chemotherapy for PROC (also known as the AURELIA study), the combined treatment group exhibited significantly better results than the chemotherapy group (mPFS: 6.7 vs 3.4 months; median OS: 16.7 vs 13.3 months) [7]. However, the main target of bevacizumab is VEGF, it has insufficient effect on other pathways of angiogenesis. The prognosis of PROC patients administered a bevacizumab combination treatment is poorer in the general population than that reported in the trial, especially in patients receiving multiple treatments. The survival benefits of this treatment are this uncertain. Thus, general applicability is limited, and identifying novel respective drugs is vital.

Anlotinib can act on several targets, including the VEGFR, PDGFR, FGFR, c-Kit, Ret, and c-Met, to restrain abnormal tumor angiogenesis and control tumor multiplication and metastasis [14, 28]. Furthermore, this compound has shown remarkable efficacy in the intervention of many tumor types, e.g., non-small cell lung cancer [8], soft tissue sarcoma [9], and thyroid cancer [10], with pronounced antiangiogenic effects [25]. In the current study, 97.14% of the included cases were posterior-line patients, with poor response to chemotherapy and intractable treatment, and it is shown that anlotinib had promising effectiveness and tolerable safety, either as monotherapy or in combination with chemotherapy. In addition, for 68.57% of the included cases who previously received bevacizumab or other anti-angiogenic therapy, anlotinib demonstrated effectiveness. Some patients continued treatment, as they had not yet met the PFS evaluation endpoint. The mPFS calculated for all cases with PD by the time of data analyses markedly exceeded that of the currently known chemotherapy group [7] (6.50 VS 3.4 months) and was similar to that of the group receiving bevacizumab combined with chemotherapy (6.80 VS 6.7 months).

In a retrospective study on 15 patients with PROC, anlotinib showed promising efficacy, with an ORR of 14.3% and a DCR of 85.7% [13]. In a different study, 17 PROC patients receiving anlotinib monotherapy produced an ORR of 23.5% and a DCR of 82.3%, whereas in 19 patients receiving this compound in combination with chemotherapy, the ORR was 36.8% and the DCR was 94.7% [29]. The results of the present showed comparable short-term efficacy results. However, the DCR in those who received anlotinib monotherapy was lower, compared to the results of the two previous studies [13, 29], which was likely due to differences in sample size. Of note, the majority of patients included in this study had previously received multiline therapy, and some of them experienced disease progression after using bevacizumab or other anti-angiogenic drugs, which emphasizes the effectiveness of anlo-

tinib in the intervention of PROC in the real world.

The most common adverse effects anti-angiogenic agents are hypertension, proteinuria, and hand-foot syndrome [17, 18, 26]. The previously reported safety profile of anlotinib-containing therapy of OC and other tumor types included hand-foot skin reaction, hypertension, proteinuria, hypothyroidism, leucopenia, and neutropenia [14]. In the current study the most common adverse reactions were decreased appetite, fatigue, nausea and vomiting, hypertension, and hand foot syndrome. One patient showed grade-3 oral mucositis, two patients stopped treatment owing to intolerable adverse reactions, and most of the other adverse events were less severe than grade-3 and were manageable after dose adjustment and symptomatic treatment. Therefore, anlotinib demonstrated outstanding efficacy and favorable safety in the intervention of PROC.

Our study had some limitations, including the lack of a parallel control, i.e., "no chemotherapy" or "other combination therapy" as a comparison. Further, most patients had multiple previous courses of treatment, and limited subsequent options complicate the stratification of combination chemotherapy regimens. The sample size was small, and inter-groups differences were not pronounced, thus a larger sample size would be required for confirmation. Some patients were continuing their treatment and had not met the PFS evaluation endpoint. Moreover, pathological heterogeneity was not strictly distinguished in this study, but this is more reflected the diversity of patients for clinical practice. In the future, it is necessary to carry out a prospective study on the treatment of ovarian cancer with arotinib to verify it.

Conclusions

To summarize, anlotinib is promising for the treatment of PROC, either in a monotherapy or in combined with chemotherapy. This compound showed exceptional anti-tumor activity and offered survival benefits for patients with PROC, even in patients with a history of treatment with other antiangiogenic drugs.

Acknowledgements

The study was supported by the Beijing Medical and Health Public Welfare Foundation "Medical Science Research Fund" Project (YWJKJJ-HKYJJ-B183069).

Disclosure of conflict of interest

None.

Abbreviations

PROC, platinum-resistant recurrent ovarian cancer; AEs, adverse events; Mpfs, median progression free survival; ORR, objective response rate; DCR, disease control rate; VEGF, vascular endothelial growth factor; FDA, Food and Drug Administration; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; PFS, progression free survival; PR, partial response; SD, stable disease; PDGF, platelet-derived growth factor; FGF, fibroblast growth factor.

Address correspondence to: Mei Zhang, Oncology Department of Integrated Traditional and Western Medicine, The First Affiliated Hospital of Anhui Medical University, No. 218 Jixi Road, Hefei 230022, Anhui, China. Tel: +86-13856990019; E-mail: zhangmei@ahmu.edu.cn

References

[1] Luan X, Li W and Di W. Advances on serum tumor markers of early diagnosis of ovarian cancer. Int J Gynecol Obstet 2009; 36: 458-461.

[2] Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, Jemal A, Yu XQ and He J. Cancer statistics in China, 2015. CA Cancer J Clin 2016; 66: 115-132.

[3] Zanotelli MR, Henningsen JD, Hopkins PM, Dederich AP, Herman T, Puccinelli TJ and Salih SM. An ovarian bioreactor for in vitro culture of the whole bovine ovary: a preliminary report. J Ovarian Res 2016; 9: 47.

[4] Folkman J. Angiogenesis in cancer, vascular, rheumatoid and other disease. Nat Med 1995; 1: 27-31.

[5] Wu Y and Li E. Progression of VEGF in the malignant tumor. Journal of Modern Oncology 2005; 13: 18-21.

[6] Liang Y and Zhao H. Application progress of antiangiogenic drugs in platinum - resistant ovarian cancer. Practical Oncology Journal 2020; 34: 66-69.

[7] Pujade-Lauraine E, Hilpert F, Weber B, Reuss A, Poveda A, Kristensen G, Sorio R, Vergote I, Witteveen P, Bamias A, Pereira D, Wimberger P, Oaknin A, Mirza MR, Follana P, Bollag D and Ray-Coquard I. Bevacizumab combined with chemotherapy for platinum-resistant recurrent

ovarian cancer: the AURELIA open-label randomized phase III trial. J Clin Oncol 2014; 32: 1302-1308.
[8] Han B, Li K, Wang Q, Zhang L, Shi J, Wang Z, Cheng Y, He J, Shi Y, Zhao Y, Yu H, Zhao Y, Chen W, Luo Y, Wu L, Wang X, Pirker R, Nan K, Jin F, Dong J, Li B and Sun Y. Effect of anlotinib as a third-line or further treatment on overall survival of patients with advanced non-small cell lung cancer: the ALTER 0303 phase 3 randomized clinical trial. JAMA Oncol 2018; 4: 1569-1575.
[9] Chi Y, Fang Z, Hong X, Yao Y, Sun P, Wang G, Du F, Sun Y, Wu Q, Qu G, Wang S, Song J, Yu J, Lu Y, Zhu X, Niu X, He Z, Wang J, Yu H and Cai J. Safety and efficacy of anlotinib, a multikinase angiogenesis inhibitor, in patients with refractory metastatic soft-tissue sarcoma. Clin Cancer Res 2018; 24: 5233-5238.
[10] Sun Y, Niu W, Du F, Du C, Li S, Wang J, Li L, Wang F, Hao Y, Li C and Chi Y. Safety, pharmacokinetics, and antitumor properties of anlotinib, an oral multi-target tyrosine kinase inhibitor, in patients with advanced refractory solid tumors. J Hematol Oncol 2016; 9: 105.
[11] Sun L, Yang M, Zhang X, Li H, Wu L, Zhang Y and Cai S. Anlotinib combined with etoposide for platinum-resistant recurrent ovarian cancer: a case report. Medicine (Baltimore) 2020; 99: e20053.
[12] Zhang P, Ma L, Wang X, Zhang R and Dong Y. Successful treatment of advanced ovarian cancer with anlotinib: a case report. J Int Med Res 2020; 48: 300060520976824.
[13] Ni J, Cheng X, Chen J, Guo W and Dai Z. Anlotinib as exploratory therapy for platinum-resistant ovarian cancer: a retrospective study on efficacy and safety. Onco Targets Ther 2020; 13: 9857-9863.
[14] Shen G, Zheng F, Ren D, Du F, Dong Q, Wang Z, Zhao F, Ahmad R and Zhao J. Anlotinib: a novel multi-targeting tyrosine kinase inhibitor in clinical development. J Hematol Oncol 2018; 11: 120.
[15] Lheureux S, Braunstein M and Oza AM. Epithelial ovarian cancer: evolution of management in the era of precision medicine. CA Cancer J Clin 2019; 69: 280-304.
[16] Zheng RS, Sun KX, Zhang SW, Zeng HM, Zou XN, Chen R, Gu XY, Wei WW and He J. Report of cancer epidemiology in China, 2015. Zhonghua Zhong Liu Za Zhi 2019; 41: 19-28.
[17] Zhang J, Li A, Jiang Q, Zheng F and Zhu H. Efficacy and safety of apatinib treatment in platinum-resistant recurrent epithelial ovarian cancer: a real world study. Drug Des Devel Ther 2019; 13: 3913-3918.
[18] Duncan TJ, Al-Attar A, Rolland P, Scott IV, Deen S, Liu DT, Spendlove I and Durrant LG. Vascular endothelial growth factor expression in ovarian cancer: a model for targeted use of novel therapies? Clin Cancer Res 2008; 14: 3030-3035.
[19] Jin M, Cai J, Wang X, Zhang T and Zhao Y. Successful maintenance therapy with apatinib in platinum-resistant advanced ovarian cancer and literature review. Cancer Biol Ther 2018; 19: 1088-1092.
[20] Ding J, Cheng XY, Liu S, Ji HY, Lin M, Ma R and Meng FL. Apatinib exerts anti-tumour effects on ovarian cancer cells. Gynecol Oncol 2019; 153: 165-174.
[21] Avril S, Dincer Y, Malinowsky K, Wolff C, Gündisch S, Hapfelmeier A, Boxberg M, Bronger H, Becker KF and Schmalfeldt B. Increased PDGFR-beta and VEGFR-2 protein levels are associated with resistance to platinum-based chemotherapy and adverse outcome of ovarian cancer patients. Oncotarget 2017; 8: 97851-97861.
[22] Sun Y, Fan X, Zhang Q, Shi X, Xu G and Zou C. Cancer-associated fibroblasts secrete FGF-1 to promote ovarian proliferation, migration, and invasion through the activation of FGF-1/FGFR4 signaling. Tumour Biol 2017; 39: 1010428317712592.
[23] Sima N, Sun W, Gorshkov K, Shen M, Huang W, Zhu W, Xie X, Zheng W and Cheng X. Small molecules identified from a quantitative drug combinational screen resensitize cisplatin's response in drug-resistant ovarian cancer cells. Transl Oncol 2018; 11: 1053-1064.
[24] Dasa SSK, Diakova G, Suzuki R, Mills AM, Gutknecht MF, Klibanov AL, Slack-Davis JK and Kelly KA. Plectin-targeted liposomes enhance the therapeutic efficacy of a PARP inhibitor in the treatment of ovarian cancer. Theranostics 2018; 8: 2782-2798.
[25] Shoji T, Komiyama S, Kigawa J, Tanabe H, Kato K, Itamochi H, Fujiwara H, Kamiura S, Hamano T and Sugiyama T; Japanese Gynecologic Oncology Group. An open-label, randomized, phase II trial evaluating the efficacy and safety of standard of care with or without bevacizumab in platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer patients previously treated with bevacizumab for front-line or platinum-sensitive ovarian cancer: rationale, design, and methods of the Japanese Gynecologic Oncology Group study JGOG3023. BMC Cancer 2018; 18: 771.
[26] Zhang W, Shen Z, Luo H, Hu X, Zheng L and Zhu X. The benefits and side effects of bevacizumab for the treatment of recurrent ovarian cancer. Curr Drug Targets 2017; 18: 1125-1131.
[27] Oza A, Kaye S, Van Tornout J, Sessa C, Gore M, Naumann RW, Hirte H, Colombo N, Chen J,

Gorla S, Poondru S, Singh M, Steinberg J, Yuen G and Banerjee S. Phase 2 study evaluating intermittent and continuous linsitinib and weekly paclitaxel in patients with recurrent platinum resistant ovarian epithelial cancer. Gynecol Oncol 2018; 149: 275-282.

[28] Lin B, Song X, Yang D, Bai D, Yao Y and Lu N. Anlotinib inhibits angiogenesis via suppressing the activation of VEGFR2, PDGFRβ and FGFR1. Gene 2018; 654: 77-86.

[29] Cui Q, Hu Y, Ma D and Liu H. A retrospective observational study of anlotinib in patients with platinum-resistant or platinum-refractory epithelial ovarian cancer. Drug Des Devel Ther 2021; 15: 339-347.