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A phase II study of apatinib in patients with recurrent epithelial ovarian cancer

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HIGHLIGHTS

- Apatinib is an oral, novel antiangiogenical VEGFR2 tyrosine kinase inhibitor.
- Platinum resistant, recurrent, pretreated EOC responded positively to apatinib.
- ORR is 41.4%, and DCR is 68.9% in this trial.
- mPFS is 5.1 months, and mOS is 14.5 months in this trial.
- The toxicity of apatinib is controllable and tolerable.

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ABSTRACT

Objective. Antiangiogenic treatments have been implicated to play a major role in epithelial ovarian cancer (EOC). Apatinib, a novel oral antiangiogenic agent targeting vascular endothelial growth factor receptor (VEGFR2), is currently being studied in different tumor types and is already used in gastric adenocarcinoma. This study was performed to assess the efficacy and safety of apatinib in patients with recurrent, pretreated EOC.

Patients and methods

Patients with recurrent, platinum-resistant, pre-treated EOC who failed available standard chemotherapy were enrolled. Apatinib was administered as 500 mg daily. Primary objective is the overall response rate (ORR) according to MASS criteria. Secondary objectives are progression free survival (PFS), overall survival (OS), disease control rate (DCR), safety and tolerability. The treatment duration is until disease progression or intolerability of apatinib.

Results

29 eligible patients were enrolled in this multicenter, open-label, single arm study and received apatinib for a median of 36.8 weeks (range 13–64.8 weeks). Median follow-up time was 12 months. 28 patients were eligible for efficacy analysis. ORR is 41.4% (95% confidence interval (CI), 23.3%–59.4%). DCR is 68.9% (95% CI, 52.1%–85.8%). Median PFS is 5.1 months (95% CI, 3.8 m–6.5 m). Median OS is 14.5 months (95% CI, 12.4 m–16.4 m). The most common treatment-related adverse events (AEs) were hand-foot syndrome (51.7%), hypertension (34.6%),

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nausea and vomiting (31.0%). 3 patients had no significant toxicity. 9 patients experienced grade 3 treatment-related AEs.

Conclusions

Apatinib 500 mg daily p.o. is a feasible treatment in patients with recurrent, platinum-resistant, pretreated EOC. Multi-center prospective studies enrolling more patients are needed.

1. Background

Ovarian carcinoma is the most deadly gynecologic malignancy in women worldwide [1]. The vast majority of ovarian carcinomas are epithelial ovarian cancer (EOC), occurring in about 70% of ovarian cancer cases. Ovarian cancer's early stages (I/II) are difficult to diagnose because most symptoms are nonspecific and thus of little use in diagnosis. As a result, it often goes undetected until it spreads within the pelvis and abdomen in later stages (III/IV) [2]. Despite improved surgical skills and a highly initial response to the chemotherapy of paclitaxel plus carboplatin, about 75% of patients with advanced ovarian carcinoma develop a tumor relapse within 2 years [2]. After recurrence, only approximately 30% of platinum-sensitive patients respond to second-line chemotherapy while those with platinum-resistant disease are only 10–25%. The overall survival rate at 5 years is 40–50% and 75% of patients die of recurrent disease [2]. Thus, identification and development of novel agents with limited toxicity that target the mechanisms of tumor growth and metastasis are needed.

Angiogenesis involves the formation of new blood vessels to feed tumors and plays an important role in the development and progression of cancer. VEGFR family mainly involves three kinds of trans-membrane proteins (VEGFR-1, VEGFR-2 and VEGFR-3) characterized by a tyrosine kinase activity [3]. Among these receptors, VEGFR-2 is the most important mediator of the VEGF-induced angiogenic signaling [4,5]. More and more evidences support the assumption of VEGF/VEGFR as target molecules for the treatment of the ovarian cancer.

Bevacizumab is a recombinant humanized monoclonal IgG1 antibody that targets vascular endothelial growth factor-A (VEGF-A), and is approved in the treatment of ovarian cancer, both as a single-agent drug and in combination with cytotoxic chemotherapy. It has been published that the addition of bevacizumab to standard chemotherapy is used as a front-line treatment of advanced ovarian cancer [6]. In addition, combination of bevacizumab with chemotherapy improves response rate in recurrent ovarian cancer (platinum-sensitive and platinum-resistant disease), but still not ideal [6,7].

Apatinib is an oral, novel angiogenesis inhibitor targeting the intracellular ATP binding site of VEGFR2 with a binding affinity 10 times that of vatalanib or sorafenib, and prevents phosphorylation and subsequent downstream signaling. By inhibiting VEGFR2, apatinib may decrease tumor micro-vessel density and slow or stop the tumor growth and development [8]. Apatinib has been licensed by the Food and Drug Administration of the Peoples Republic of China (CFDA) for advanced gastric adenocarcinoma and adenocarcinoma of the gastro-esophageal junction and is on the market in China [9,10]. The randomized, double-Blind, placebo-controlled phase III trial of Apatinib in patients with chemotherapy-refractory advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction was published in Journal of Clinical Oncology in 2016 [10]. These data show that apatinib significantly improved OS and PFS with an acceptable safety profile in patients with advanced gastric cancer refractory to two or more lines of prior chemotherapy. It seems that apatinib can circumvents cancer cell resistance to other antineoplastic agents, which has been also approved in several Phase II/III studies, including in soft tissue sarcoma, breast, lung cancer and liver cancer [10,11].

The aim of this trail is to assess the efficacy and safety of apatinib as a single agent in patients with recurrent platinum-resistant EOC who failed available standard chemotherapy since the available treatments including chemotherapy and target therapy for recurrent platinum resistant EOC are limited, and the efficacy is poor (response rate is <30%).

2. Materials and methods

2.1. Patients

Patients with recurrent, platinum-resistant, pre-treated EOC who failed available standard chemotherapy were enrolled in this multicenter phase ΠI trial. This study was approved by the ethics committee of Hunan Caner Hospital. Every patient signed a consent form prior to enrolment and must be willing to comply with treatment and follow up assessments and procedures. In detail, patients included in the study must meet all the following criteria: 1) 18 years < the age of female subjects < 70 years. 2) Histologically or cytologically confirmed diagnosis of epithelial ovarian cancer, cancer of the fallopian tube, or peritoneal cancer. 3) Definition of relapse: demonstration of measurable tumor according to MASS criteria [12] by an imaging procedure ± CA-125 > twice of the upper laboratory normal value. 4) Patients must have failed at least 2 available standard chemotherapy regimens ± secondary cytoreductive surgery when relapse. 5) Adequate hematologic, coagulation, hepatic, renal, and cardiac function, with an Eastern Cooperative Oncology Group (ECOG) performance status 0–2.6) Adequate contraception. 7) Able to swallow and retain oral medication. 8) A life expectancy of at least 12 weeks. Patients will be excluded from the study for any of the following reasons: 1) Diagnosis of any second malignancy within the last 5 years except basal cell or squamous cell skin cancer or in situ carcinoma of the cervix uteri. 2) History or clinical evidence of central nervous system (CNS) metastases or leptomeningeal carcinomatosis. 3) Clinically significant gastrointestinal abnormalities which might interfere with oral dosing. 4) History of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 28 days prior to beginning study treatment. 5) History of any one or more of the following cardiovascular conditions within the past 6 months: Cardiac angioplasty or stenting, myocardial infarction, unstable angina, symptomatic peripheral vascular disease, coronary artery by-pass graft surgery, class II, III or IV congestive heart failure as defined by the New York Heart Association (NYHA), history of cerebrovascular accident, pulmonary embolism or untreated deep venous thrombosis (DVT) within the past 6 months. 6) Macroscopic hematuria. 7) Evidence of active bleeding or bleeding diathesis. 8) Uncontrolled hypertension. 9) Urine protein ≥++ and confirmed > 1.0 g by the 24 h quantity. 10) Pregnancy or lactation period.

2.2. Drug administration

Apatinib was provided by Jiangsu Hengrui Medicine Co., Ltd. A starting dose of apatinib was administered 250 mg p.o. twice daily. Dose reduction was allowed to 250 mg daily if patients experienced grade 3 hematologic adverse events or grade 3 hypertension, hand and foot syndrome, proteinuria or other grade 3/4 adverse events which investigators considered dose reduction necessary. Patient discontinued oral administration of apatinib if they experienced disease progression, unacceptable toxicity after dose of reduction, or toxicity requiring cumulative dose interruption of > 14 days or twice in an initiating treatment cycle.

2.3. Study design and assessments

This is a multicenter, open-label, single-arm, phase II study performed at three centers in China. This trial has been designed by the study initiators at the Department of Gynecologic Oncology at the Hunan cancer Hospital and under cooperation with the Department of Gynecology and Obstetrics of First People's Hospital of Loudi, and the Department of Gynecology and Obstetrics of First People's Hospital of Huaihua. The final protocol was approved by the ethics committee of

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