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Clinical efficacy and safety of apatinib combined with oral VP-16 for the treatment of advanced ovarian cancer: Preliminary evaluation of a clinical drug regimen

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Abstract

To investigate the clinical efficacy and safety of apatinib in combination with oral VP-16 for the treatment of chemotherapy-resistant advanced ovarian carcinoma. Twenty-seven advanced ovarian carcinoma patients were treated with oral VP-16 chemotherapy combined with oral apatinib mesylate (500 mg/d). CA125, VEGF, and CEA were examined every 3-4 weeks, and tumour changes were monitored by CT every 8-12 weeks. PFS was obtained by follow-up after discharge. For all patients, the ORR (including CR and PR) was 25.0%, and the DCR (including CR, PR and SD) was 75.0%. CEA and CA199 significantly decreased ($p<0.05$), but the decrease in VEGF was not significant. The average PFS was 5.13 months. The ECOG score had a significant effect on PFS ($p<0.05$), while there were no significant differences in PFS based on age ($p=0.394$). The main side effects of this regimen were hypertension, proteinuria, hand-foot syndrome and myelosuppression, which were tolerated by patients after active symptomatic treatment. Apatinib combined with oral VP-16 is an effective regimen for the treatment of chemotherapy-resistant advanced ovarian cancer. This combination therapy should be widely used in clinical practice.

Introduction

Recent studies have shown that anti-angiogenic drugs combined with chemotherapy can significantly improve the prognosis of patients with platinum-resistant ovarian cancer [1, 2]. The combination of bevacizumab and single-agent chemotherapy can significantly prolong progression-free survival (PFS) (6.7 months vs 3.4 months) compared with chemotherapy alone [3]. Therefore, chemotherapy combined with anti-angiogenic drugs may have survival benefits for patients with platinum-resistant ovarian carcinoma [4] . Based on this hypothesis, it is reasonable to speculate whether anti-angiogenic drugs besides bevacizumab can be combined with chemotherapeutics to achieve robust effects in the treatment of platinum-resistant ovarian carcinoma [5, 6]. In addition, apatinib, an anti-angiogenic small molecule developed autonomously in China, has shown good efficacy in many solid tumours [7-9]. Preclinical studies showed synergy between apatinib, cytotoxic drugs, and their combination therapy does not form a toxic superposition. Thus, the foundation has been laid for the combination of these two drugs [10]. Apatinib is a small molecule tyrosine kinase inhibitor, and VP-16 is a cytotoxic drug commonly used in clinical practice in China. Both drugs are administered orally. When these two drugs are administered together, the patient does not need to be hospitalized, which makes this regimen quite convenient. Therefore, it is necessary to investigate the clinical efficacy and safety of the combination of apatinib and oral VP-16 for the treatment of platinum-resistant recurrent ovarian cancer. The aim of this research was to study the application value of apatinib and oral VP-16 in combination for the treatment of platinum-resistant recurrent ovarian cancer. Safety of this combination therapy was evaluated to supply a safe, effective and convenient treatment for advanced ovarian cancer patients.

Materials and Methods

Patients and selection criteria

From June 1, 2018, to June 30, 2019, a total of 27 advanced ovarian cancer patients who had failed second-line chemotherapy and experienced drug-resistant relapse were selected in the People's Hospital of Lishui District, Nanjing, China.

Inclusion criteria: (1) age ≥ 18 years; (2) Eastern Cooperative Oncology Group (ECOG) score of physical condition of less than 3; (3) ovarian cancer diagnosis by cytology or histology, disease progression during treatment or recurrence after treatment, and previous treatment with more than 2 chemotherapy regimens; (4) fewer than 4 months from the end of the previous antitumor therapy and the beginning of this study; and (5) good organ function: WBC $>3.0\times10^9$/L, platelets $>80\times10^9$/L, haemoglobin >90 g/L, albumin >29 g/L, ALT and AST <2.5 times normal, bilirubin <1.5 times normal, and urine protein <2.5 times normal.

Exclusion criteria: (1) the use of small molecule drugs, such as vascular endothelial growth factor (VEGF) receptor (VEGFR) inhibitors, within 6 months; (2) anticancer therapy, including chemotherapy, radiotherapy, surgery and molecular targeted therapy, within 4 weeks before treatment on this study; (3) inability to reduce hypertension to the normal range with antihypertensive drug treatment (systolic blood pressure > 150 mmHg or diastolic blood pressure >90 mmHg); (4) severe circulatory disease, such as congestive heart failure, symptomatic coronary artery disease, arrhythmia, myocardial infarction, etc.; (5) uncontrollable nausea, vomiting, diarrhoea, or other intestinal diseases; and (6) history of venous thrombosis or pulmonary embolism. This research was permitted by the Hospital Ethics Committee. Patients were educated of the pros, cons and risks of the study and signed the informed consent form.

Treatment programmes

Apatinib 500 mg/d (apatinib dose was reduced to 250 mg if the patient experienced a severe adverse effect) combined with VP-16 50 mg was administered on d1-d14; each treatment course lasted 21 days, and oral VP-16 was included in up to 6 courses. Thereafter, single-agent therapy with apatinib was maintained until progressive disease or unbearable toxicity occurred.

Therapeutic monitoring

At the beginning of treatment, the patients underwent full abdominal CT imaging, and serum carbohydrate antigen 125 (CA125), carcinoembryonic antigen (CEA), and VEGF levels were detected. Serum CA125, CEA, and VEGF were reviewed before the start of each treatment course. CT images were reviewed every two courses to assess changes in tumour lesions. According to the RECIST 1.1 standard, the outcomes were characterized as complete response (CR), partial response (PR), stable

disease (SD), and progressive disease (PD), and the response rate (RR) was calculated as CR+PR. The disease control rate (DCR) was calculated as CR+PR+SD. According to the NCI-CTC4.0 standard evaluation, adverse reactions were graded from 0-4. All adverse reactions were recorded and classified.

Follow-up

Patient follow-up occurred by outpatient visits or telephone calls until June 2019. PFS was defined as the length of time from initiation of the Apatinib+VP-16 treatment regimen to disease progression or death.

Statistical analysis

Statistical analyses were performed using SPSS 17.0. Count data are reported as n (%), the survival curve was generated by the Kaplan-Meier method, and the median PFS based on different clinical features was compared by the log-rank test. Measurement data are presented as $\bar{x}\pm s$, and the *t* test was performed to determine the significance of differences between groups. $P<0.05$ was considered to indicate statistical significance.

Results

Treatment effect

Of the 27 patients initially included in this study, 24 were evaluated for efficacy; 3 patients stopped treatment due to serious adverse reactions. After combination therapy, the following outcomes were obtained: CR: 0; PR: 6; SD: 11; PD: 7; ORR (CR+PR): 25.0%; and DCR (CR+PR+SD): 75.0%. The average PFS was 5.13 months (**Table 1**).

Table 1: Prognosis of 24 patients with advanced ovarian cancer.

Endpoint	CR	PR	SD	PD
Cases, *n*	0	4	13	7
Proportion, %	0	16.7	54.1	29.2

Survival

The average PFS of patients in this study stratified by ECOG score was as follows: ECOG 0-1, 6.15 months, 95% CI (5.013-7.284); and ECOG2, 3.73 months, 95% CI (2.629-4.829). The difference in PFS based on ECOG score was statistically significant (P = 0.017). The average PFS of patients stratified by age was as follows: 60 years or younger, 5.06 months, 95% CI (3.841-6.281); and older than 60 years, 5.15 months, 95% CI (3.779-6.539). There was no significant difference in PFS between these groups (P = 0.923) (**Fig. 1, 2** and **Table 2**).

Table 2: Comparison of median PFS after treatment based on different clinical features.

Variable		*n*	PFS (months)	*P value*
ECOG score	0-1	14	6.15	0.017
	2	10	3.73	
Age	≤60 years	10	5.06	
	>60 years	14	5.15	0.923

Changes in tumour markers

Peripheral blood CEA and CA125 levels in patients significantly decreased with treatment, whereas peripheral blood VEGF levels showed a decreasing trend that was not significant (**Table 3**).

Table 3: Changes in blood tumour markers before and after treatment ($x\pm s$).

Treatment course	CEA (μg/L)	CA125 (U/mL)	VEGF (pg/mL)
1	60.82±29.10	70.57±45.72	930.57±254.65
2	55.48±25.46	59.24±29.44	892.41±224.46
3	41.47±18.94	50.14±24.97	882.73±197.55
4	37.60±16.57	48.23±16.76	873.93±177.85
5	34.62±16.95	43.61±18.80	831.84±133.39
6	34.46±13.39	41.97±10.06	816.04±134.29
F value	7.112	3.907	1.131
P value	0.000	0.002	0.347

Note: CEA, carcinoembryonic antigen; VEGF, vascular endothelial growth factor; CA125, carbohydrate antigen 125.

Adverse effects

Common adverse effects of the treatment including hypertension, proteinuria, hand-foot syndrome, fatigue, etc., required a dose reduction or treatment suspension, and symptoms were relieved by symptomatic treatment. One patient discontinued treatment due to gastrointestinal reactions, one discontinued due to a history of hypertension, and one discontinued due to myelosuppression. The study did not observe treatment-related adverse events beyond grade 4, and no unexpected adverse events were reported (**Table 4**).

Discussion

At present, the treatment goals for multiline drug-resistant recurrent metastatic ovarian cancer are to improve patient quality of life, avoid or reduce tumour- or treatment-associated pain, and prolong patient survival [11]. Chemotherapy and molecular

Table 4: Adverse effects of the treatment in patients.

Adverse events	Toxicity grade			
	1	2	3	4
Hypertension	1	4	5	1
Albuminuria	2	4	0	0
Hand-foot syndrome	5	3	2	0
Weakness	4	5	0	0
Myelosuppression	2	3	2	1
Gastrointestinal reaction	3	3	2	1
Bleeding	1	2	0	0

targeted therapy are the first choices for advanced ovarian cancer, but there is no consensus on the exact drug regimen [12]. Advanced ovarian cancer often shows chemoresistance, creating difficulties in clinical treatment [13]. VP-16 is a commonly used chemotherapy in clinical practice. It has good curative effects in the treatment of various tumours. The oral dosage form has few side effects, a stable concentration in blood, and the advantage of convenient dosing, as affirmed by clinicians and patients. A study on the efficacy of VP-16 and bevacizumab for the treatment of advanced ovarian cancer began in 2016 at Sun Yat-sen University, Guangzhou, China Cancer research institute. In the intent-to-treat population, the ORR was 54.3% and the DCR was 85.7%, whereas these values were 61.3% and 96.8% in the total population. The median PFS was found to be 8.1 months. Preclinical studies have shown that VP-16 has a good effect in combination with apatinib in advanced ovarian cancer [9]. On the basis of these results, we further stratified the patients to determine whether ECOG score and age affect the efficacy of the treatment regimen. In present study, the combination of the two oral drugs led to a DCR of 75% and an average PFS of 5.13 months, which were satisfactory.

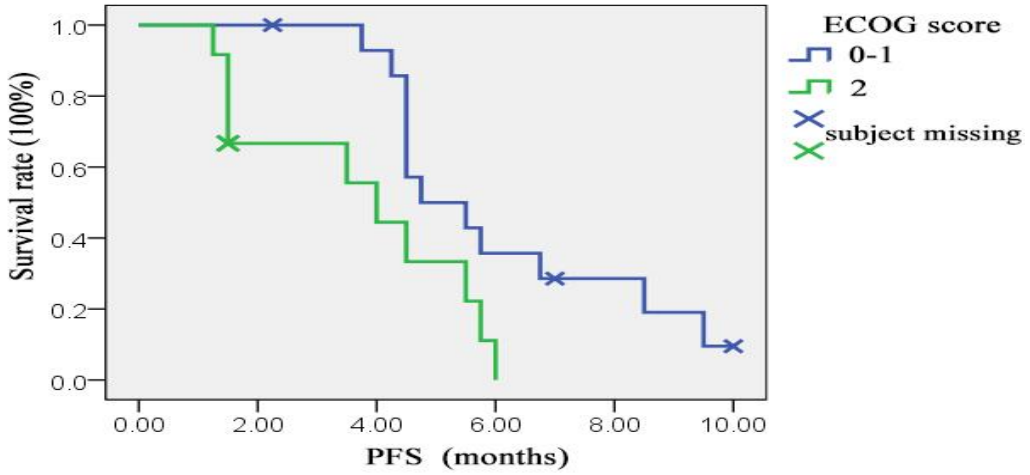

Fig. 1: Impact of ECOG score on PFS (months). The average PFS of patients with ECOG 0-1 was 6.15 months, 95% CI (5.013-7.284); and ECOG2, 3.73 months, 95% CI (2.629-4.829).

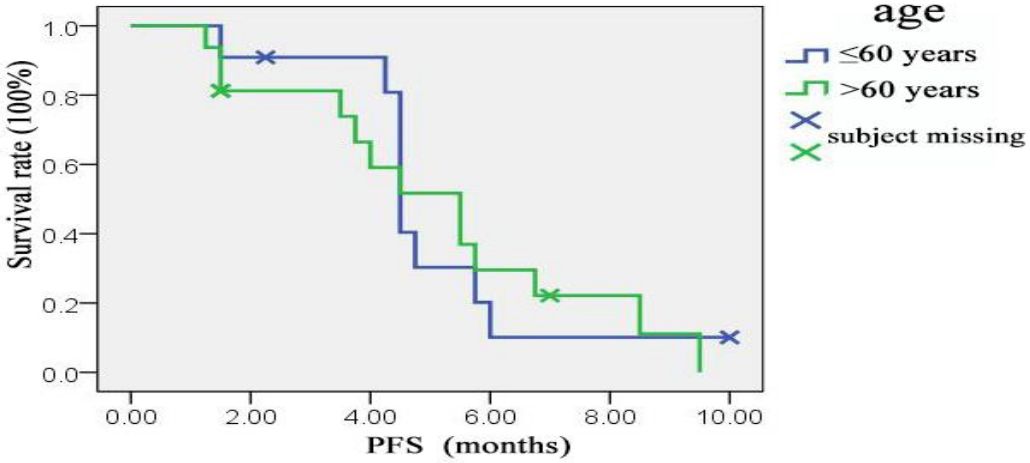

Fig. 2: Impact of age on PFS (months). The average PFS of patients that was 60 years or younger was 5.06 months, 95% CI (3.841-6.281); and older than 60 years was 5.15 months, 95% CI (3.779-6.539).

Age had minor effect on PFS, while patients with different ECOG scores had large differences in PFS. It might be the reason that patients with a poor general condition have a low tolerance to drugs, and poorer conditions may predict poor results and prognoses. The decreases in the CEA and CA125 tumour markers were obvious; the combination therapy inhibited tumour development, leading to a decrease in tumour-associated antigens. The decrease in VEGF in peripheral blood was not significant, probably because apatinib can inhibit and block the binding of VEGF/VEGFR-2 and autophosphorylation of VEGFR-2 [14]. The primary target in peripheral blood is VEGFR, but not free VEGF. Based on these results, we speculated that CEA and CA125 have utility as reference indicators for the assessment of anticancer treatment efficacy, but further studies are necessary to clarify the application value of VEGF.

The main side effects in this trial were hypertension, proteinuria, hand-foot syndrome and myelosuppression. Previous studies have reported that the most common adverse effect of apatinib during treatment is hypertension, which occurs in approximately 30%-40% of patients and is generally classified as primary or secondary hypertension; however, patients with underlying diseases such as hypertension should be carefully observed for clinical blood pressure to prevent other adverse events. Above mentioned all side effects can be controlled by active clinical symptomatic treatment or an appropriate dose reduction; therefore, the safety of this trial was within the controllable range.

Conclusion

The combination of apatinib and oral VP-16 is an effective regimen for the treatment of chemotherapy-resistant advanced ovarian cancer. This treatment regimen has a high ORR and is safe, effective, and convenient. It provides a safe, effective and convenient therapeutic schedule for advanced ovarian cancer patients. It is worthy of promotion and application in the field of oncology.

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Conflict of interest

The authors declare no conflict of interest.

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