Clinical Case Report

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Use of apatinib combined with pemetrexed for advanced ovarian cancer

A case report

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Abstract

Introduction: Ovarian cancer is the most deadly gynecologic cancer, and the therapy is very difficult. Apatinib is a novel tyrosine kinase inhibitor targeting vascular endothelial growth factor receptor-2. At present, there are few studies or case reports on apatinib treatment for patients with ovarian cancer.

Case presentation: A 75-year-old Chinese woman had a medical history of ovarian high-grade serous papillary adenocarcinoma, who got many lines of chemotherapy and apatinib—an antiangiogenesis drug therapy. Either alone or in combination, apatinib may extend the survival time of patients with advanced ovarian cancer.

Conclusion: Apatinib may be an option for advanced ovarian cancer after failure of chemotherapy or other targeted therapy. The role of apatinib in the treatment of advanced ovarian cancer needs further study.

Abbreviations: AUC = area under the curve, CA125 = cancer antigen 125, CT = computed tomography, CTCAE = common terminology criteria for adverse events, DNA = deoxyribonucleic acid, HCC = hepatocellular carcinoma, NCCN = National Comprehensive Cancer Network, NSCLC = nonsmall-cell lung cancer, OC = ovarian cancer, PD = progressive disease, PFS = progression-free survival, PR = partial remission, SD = stable disease, TKI = tyrosine kinase inhibitor, TNBC = triple-negative breast cancer, TTP = time to progression, VEGF = vascular endothelial growth factor.

Keywords: advanced ovarian cancer, apatinib, pemetrexed

1. Introduction

Ovarian cancer (OC) is the most deadly gynecologic cancer. The disease is difficult to detect in the early stages, and patients are diagnosed with disease progression later. Treating the disease using conventional surgery and chemotherapy is quite difficult. Even if the disease is temporarily relieved, it usually recurs after 2 or 3 years. Unfortunately, too many patients die from recurrent and drug-resistant disease. Thus, it is necessary to explore new diagnostic and therapeutic modalities so as to improve the poor prognosis of these patients. The goals of treatment of recurrent OC are to prolong survival, delay time to progression (TTP), and control disease-related symptoms. The first-line treatment for most patients with recurrent OC consists of a debulking surgery and chemotherapy with platinum combined with paclitaxel or docetaxel.[1,2] Many patients relapse despite significant initial response to platinum-based chemotherapies. However, no standard chemotherapy regimen (beyond the second-line) has been established. Fortunately, a number of targeted therapies are being developed currently for these patients who have shown promising results in recent clinical trials. These treatments often target the vascular endothelial growth factor (VEGF) pathway (e.g., bevacizumab and aflibercept), DNA repair mechanisms (e.g., iniparib and olaparib), or they are directed against folate-related pathways (e.g., pemetrexed, farletuzumab, and vintafolide). Predictive biomarkers for response need to be identified because many targeted therapies are only effective in a subset of patients.

Apatinib (Hengrui Pharmaceutical Co., Ltd., Shanghai, People's Republic of China) is a small-molecule TKI targeting VEGF receptor-2, which has been proved to be effective and safe in treating chemotherapy-refractory advanced gastric cancer.[3] Recently, apatinib is more commonly used in clinical practice for metastatic breast cancer, esophageal cancer, nonsmall-cell lung cancer, and hepatocellular carcinoma.

Pemetrexed is a multitargeted antifolate agent that inhibits several enzymes required for DNA synthesis, including thymidylate synthase, dihydrofolate reductase, and glycinamide ribonucleotide formyl transferase.[4] Its multiple targets may help to achieve a broader spectrum of antitumor efficacy compared with other antimetabolites. Single-agent pemetrexed treatment in 51 women with recurrent OC demonstrated a response rate of 19%, including 2% complete response, and disease stabilization in 35% of patients.[5] This study aimed to present the case of a female patient with recurrent OC treated with apatinib combined with pemetrexed in Changzhou No. 2 People's Hospital, China.

Editor: N/A.

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The authors have no conflicts of interest to disclose.

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Medicine (2018) 97:27(e11036)

Received: 24 March 2018 / Accepted: 17 May 2018

http://dx.doi.org/10.1097/MD.0000000000011036

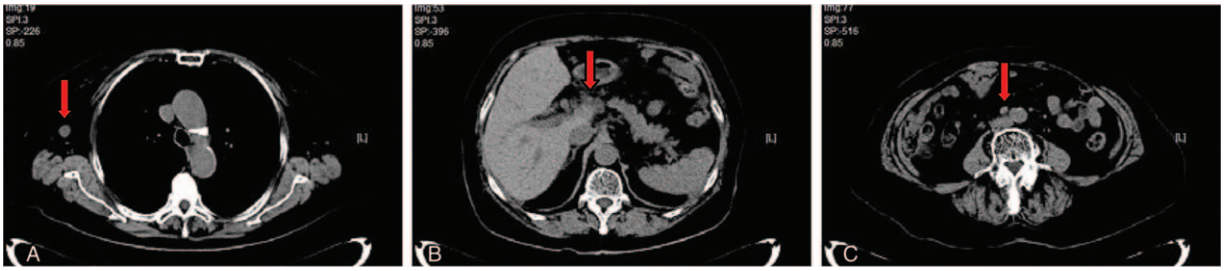

Figure 1. CT shows the lymph node metastasis before therapy (September 22, 2016). (A) Axillary lymph nodes, (B) the left hepatic lobe nodes, (C) abdominal lymph nodes. CT = computed tomography.

2. Case presentation

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

A 75-year-old Chinese woman had a medical history of ovarian high-grade serous papillary adenocarcinoma. On March 10, 2014, she felt abdominal distension and was brought to Changzhou No. 2 People's Hospital. The computed tomography (CT) scan showed a large number of ascites. Her serum cancer antigen (CA) 125 levels was more than 60,000 U/mL, and serum HE4 levels were more than 1000. She underwent surgery including total hysterectomy, bilateral adnexectomy, appendectomy, omentum majus resection, and transverse colon resection, on March 25, 2014. The surgery was successful according to the intraoperative findings (i.e., the size of intraperitoneal residual tumors was less than 1 cm in diameter), although lymph nodes were not dissected. Intraoperatively, there were miliary lesions in the peritoneum, the leaves of the diaphragm, the liver, and the surface of the intestine. Histopathologically, the tumor was a high-grade serous papillary adenocarcinoma (Stage IIIc, pT3cNxM0). Postoperatively, the patient was treated with intraperitoneal chemotherapy using one cycle of "DDP 60 mg + 5-FU 0.75 g + VP-16 0.1 g." Then, the patient was submitted to eight cycles of paclitaxel (135 mg/m^2 d1 q21d) and carboplatin [area under the curve (AUC) 5 d2 q21d] intravenous chemotherapy, from May 5, 2014, to January 13, 2015.The follow-up revealed no recurrent disease for the next 1 year and 2 months until July 2015.

The patient experienced the first relapse on July 28, 2015, which was diagnosed by examining elevated serum CA125 levels, the pelvic abdominal cavity, and posterior peritoneal lymph nodes enlarged on CT scan. Her serum CA125 level increased to 61.68 U/mL, and the serum HE4 level was 186.90 pmol/L. She was treated with paclitaxel (175 mg/m^2 d1 q21d) and carboplatin (AUC 5 d1 q21d) as second-line chemotherapy for 6 cycles again from July 3, 2015, to January 22, 2016. During this time, the patient had a III degree bone marrow suppression (CTCAE 4.0) and pneumonia, resulting in irregular chemotherapy. Her serum CA125 level decreased to a normal level, and CT scan indicated a reduction in pelvic lymph nodes. In August 2016, the patient's serum CA125 level was 792.30 U/mL. The CT scan revealed metastasis in the left hepatic lobe, axillary lymph nodes, abdominal lymph nodes, and peritoneal region (figures not given). Following this, the patient was treated with "etoposide 100 mg/d1–d3 + cisplatin 30 mg/d1–d3 + ifosfamide 2 g/d1–d3" chemotherapy. After 1 cycle, the patient showed a IV degree of bone marrow suppression and high fever. Therefore, she gave up the chemotherapy.

The patient was afraid of side effects and refused chemotherapy again. On September 21, 2016, the patient's CT scan revealed metastasis in the left hepatic lobe, axillary lymph nodes, abdominal lymph nodes (Fig. 1)., and apatinib was administered at a dose of 500 mg/day orally for 1 month. The side effects of apatinib were hypertension and fatigue. However, its toxicity was controllable and tolerable. The size of the enlarged lymph nodes in the liver, axillary, and retroperitoneal regions was reduced after 3-month treatment (Fig. 2). The efficacy was evaluated as stable disease (SD). On January 5, 2017, the patient developed severe abdominal distension. The serum CA125 level rose to 1774 U/mL. CT scan indicated abdominal effusion, but no significant progress in the substantial organ. The therapeutic evaluation was a progressive disease (PD) (Fig. 3).

The patient continued to receive 4 cycles of pemetrexed (500 mg/m^2 d1 q21d) chemotherapy from January 12, 2017, to May

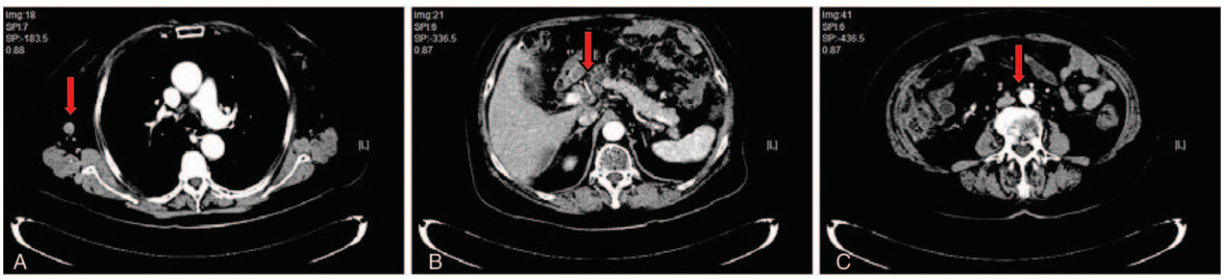

Figure 2. CT shows the lymph node metastasis after nearly 3months of apatinib treatment (December 12, 2016). (A) Axillary lymph nodes, (B) the left hepatic lobe nodes, (C) abdominal lymph nodes. CT = computed tomography.

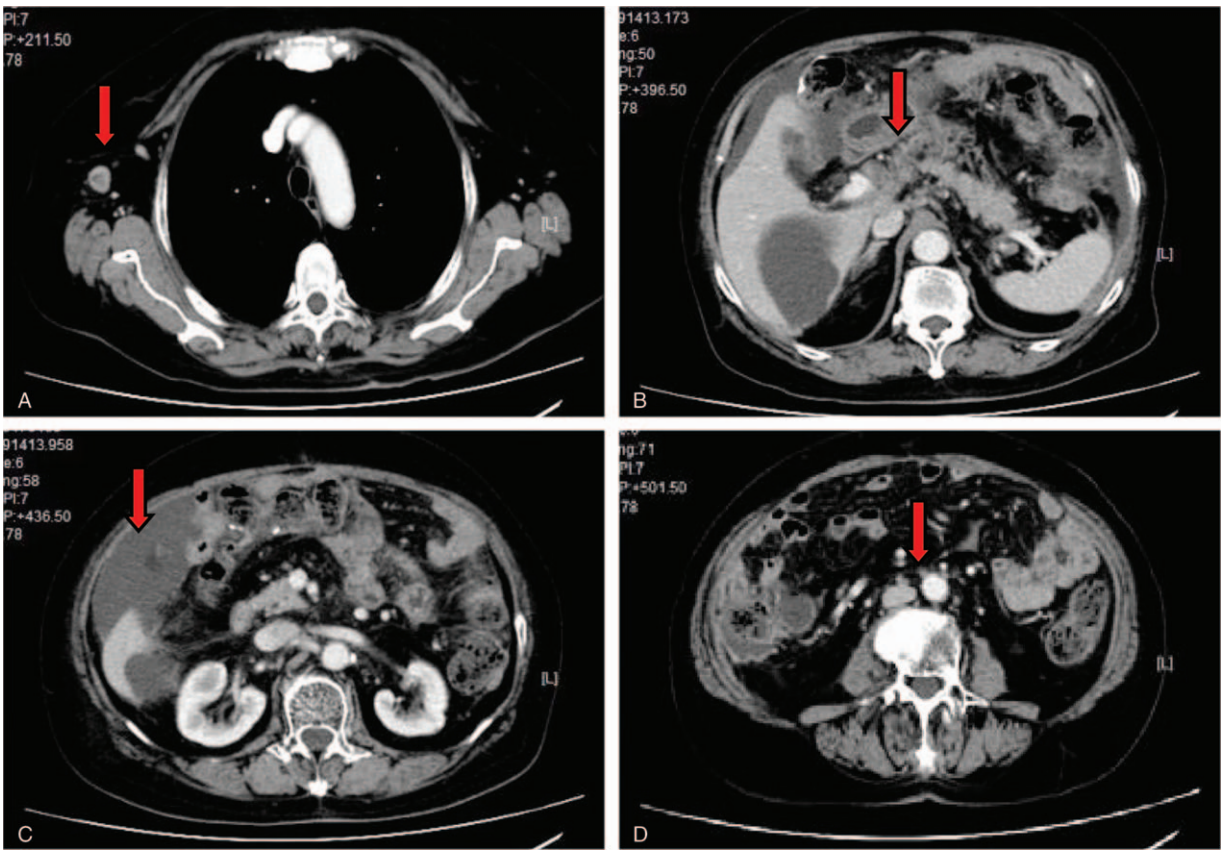

Figure 3. CT shows the lymph node and peritoneal region metastasis after 4 months of apatinib treatment (January 09, 2017). (A) Axillary lymph nodes, (B) the left hepatic lobe nodes, (C) peritoneal region, and (D) abdominal lymph nodes. CT = computed tomography.

11, 2017, combined with apatinib. During this period, her serum CA125 level continually reduced, and the abdominal distension disappeared. The serum CA125 level decreased to 119.10 U/mL, and CT scan indicated PR (Fig. 4). Throughout apatinib treatment, the serum CA125 level was low (Fig. 5). The patient was recommended to take pemetrexed combined with apatinib for maintenance treatment until May 2017 according to the single-agent therapies mentioned in the NCCN Guidelines for Ovarian Cancer (version 2, 2016),. The side effects of combined therapy were hypertension and fatigue, but controllable and tolerable. No more side effects were detected. Hence, the patient had good therapeutic compliance. Her progression-free survival (PFS) was 5 months.

3. Discussion

Patients with advanced epithelial OC or OC often receive first-line and second-line cytotoxic chemotherapy for metastatic disease. However, some patients are rarely cured. No other treatment options exist for these patients if they do not respond to second-line chemotherapy. The occurrence and development of most solid tumors are closely related to tumor angiogenesis. In the field of molecular targeted therapies, apatinib, as the tyrosine kinase inhibitor of VEGF receptor-2, could prevent the growth of tumors. Some clinical trials have proved the effect of apatinib on advanced gastric cancer.[3,6] Treatment with apatinib significantly improved both PFS and overall survival in patients with advanced-stage gastric cancer refractory to two or more lines of prior chemotherapy. The overall survival rate was 4.7 months in the placebo group and 6.5 months in the apatinib group (hazard ratio 0.709, $P = .0149$].[3] The toxicities included fatigue, hypertension, and hand-foot syndrome, which were well controlled. Based on these clinical trials, apatinib was recommended for treating advanced gastric adenocarcinoma and adenocarcinoma of the gastroesophageal junction by the Food and Drug Administration of the People's Republic of China. A phase II clinical trial[7] reported that apatinib was effective for patients with advanced hepatocellular carcinoma (HCC). Patients with advanced HCC were randomized into two groups: apatinib 750 mg and 850 mg daily until progression of the disease. TTP was 3.32 and 4.21 months in the two groups ($P > .05$), respectively. Adverse events were similar in both groups. A dose of 750 mg once daily was recommended for the next clinical study. Hu et al[8,9] conducted a phase II study on heavily pretreated patients with metastatic triple-negative breast cancer. The overall response rate and clinical benefit rate were 10.7% and 25.0%, respectively. The median PFS and overall survival were 3.3 and 10.6 months, respectively. The results indicated that 500 mg rather than 750 mg was the recommended starting dose of apatinib for the heavily pretreated patients with mTNBC having a measurable rate of partial response and PFS. Lin Ding et al explored the use of apatinib in treating nonsmall-cell lung cancer (NSCLC), suggesting satisfactory efficacy. Two patients with advanced nonsmall-cell lung cancer received apatinib after failure in the first-line or third-line chemotherapy. One patient's PFS increased to 4.6 months after palliative therapy

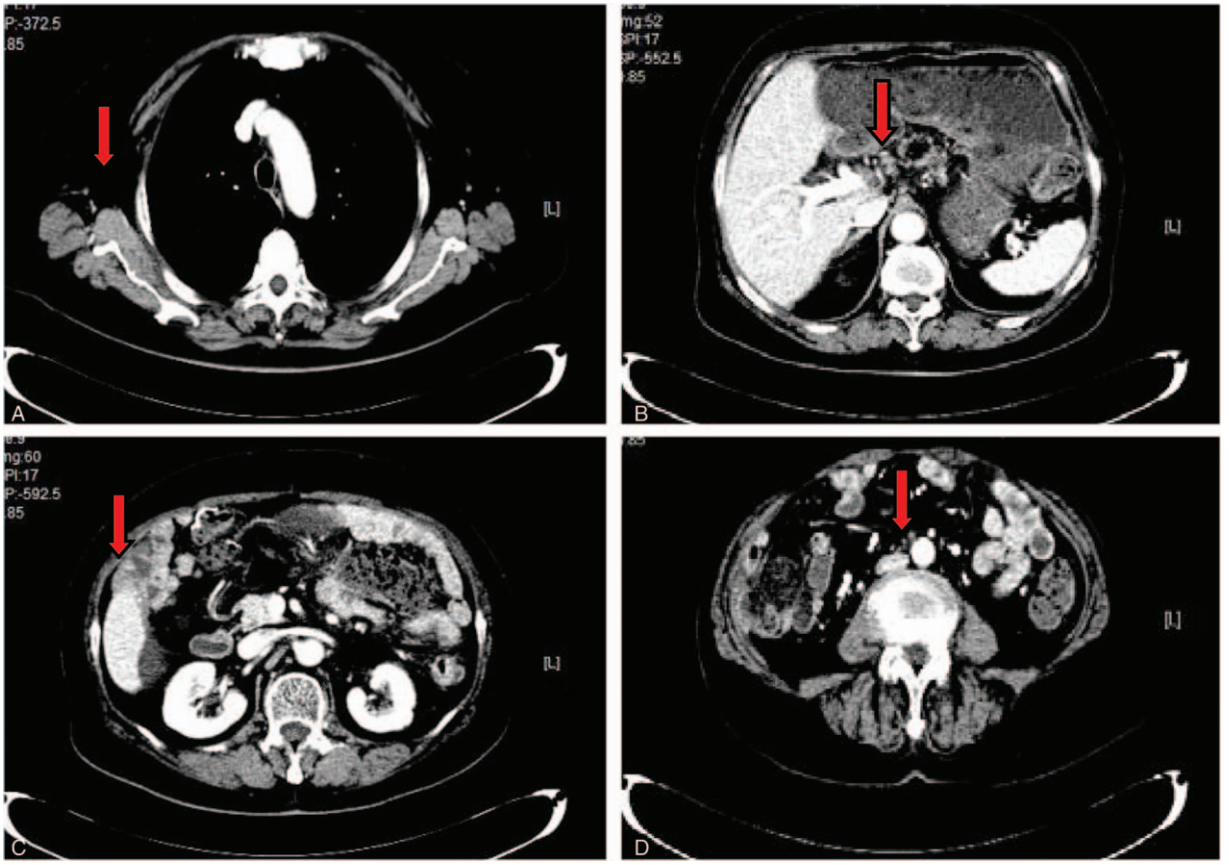

Figure 4. CT shows the lymph node and peritoneal region metastasis after nearly 4 months of apatinib combined with pemetrexed treatment (April 27, 2017). (A) Axillary lymph nodes, (B) the left hepatic lobe nodes, (C) peritoneal region, and (D) abdominal lymph nodes. CT = computed tomography.

of apatinib. It was nearly 6 months for the other patient.[10] Recently, apatinib also exhibited satisfactory efficacy in malignant fibrous histiocytoma[11] and extrahepatic bile duct carcinoma.[12] According to the treatment guideline, surgery and chemotherapy are the most prevalent management strategies for patients with advanced OC. However, targeted therapy has been a hot topic in the multidisciplinary therapy of advanced OC. Deng et al[13] performed a case study on a patient with advanced epithelial OC. The patient's PFS was 11.3 months. Zhang et al[14] also conducted a study on a patient treated with three cycles of apatinib combined with epirubicin. The patient had been undergoing apatinib treatment for 16 months without major toxic effects except mild HFS and occasional diarrhea.

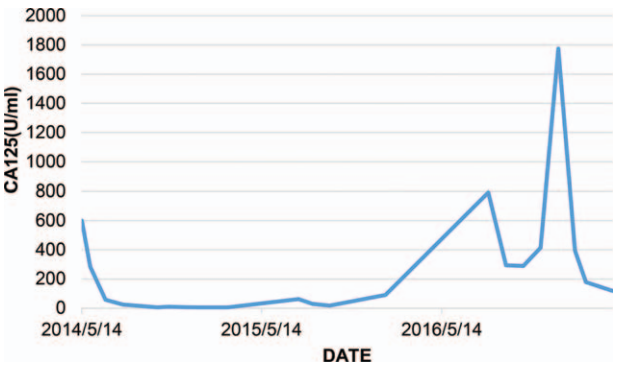

Figure 5. Serum CA125 level throughout the treatment.

Pemetrexed is a new-generation, multitargeted antifolate that exerts its action by inhibiting several DNA synthesis pathway enzymes essential for cell replication. In clinical studies, pemetrexed has demonstrated antitumor activity in a variety of solid tumor cell lines, including breast cancer,[15] NSCLC,[16] bladder cancer, head and neck cancer, and cervical cancer.[17] With the expression of the reduced folate carrier in ovarian cell lines, pemetrexed had been investigated in recurrent and refractory OC, alone or in association with cisplatin and carboplatin, given the additive effect or, perhaps, synergy with these antineoplastic agents.[5,18] Although apatinib showed notable efficacy in some solid tumors, no data are available about apatinib combined with pemetrexed in OC. Based on previous data regarding the use of apatinib in advanced OC, the patient in the present case study was administered multidisciplinary therapy, including apatinib combined with pemetrexed. In clinical experience, many patients with gastric cancer could not tolerate the toxicity of 850 mg apatinib alone daily. In this case, 500 mg apatinib daily combined with pemetrexed was prescribed. No obvious adverse reactions were noted in the follow-up cycles, and the therapy continued ceaselessly. The patient was evaluated as partial response, and the PFS was 4 months until May 2017. During multiline chemotherapy, the physical condition of the old patient was poor. The patient and her family were worried about adverse reactions. Irregular drug (time more than 21 d) treatment might affect the therapeutic effect.

This case study suggested that the combined therapy of apatinib and pemetrexed displayed satisfactory efficacy, implying that apatinib might cooperate superiorly with pemetrexed for advanced OC.

Author contributions

Conceptualization: Huiting Sun, Min Xiao, Ruxia Shi.
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Writing – original draft: Huiting Sun, Min Xiao.
Writing – review & editing: Sufen Liu, Ruxia Shi.

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