Efficacy of apatinib on advanced ovarian cancer patients who failed first and second-line chemotherapy

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Abstract

**Purpose:** To investigate the efficacy and safety of apatinib in the treatment of advanced epithelial ovarian cancer (EOC) patients who failed first and second-line chemotherapy.

**Methods:** The clinical data of 100 patients diagnosed with advanced ovarian cancer were retrospectively analyzed. They were divided into two groups, with 50 patients in each group. One group was treated with apatinib mesylate (Apatinib group), while the other group was treated with gemcitabine (Gemcitabine group). Clinical efficacy, adverse reactions, and quality-of-life scores were assessed, while the survival status of patients was recorded during follow-up.

**Results:** After treatment, the objective response rate (ORR) and disease control rate (DCR) were 24.0 % (12/50) and 70.0 % (35/50) in Apatinib group, and 12.0 % (6/50) and 52.0 % (26/50) in Gemcitabine group. In terms of adverse reactions, the incidence of hand-foot syndrome and hypertension were significantly higher in Apatinib group than in Gemcitabine group, but the incidence of nausea and vomiting, anemia, neutropenia, and thrombocytopenia were significantly lower in Apatinib group than in Gemcitabine group (p < 0.05). Follow-up results revealed the median overall survival (OS) of patients to be 10.1 and 9.0 months, respectively, in Apatinib and Gemcitabine groups. Results of the log-rank test showed that OS in Apatinib group was significantly longer than that of Gemcitabine group.

**Conclusion:** Apatinib demonstrates clear effectiveness and a superior safety profile than Gemcitabine in the management of patients with advanced ovarian cancer who did not respond effectively to multiple rounds of chemotherapy.

**Keywords:** Apatinib, Gemcitabine, Ovarian cancer, Objective response rate, Disease control rate, Quality of life

INTRODUCTION

Ovarian cancer has high morbidity and mortality rates, with a 5-year survival of 30 % only, seriously threatening female health [1]. Ovarian cancer is generally treated with a combination of surgery and chemotherapy, but it is generally difficult to completely resect the lesion through surgery due to the rapid spread of cancer cells [2]. About 25 % of patients are insensitive to...
platinum-based first-line therapies, and cancer cells are prone to drug resistance. However, the overall response rate is low after multi-line chemotherapy [3,4]. The second-line therapy of ovarian cancer has lower effectiveness and a relatively shorter maintenance time. At present, there is a lack of standardized third-line therapeutic regimen.

According to reports, gemcitabine is unaffected by platinum resistance and is also less susceptible to typical multidrug resistance. Therefore, it can be used to treat various solid tumors after multiple lines of resistance [5]. Apatinib is a small molecule tyrosine kinase inhibitor that primarily acts on the vascular endothelial growth factor receptor-2 (VEGFR-2), and can exert an anti-tumor effect by inhibiting tumor angiogenesis [6]. It has been found in basic experiments and clinical studies that apatinib can inhibit the growth of cervical cancer cells and exert certain efficacy on recurrent ovarian cancer [7,8]. In this study, the efficacy and safety of apatinib and gemcitabine alone in the treatment of advanced ovarian cancer patients who have failed first and second-line chemotherapy were investigated.

METHODS

General patient data

The clinical data of 100 patients histopathologically diagnosed with advanced ovarian cancer were retrospectively analyzed.

Inclusion criteria

Patients histopathologically diagnosed with primary epithelial ovarian cancer (EOC) in clinical stage III-IV, those with at least one measurable lesion ≥ 10 mm shown in abdominal CT or MRI, those with progressive disease after second-line routine treatment, those with a Karnofsky performance scale (KPS) score ≥ 70 points, and those with an expected survival time > 3 months were all included in the study.

Exclusion criteria

Patients excluded were those administered with small molecule inhibitors of VEGFR in the past 6 months or underwent chemotherapy, radiotherapy, surgery, or molecularly targeted therapy 4 weeks before administration, and patients with factors affecting their oral drug absorption (such as inability to swallow, chronic diarrhea and intestinal obstruction), and patients with severe heart, lung, liver or kidney disease, or bone marrow hematopoietic dysfunction; or those complicated with other malignancies.

The baseline data of all the patients, such as age, gender, tumor stage, pathological type, and KPS score, are shown in Table 1. This study adhered to the guidelines of Declaration of Helsinki [9], and all patients enrolled were informed and signed the consent document. This study was approved by the Ethics Committee of The 1st Affiliated Hospital of Jinan University (approval no. 2022ER116-2).

Treatments

In Apatinib group, two tablets of apatinib mesylate (Jiangsu Hengrui Pharmaceutical Co., Ltd., NMPN H20140103, specification: 0.259 × 10 tablets) were orally administered half an hour after a meal once a day.

In gemcitabine group, gemcitabine hydrochloride for injection (Jiangsu Hansoh Pharmaceutical Group Co. Ltd, NMPN H20030104, specification: 1 g) was intravenously infused for 30 min on the 1st and 8th day based on body surface area (1 g/m²) at intervals of 21 days. The treatment lasted for 6 weeks.

Parameters evaluated

After treatment, the efficacy was assessed according to the Response Evaluation Criteria In Solid Tumors (RECIST): progressive disease (PD), stable disease (SD), partial response (PR), and complete response (CR).

$$\text{ORR} = \frac{(\text{CR}+\text{PR})}{\text{TC}} \times 100 \quad \text{(1)}$$

$$\text{DCR} = \frac{(\text{CR}+\text{PR}+\text{SD})}{\text{TC}} \times 100 \quad \text{(2)}$$

where TC = total cases

During chemotherapy, the adverse reactions (grade I-IV) were observed, assessed, and recorded in accordance with National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) 4.0.

Quality-of-life (QoL)

At 4 weeks after treatment, the quality of life of ovarian cancer patients was assessed using the quality-of-life measurement scale. The scale consists of Functional Assessment of Cancer Therapy-General (FACT-G) (physical function, psychological function, social function, and adverse reactions) and ovarian cancer-specific modules. The higher the score, the better the quality of life [10].
Overall survival (OS)

The survival status of patients was recorded during follow-up. Overall survival (OS) refers to the time from the start of drug therapy to the patient’s death for any reason or to the last follow-up.

Statistical analysis

SPSS 22.0 (IBM, Armonk, NY, USA) was used for statistical analysis. Measurement data are expressed as mean ± standard deviation (SD), and compared between two groups by t-test. Enumeration data are expressed as a rate (%), and compared between two groups by χ² test. The survival curve was plotted using the Kaplan-Meier method, and whether there was a statistically significant difference in the survival rate between the two groups was detected by log-rank test. P < 0.05 was considered to be statistically significant.

RESULTS

Short-term efficacy

After treatment, there were 12 cases of PR, 23 cases of SD, and 15 cases of PD in Apatinib group, and the ORR and DCR were 24.0 % (12/50) and 70.0 % (35/50), respectively. There were 6 cases of PR, 20 cases of SD, and 24 cases of PD in Gemcitabine group, and the ORR and DCR were 12.0 % (6/50) and 52.0 % (26/50), respectively. There were no statistically significant differences observed between the two groups in terms of both ORR and DCR (p = 0.118, p = 0.065) (Table 1).

Incidence of adverse reactions

In the Apatinib group, mild common adverse reactions were observed, including hypertension, hand-foot syndrome, proteinuria, and fatigue, which could all be tolerated by patients. Myelosuppression was the common adverse reaction in Gemcitabine group. There was no statistically significant difference in the incident, % of fatigue, liver function damage, and proteinuria between the two groups (p > 0.05). The incidence, % of hand-foot syndrome and hypertension was significantly higher in Apatinib group than in Gemcitabine group, but the incident, % of nausea and vomiting, anemia, neutropenia, and thrombocytopenia were significantly lower in Apatinib group than that in Gemcitabine group, showing statistically significant differences (p < 0.05, Table 2).

Post-treatment quality of life

At 4 weeks after treatment, the quality of life of all patients was assessed using the quality of life measurement scale. It was found that the FACT-G and specific module scores of patients in Apatinib group were higher than those in Gemcitabine group, but the differences were not statistically significant (p > 0.05, Table 3).

Table 1: Baseline characteristics of the studied patients (n = 50)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Apatinib group</th>
<th>Gemcitabine group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>58.5±7.7</td>
<td>56.9±8.1</td>
<td>0.314</td>
</tr>
<tr>
<td>FIGO stage</td>
<td>0.504</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>38 (76.0 %)</td>
<td>34 (68.0 %)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>12 (24.0 %)</td>
<td>16 (32.0 %)</td>
<td></td>
</tr>
<tr>
<td>Pathological type</td>
<td></td>
<td></td>
<td>0.221</td>
</tr>
<tr>
<td>Serous</td>
<td>34 (68.0 %)</td>
<td>40 (80.0 %)</td>
<td></td>
</tr>
<tr>
<td>Mucinous</td>
<td>14 (28.0 %)</td>
<td>7 (14.0 %)</td>
<td></td>
</tr>
<tr>
<td>Endometrioid</td>
<td>2 (4.0 %)</td>
<td>3 (6.0 %)</td>
<td></td>
</tr>
<tr>
<td>KPS score (points)</td>
<td></td>
<td></td>
<td>0.313</td>
</tr>
<tr>
<td>80-90</td>
<td>24 (48.0 %)</td>
<td>19 (38.0 %)</td>
<td></td>
</tr>
<tr>
<td>70-80</td>
<td>26 (52.0 %)</td>
<td>31 (62.0 %)</td>
<td></td>
</tr>
<tr>
<td>Previous chemotherapy</td>
<td></td>
<td></td>
<td>0.305</td>
</tr>
<tr>
<td>Second-line chemotherapy</td>
<td>22 (44.0 %)</td>
<td>17 (34.0 %)</td>
<td></td>
</tr>
<tr>
<td>Third-line chemotherapy</td>
<td>28 (56.0 %)</td>
<td>33 (66.0 %)</td>
<td></td>
</tr>
<tr>
<td>Clinical efficacy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial response (n, %)</td>
<td>12 (24.0)</td>
<td>6 (12.0 %)</td>
<td></td>
</tr>
<tr>
<td>Stable disease (n, %)</td>
<td>23 (46.0)</td>
<td>20 (40.0 %)</td>
<td></td>
</tr>
<tr>
<td>Progressive disease (n, %)</td>
<td>15 (30.0)</td>
<td>24 (48.0 %)</td>
<td></td>
</tr>
<tr>
<td>Objective response rate (%)</td>
<td>24.0</td>
<td>12.0 %</td>
<td>0.118</td>
</tr>
<tr>
<td>Disease control rate (%)</td>
<td>70.0</td>
<td>52.0 %</td>
<td>0.065</td>
</tr>
</tbody>
</table>

Note: FIGO: Federation International of Gynecology and Obstetrics; KPS: Karnofsky Performance Status.
Table 2: Comparison of adverse reactions of patients in the two studied groups (n = 50)

<table>
<thead>
<tr>
<th>Item</th>
<th>Apatinib group</th>
<th>Gemcitabine group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade I-IV n, (%)</td>
<td>Grade III-IV n, (%)</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>8 (16.0)</td>
<td>6 (12.0)</td>
<td>0.564</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>3 (6.0)</td>
<td>16 (32.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Anemia</td>
<td>11 (22.0)</td>
<td>41 (82.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>7 (14.0)</td>
<td>38 (76.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>3 (6.0)</td>
<td>34 (68.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>42 (84.0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Proteinuria</td>
<td>6 (12.0)</td>
<td>2 (4.0)</td>
<td>0.140</td>
</tr>
<tr>
<td>Liver function damage</td>
<td>4 (8.0)</td>
<td>12 (24.0)</td>
<td>0.123</td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td>22 (44.0)</td>
<td>10 (20.0)</td>
<td>0.010</td>
</tr>
</tbody>
</table>

Table 3: Comparison of post-treatment quality of life scores of patients in the two studied groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Score</th>
<th>Apatinib group</th>
<th>Gemcitabine group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FACT-G Physical function</td>
<td>18.34 ± 3.41</td>
<td>17.80 ± 3.19</td>
<td>0.416</td>
<td></td>
</tr>
<tr>
<td>Psychological function</td>
<td>46.21 ± 6.52</td>
<td>45.61 ± 5.69</td>
<td>0.525</td>
<td></td>
</tr>
<tr>
<td>Social function</td>
<td>19.71 ± 2.65</td>
<td>19.14 ± 3.90</td>
<td>0.395</td>
<td></td>
</tr>
<tr>
<td>Adverse reaction</td>
<td>22.32 ± 3.05</td>
<td>21.67 ± 2.85</td>
<td>0.274</td>
<td></td>
</tr>
<tr>
<td>Specific module</td>
<td>32.46 ± 3.66</td>
<td>30.93 ± 4.28</td>
<td>0.058</td>
<td></td>
</tr>
</tbody>
</table>

Follow-up results

The patients were monitored for a period of 3 to 16 months, with a median duration of 9.6 months. At the most recent follow-up, the median overall survival (OS) for patients in the Apatinib group was 10.1 months, while in the Gemcitabine group, it was 9.0 months. Besides, the survival curve was plotted using the Kaplan-Meier method (Figure 1). The results of log-rank test showed that the OS in Apatinib group was significantly longer than that in Gemcitabine group, displaying a statistically significant difference (p = 0.039).

Figure 1: Kaplan-Meier survival curves of patients in Apatinib group and Gemcitabine group. The overall survival rate of patients in Apatinib group was significantly higher than that of Gemcitabine group (p = 0.039).

DISCUSSION

Currently, first- and second-line chemotherapy remains the preferred therapeutic regimen for patients with advanced ovarian cancer. However, most patients are easily resistant to drugs during chemotherapy, and their survival rate may be as low as 30%. Multi-drug resistance has become the main cause of chemotherapy failure in patients with ovarian cancer [11,12]. Recently, clinical targets related to ovarian cancer have been sought in a large number of studies, in an effort to raise the long-term survival rate of patients with ovarian cancer through targeted therapy. VEGFs, a class of important angiogenesis factors, serve as an important player in the growth of solid tumors. VEGFs can be inhibited to regulate angiogenesis, thereby suppressing tumor growth, and this has become an effective anti-tumor treatment. In recent years, there has been well-established evidence that anti-VEGF treatment improves the clinical effectiveness of ovarian cancer, and extends the survival time of patients with advanced ovarian cancer [13].

Apatinib is a small molecule targeted drug that resists tumor angiogenesis by primarily causing activation failure of tyrosine kinase. It achieves this by binding to the ATP of VEGFR-2 tyrosine kinase, which decreases VEGFs dependent on the VEGFR-2 pathway, ultimately inhibiting tumor angiogenesis [14]. Several recent studies have demonstrated the significant efficacy of apatinib in various advanced tumors [15]. In phase II prospective study on the combination of apatinib
and VP16 in the treatment of platinum-resistant recurrent ovarian cancer in 2018, the ORR and progression-free survival (PFS) were 54.3 % and about 8.1 months in the combination group, respectively, but about 78 % of patients enrolled were in the early and middle stages, with only 8 patients in stage IV [6]. In terms of monotherapy, a Chinese study at the 2017 ESMO Conference showed that the median PFS in the treatment of cervical cancer and ovarian cancer with apatinib alone reached 8 months and 5 months, the ORR was 46.2 and 53.3 %, and the DCR was 100 and 73.3 %, respectively. According to another phase II study, the ORR, DCR, median PFS, and median OS were 41.4 %, 68.9 %, 5.1 months, and 14.5 months, respectively, in the treatment of recurrent ovarian cancer with apatinib alone [8]. As can be seen from previous data, both apatinib alone and its combination with other drugs may benefit patients with advanced ovarian cancer.

Gemcitabine, a cell cycle-specific drug, affects cell DNA synthesis and induces cell arrest in the G1/S phase mainly through inhibiting nucleotide metabolism, thereby exerting an anti-tumor effect. The total response rate of gemcitabine alone is about 14 - 22 % in the treatment of recurrent ovarian cancer, especially platinum-resistant or progressive ovarian cancer during paclitaxel therapy [5]. In phase III clinical trial, the efficacy of gemcitabine and liposomal doxorubicin was compared among 195 ovarian cancer patients who used to receive taxanes and had resistance to platinum. The results showed that the ORR, PFS, and OS are 6.1 %, 3.6 months, and 12.7 months, respectively, in gemcitabine group, and it was concluded that gemcitabine can be used as an alternative to liposomal doxorubicin in the treatment of patients with platinum-resistant ovarian cancer [16]. The above findings indicate that gemcitabine may be applied in the treatment of advanced ovarian cancer.

In this present study, the efficacy and safety of apatinib and gemcitabine alone were compared in the treatment of ovarian cancer patients who failed first and second-line chemotherapy. From the findings, Apatinib group exhibited an ORR of 26.1 %. This value is lower than the ORR (41.4 %) observed in a multi-center, open-label, and single-arm phase II clinical trial conducted by Miao et al [8] in patients with recurrent ovarian cancer. However, it is higher than the ORR (20.4 %) observed after chemotherapy for EOC patients in the study conducted by Ferrandina et al [17]. The follow-up results revealed that the median OS was 9.0 months in Gemcitabine group, similar to that reported by Mutch et al [16]. The median OS was 10.1 months in Apatinib group, and it had a statistically significant difference compared with that in Gemcitabine group, indicating that apatinib improved the survival status of patients to a certain extent, when compared with gemcitabine. However, the OS in this study was shorter than that (14.5 months) in the study by Miao et al [8], and the reason is related to the different clinical stages and basic conditions of the patients.

In the Apatinib group, hypertension, hand-foot syndrome, and proteinuria were the most common adverse reactions, similar to a previous report on apatinib in the treatment of metastatic gastric cancer and breast cancer [18].

Limitations of this study
There were many deficiencies in this study, such as a small sample size, a short follow-up period, insufficient content of follow-up, and a non-consideration of the influence of previous treatment on the research results.

CONCLUSION
Apatinib has definite efficacy and higher safety in the treatment of advanced ovarian cancer patients who failed multi-line chemotherapy, and results in a significantly prolonged OS compared with that of gemcitabine-treated patients. Large-sample multi-center randomized controlled trials are, however, required to validate the findings of this study.

DECLARATIONS
Acknowledgements
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Funding
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Ethical approval
This study was approved by the Ethics Committee of The 1st Affiliated Hospital of Jinan University, China (approval no. 2022ER116-2).

Availability of data and materials
The datasets used and/or analyzed during the current study are available from the correspond-
d staining author on reasonable request.

**Conflict of Interest**

No conflict of interest associated with this work.

**Contribution of Authors**

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them. Aiping Wen and Lei Zhao contributed equally to this work.

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