Apatinib in treating clinical and biochemical recurrent ovarian cancer

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Research

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Abstract

Background: Apatinib, a small molecule inhibitor of vascular endothelial growth factor receptor 2 (VEGFR-2), exerts antiangiogenic effects. Taken orally, apatinib shows clinical activity in the treatment of recurrent or platinum-resistant ovarian cancer (OC) as monotherapy or in combination with other chemotherapeutic agents. We investigated the efficacy of apatinib in recurrent OC and preliminarily evaluated the clinical activity of apatinib in biochemical-only recurrent OC patients.

Results: We retrospectively analyzed clinical material of 41 recurrent patients who had received apatinib monotherapy or apatinib plus chemotherapy between June 2016 and August 2018. Apatinib was administered at a 500 mg daily dose. Response was determined according to measurable disease or serum carbohydrate antigen (CA)-125 levels. Progression-free survival (PFS) was estimated by Kaplan-Meier method. All patients were evaluable, 19 (46.34%) had biochemical relapse and 22 (53.66%) had clinical relapse. The objective response rate (ORR) and disease control rate (DCR) in the overall population were 31.71% and 78.05%, respectively. The median PFS was 7 months (95% confidence interval 5.43-8.57). In patients with biochemical relapse only, the median PFS was 6 months, with ORR of 26.32% and DCR of 89.47%.

Conclusions: Apatinib is a well-tolerated and effective agent in patients with recurrent OC and has the potential to delay clinical progression in patients with asymptomatic biochemical relapse.

Background

Ovarian cancer (OC) is the fifth-leading cause of death due to gynecological malignancies (1). Due to a lack of specific symptoms, nearly 75% of patients are diagnosed with advanced OC at the initial visit, contributing to the low 5-year survival rate (approximately 20%) (2). Cytoreductive surgery and platinum-paclitaxel combination chemotherapy are established as the primary treatments for advanced OC. However, the majority of patients who respond to initial treatment eventually experience a relapse and show low response to retreatment with cytotoxic therapy. Thus, the investigation of other effective treatment strategies remains a substantial clinical need.

Determination of disease relapse is based on the results of testing for serum carbohydrate antigen (CA)-125 and imaging. Biochemical recurrence is defined as rising CA-125 levels exceeding twice the upper limit of the normal range, without the disease being visualized on scans; it generally precedes the onset of clinical evidence by an average of 2 to 6 months (3, 4). In such cases, the choice between either a watch-and-wait policy or early therapeutic intervention is controversial. Thus, there remains an opportunity to optimize therapy, to delay clinical disease progression to the extent that would require intravenous chemotherapy.

Recently, the strategy of targeting angiogenesis has achieved success for the treatment of OC. Bevacizumab, a humanized monoclonal antibody that binds to all vascular endothelial growth factors

(VEGF), has been approved by the European drug administration for the treatment of advanced ovarian carcinoma, specifically for recurrent platinum-sensitive or -resistant OC (5).

Apatinib is an oral vascular endothelial growth factor receptor 2 (VEGFR-2) inhibitor that inhibits tumor angiogenesis by blocking downstream signaling (6). In China, apatinib has been approved for the third-line treatment of advanced gastric adenocarcinoma and adenocarcinoma in the gastric-esophageal junction (7–9). Moreover, multiple studies have demonstrated its use in patients with other advanced malignancies, such as breast cancer (10, 11), hepatic carcinoma (12), lung cancer (13, 14), colorectal cancer (15), and soft tissue tumors (16, 17). Case reports and clinical studies have also illustrated the efficacy and safety of apatinib in recurrent OC (18–22); however, to our knowledge, its efficacy in biochemical recurrent patients is not yet known. Hence, we conducted this study to report the efficacy of apatinib in recurrent OC and preliminarily observed the outcome of apatinib monotherapy in biochemical recurrent OC patients.

Results

Patient characteristics

Between June 2016 and August 2018, a total of 41 advanced OC patients were enrolled in this study. The median age was 53 years (range, 36-67). Most patients (33, 80.48%) presented with stage IIIC (Federation International of Gynecology and Obstetrics FIGO) disease. The histological type included serous carcinoma (high grade 70.73%; low grade 21.95%), mucinous carcinoma (4.88%), and endometrioid carcinoma (2.44%). Of 41 patients, 14 (34.15%) had optimal debulking surgery, whereas the remaining 27 (65.85%) received suboptimal debulking surgery. All were tumor recurrent patients after previous therapy; of these, 19 (46.34%) patients had biochemical recurrence and 22 (53.66%) patients had a visible tumor. Among the included patients, 29 (70.73%) had received 1-2 lines of chemotherapy and 12 (29.27%) had received 3-5 lines of treatment before participating. In this study, 13 of 41 (31.71%) patients were treated with apatinib in combination with chemotherapy and 28 patients (68.69%) received apatinib monotherapy. Most patients (75.61%) had good Eastern Cooperative Oncology Group performance status (ECOG PS) (0), and patients with ECOG PS of 1 and 2 accounted for 14.63% and 9.76%, respectively. Detailed baseline clinical characteristics of the patients are shown in Table 1.

Efficacy

During a follow up in July 2019, all patients were evaluated. Efficacy analysis indicated that none of the 41 patients achieved Complete remission (CR), 13 patients achieved partial remission (PR), 19 patients maintain stable disease (SD), and 9 patients had progressive disease (PD), resulting in an objective response rate (ORR) of 31.71% and a disease control rate (DCR) of 78.05% (Table 2). The median progression-free survival (PFS) was 7 months (95% CI 5.43-8.57, Fig. 1A). Among the patients with biochemical relapse, ORR and DCR were 26.32% and 89.47% respectively (Table 2), with median PFS of 6 months (95% CI 4.39-7.61, Fig. 1B).

Safety

Adverse reactions were assessed and are summarized in Table 3. In general, most patients were tolerant to apatinib without any grade 4 adverse events (AEs). The most common grade 1-3 AE was hand-foot syndrome (46.4%). Other common AEs were mucositis (41.5%), fatigue (39.0%), anorexia (39.0%), proteinuria (36.6%), hypertension (34.1%), and thrombocytopenia (26.8%).

Discussion

Traditional therapies for OC, including debulking surgery and chemotherapy, cannot yield a good response rate in all relapsed OC patients. Efforts to understand OC biology have facilitated the development of new targeted antineoplastic agents. In cancer, angiogenesis contributes to tumor growth and invasion (23). Multiple growth factors play proangiogenic roles, including VEGF, epidermal growth factor (EGF), and platelet-derived growth factors (PDGF); of these, the VEGF pathway is pivotal in angiogenesis (24). Bevacizumab, a monoclonal antibody targeting VEGF-A, has been approved for the treatment of recurrent platinum-sensitive or -resistant OC (5). Several multitargeted receptor tyrosine kinase inhibitors (TKIs), such as imatinib, cediranib, sorafenib, sunitinib, and pazopanib, target VEGFR, PDGFR, and FGFR. Many of these inhibitors have been or are being evaluated in clinical trials in OC, and some agents have exhibited inhibitory effects (5).

Most of the studies demonstrating clinical activity in advanced OC are small case reports. Only two prospective studies tested the efficacy of apatinib treatment in advanced OC. One is a single arm clinical study, which assessed the efficacy and safety of apatinib as monotherapy in patients with recurrent platinum-resistant epithelial OC (19). The ORR and DCR in 28 patients receiving apatinib 500 mg daily were 41.4% and 68.9%, respectively, and the median PFS and OS were 5.1 months and 14.5 months (19). The other study assessed the activity of apatinib plus etoposide in the treatment of patients with platinum-resistant or -refractory OC, showing an ORR of 54% and DCR of 86% (18). The toxicity of apatinib in monotherapy and combined therapy were both manageable (18, 19). In our study, we found that, in the overall population, the median PFS was 7 months, and that the ORR was 31.71% and DCR was 78.05%, supporting the clinical activity of apatinib in recurrent OC. The safety of apatinib at a dose of 500 mg daily was similar to that reported in the above studies.

The National Comprehensive Cancer Network (NCCN) guidelines for OC suggest that biochemical recurrent patients may: 1) enroll in a clinical trial; 2) delay treatment until clinical relapse; 3) receive immediate platinum-based recurrence therapy; or 4) undergo best supportive care (25). Thus, several studies aimed to investigate low-toxicity agents to delay the appearance of measurable disease in these patients (26). However, no efficacy agent was confirmed until now. In our study, we demonstrated the efficacy of apatinib in biochemical recurrent OC patients with a median PFS of 6 months. This result implied that early treatment using apatinib in biochemical-only recurrent OC may extend time to clinical disease progression and delay time to intravenous chemotherapy, with low toxicity. However, a large sample study is needed to confirm the effect of apatinib in biochemical relapse.

One of the potential shortcomings of this study is that it was a relatively small-scale retrospective study; only 19 biochemical recurrent patients were evaluable. Prospective studies on a large sample cohort are needed to confirm the value of apatinib for the treatment of biochemical relapse patients. Additionally, this study failed to find a biomarker to predict the efficacy in biochemical recurrent patients. In this study, patients experienced similar grades of AEs to previous studies of apatinib treatment in OC. Hand-foot syndrome, mucositis, fatigue, anorexia, proteinuria, and hypertension were the most common adverse effects; however, all were tolerable.

Although our study was not the first to demonstrate the efficacy and safety of apatinib in advanced OC, we also investigated the activity of apatinib in only biochemical recurrent OC patients. This study indicates that apatinib might be a new option for such patients to delay time to clinical disease progression and intravenous chemotherapy. Further large-sample prospective studies are needed to prove this effect.

Patients And Methods

Patients

In this retrospective study, we gathered the material of patients diagnosed with OC via pathologic evaluation, who had received apatinib monotherapy or treatment with apatinib plus chemotherapy between June 2016 and August 2018 in the first and second affiliated hospital of the Third Military Medical University. Patients were considered eligible for analysis if: 1) they received at least one line standard chemotherapy after debulking surgery and 2) relapse of disease was demonstrated by a measurable tumor or by an elevated level of CA-125. The study also enrolled patients who were intolerant to chemotherapy. Additional inclusion criteria included appropriate renal, hepatic, and hematopoietic function and an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0-2. Patients with a history of bleeding, hypertension, ischemic cardiovascular disease, or proteinuria were ineligible for this study.

Treatments

The administration of apatinib as monotherapy or in combination with chemotherapy was determined according to different patient needs. Apatinib monotherapy was applied to patients who were no longer tolerant to chemotherapy or patients with biochemical recurrence of disease. Patients with relapse of a measurable tumor received treatment with apatinib and chemotherapy based on a taxane or etoposide. The recommended initial dose of apatinib was 500 mg, po qd, half an hour after a meal at the same time every day. Chemotherapy was given simultaneously with apatinib for 28 days of one cycle. If intolerable toxicity occurred, the patient was informed to gradually reduce the dose to 250 mg or discontinue the medication.

Evaluation

The first evaluation for clinical efficacy and safety was performed at the end of the first cycle. Subsequently, the interval of assessment changed to every two cycles. Treatment efficacy in patients with measurable disease was assessed by CT, MRI, and ultrasound scans. Complete remission (CR), partial remission (PR), stable disease (SD), and progressive disease (PD) were evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) (Version 1.1). Responses of biochemical recurrent patients were determined through serum CA-125 levels. The CA-125 definition for response rate was based on the Rustin criteria (27). A reduction of CA-125 to normalization that was maintained for at least 4 weeks was defined as CR, a 50% reduction as PR, a 25% increase as PD, and a situation beyond the above criteria was recognized as SD (28). CR plus PR was categorized as objective response rate (ORR) and CR, PR, plus SD was defined as disease control rate (DCR). The period from initial treatment to disease progression or death was defined as progression-free survival (PFS). Drug-related adverse effects were evaluated and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) (version 4.0).

Statistical analysis

The percentage method was used for categorical variables and drug safety analysis. PFS was analyzed by the Kaplan-Meier method, and the corresponding figures were drawn using GraphPad Prism 8.0 software (GraphPad Software Inc., San Diego, CA, USA). A P value <0.05 was regarded statistically significant.

Abbreviations

OC: Ovarian Cancer; CR: Complete Remission; PR: Partial Remission; SD: Stable Disease (SD); PD: Progressive Disease; ORR: Objective Response Rate; DCR: Disease Control Rate; PFS: Progression-Free Survival; AE: Adverse Event.

Declarations

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Ethics approval and consent to participate

This retrospective study was approved by the institutional review board of Xinqiao Hospital, Third Military Medical University, China. The patients participating in this study provided written informed consent before study initiation.

Availability of data and materials

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Xierong Kai designed the research study and revised the manuscript. Zhongyu Wang and Yake Huang performed statistical analysis and drafted the manuscript. Ling Long, Li Zhou, Yan Huang, Aiming Pu, and Sufen Li participated in the cases recruit and follow-up of this study. Lei Gan assisted in the statistical analysis. All authors read and approved the final manuscript

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Tables

Table 1. Baseline patients' characteristics

FIGO, International Federation of Gynecology and Obstetrics; ECOG PS, Eastern Cooperative Group Performance Status.

Characteristics	No. %
Median age(rang)(years)	53(36-67)
FIGO stage	
IIIA	1 (2.44%)
IIIB	3 (7.32%)
IIIC	33 (80.48%)
IV	4 (9.76%)
ECOG PS	
0	31 (75.61%)
1	6 (14.63%)
2	4 (9.76%)
Histology Type	
High-grade serous carcinoma	29 (70.73%)
Low-grade serous carcinoma	9 (21.95%)
Mucinous carcinoma	2 (4.88%)
Endometrioid carcinoma	1 (2.44%)
Debulking Surgery	
Optimal	14 (34.15%)
Suboptimal	27 (65.85%)
Biochemical recurrence	
Yes	19 (46.34%)
No	22 (53.66%)
Previous chemotherapy lines	
1-2	29 (70.73%)
3-5	12 (29.27%)
Treatment regimen	
Combined chemotherapy	13 (31.71%)
Single drug	28 (68.29%)

Table 2. Treatment response

	Imageological response	Biochemical response	Overall response
Complete response (CR)	0	0	0
Partial response (PR)	8(36.36)	5(26.32)	13(31.71)
Stable disease (SD)	7(31.82)	12(63.16)	19(46.34)
Progressive disease (PD)	7(31.82)	2(10.53)	9(21.95)
Objective response rate (ORR)	8(36.36)	5(26.32)	13(31.71)
Disease control rate (DCR)	15(68.18)	17(89.47)	32(78.05)

Table 3. Adverse events

Adverse events	Grades				
	1 (n, %)	2 (n, %)	3 (n, %)	4 (n, %)	Total (n, %)
Hand-foot syndrome	5 (12.2%)	9 (22.0%)	5 (12.2%)	0	19 (46.4%)
Mucositis	3 (7.3%)	6 (14.6%)	8 (19.5%)	0	17 (41.5%)
Anorexia	12 (29.3%)	3 (7.3%)	1 (2.4%)	0	16 (39.0%)
Fatigue	4 (9.8%)	7 (17.1%)	5 (12.2%)	0	16 (39.0%)
Pain	6 (14.6%)	4 (9.8%)	1 (2.4%)	0	11 (26.8%)
Hypertension	5 (12.2%)	6 (14.6%)	3 (7.3%)	0	14 (34.1%)
Proteinuria	11 (26.8%)	4 (9.8%)	0	0	15 (36.6%)
Diarrhea	1 (2.4%)	2 (4.9%)	0	0	3 (7.3%)
Transaminase increased	1 (2.4%)	3 (7.3%)	1 (2.4%)	0	5 (12.2%)
Neutropenia	2 (4.9%)	2 (4.9%)	1 (2.4%)	0	5 (12.2%)
Thrombocytopenia	6 (14.6%)	3 (7.3%)	2 (4.9%)	0	11 (26.8%)

Figures

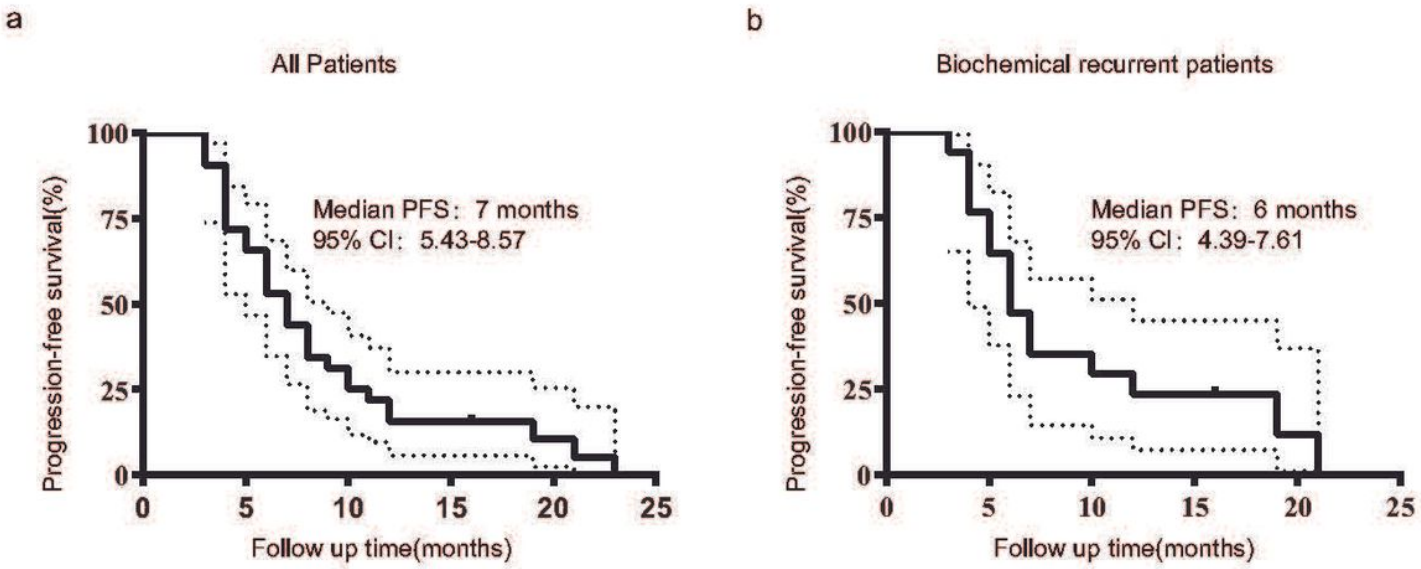

Figure 1

Kaplan-Meyer survival curve for estimated progression-free survival (PFS) in overall population (A) and in patients with biochemical relapse (B).