Case Report

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Successful treatment of advanced ovarian cancer with anlotinib: a case report

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Abstract

Ovarian cancer remains the most lethal gynecological malignant tumor, with relapse occurring in approximately 70% of advanced cases. Anlotinib is an oral small-molecule multi-targeted tyrosine kinase inhibitor that can resist neoangiogenesis and inhibit tumor growth. Previous research demonstrated clinical antitumor activity of anlotinib in various cancers. We report the case of an elderly woman with advanced ovarian cancer who received anlotinib after failure of multiple-line chemotherapy. A partial response was observed after six cycles of anlotinib monotherapy, with a reduction in the size of the metastases and significantly decreased serum CA125 levels from 1832.7 U/mL to 118.7 U/mL. She continued to take anlotinib, with a progression-free survival time of more than 4 months. Only mild hypertension was observed during the treatment. Anlotinib monotherapy may be a novel therapeutic option for patients with advanced ovarian cancer.

Keywords

Anlotinib, advanced ovarian cancer, monotherapy, targeted therapy, survival, metastasis

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Introduction

Ovarian cancer is a common gynecological malignant tumor with high mortality. The lack of effective screening strategies and distinctive early symptoms mean that approximately 75% of all ovarian cancer patients have advanced disease at the time of diagnosis.[1] Despite initial responses to surgery and

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chemotherapy, nearly 70% of patients eventually experience tumor recurrence due to acquired drug resistance, resulting in a poor prognosis and high mortality rate. The National Comprehensive Cancer Network (NCCN) guidelines for advanced ovarian cancer recommend platinum-based chemotherapy as the first-line regimen. Patients with recurrent ovarian cancer can be divided into platinum-sensitive and platinum-resistant relapse, based on the time from the last chemotherapy to relapse. Patients with platinum-resistant relapse have a poor prognosis and lack uniform treatment.

Targeted therapy for the treatment of ovarian cancer has recently made significant progress, and is expected to improve survival in patients with platinum-resistant disease. Anlotinib is a new multi-target small-molecule tyrosine kinase inhibitor, which acts effectively on targets such as vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), and fibroblast growth factor receptor (FGFR). It has double actions that resist neoangiogenesis and inhibit tumor growth.[2] It is an oral preparation with relatively few adverse reactions and good patient tolerance.[2] Anlotinib has currently been approved for the treatment of tissue sarcoma, and as third-line treatment for advanced non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). There are also ongoing clinical trials of anlotinib in several solid tumors, including thyroid cancer, colorectal cancer, and gastric cancer.

Data on the efficacy and toxicity of anlotinib monotherapy for ovarian cancer is currently lacking. Herein, we present a case of recurrent ovarian cancer successfully treated with anlotinib.

Case report

A 67-year-old woman was admitted to Dezhou People's Hospital on October 18, 2015 because of abdominal pain and distention. She had a history of type 2 diabetes mellitus for several years. A computed tomography (CT) scan of the pelvis demonstrated a left-adnexal mass, omental metastasis, and ascites. Her serum CA125 level was 845.3 U/mL. She was diagnosed with pathologically confirmed ovarian cancer based on ascites tumor cells. The tumor was FIGO stage III with omental metastasis and ascites. She initially received four cycles of first-line TP chemotherapy (paclitaxel 240 mg day 1 + cisplatin 40 mg days 3–5, every 21 days). A repeat CT scan after chemotherapy showed reduction of the lesions, evaluated as a partial response (PR) according to the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. Transabdominal surgical debulking consisting of total hysterectomy, bilateral adnexectomy, and omentectomy was performed on January 29, 2016. A diagnosis of high-grade serous ovarian cancer was made based on postoperative pathological examination. Adenocarcinoma was also found in the omentum. Immunohistochemical analysis showed that tumor cells were positive for CA125, WT-1, cytokeratin-7, P53, and Ki-67, and negative for calretinin and cytokeratin 20. BRCA1/2 genetic testing was not done. The postoperative pathological stage was pT3N0M0, III. Reexamination about 1 month after surgery showed no visible lesion on CT and her serum CA125 level had decreased to 13.3 U/mL, suggesting that the tumor had been completely removed by surgery. Two cycles of TP chemotherapy (paclitaxel 270 mg day 1 + cisplatin 40 mg days 3–5, every 21 days) were administered postoperatively. CT was not performed after completing the two cycles of adjuvant chemotherapy, but CA125 detection was performed regularly. Her serum CA125 levels remained within normal limits until February 10, 2017, when the level increased to

76.5 U/mL. However, a CT scan on February 23, 2017 showed no signs of tumor recurrence. Three more cycles of TP chemotherapy were carried out and the patient refused further treatment. After completing two cycles of the chemotherapy, her serum CA125 level had decreased to within the normal range, and no tumor recurrence was observed on a CT scan on April 26, 2017.

A follow-up CT performed approximately 7 months after the last chemotherapy (December 7, 2017) showed new liver metastasis, and she was re-staged as stage IV. In light of the platinum-sensitive relapse, she received one cycle of TC chemotherapy (paclitaxel 210 mg day 1 + carboplatin 400 mg day 2, every 21 days) and four cycles of DC chemotherapy (docetaxel 120 mg day 1 + carboplatin 400 mg day 2, every 21 days). A repeat CT scan after five cycles of chemotherapy indicated PR. She subsequently underwent CT-guided hepatic microwave ablation on April 11, 2018, and a CT scan on August 23, 2018 showed complete response of the ablated liver lesion.

CT examination about 7 months after the last chemotherapy (December 25, 2018) revealed multiple metastases, including in the paracardio-diaphragmatic angle, parahepatic ligamentum, parascending colon, and retroperitoneal nodules. The patient received two cycles of IN chemotherapy (irinotecan 160 mg day 1, 120 mg day 5 + nedaplatin 40 mg days 2–4, every 21 days). However, she abandoned treatment due to side effects. Her serum CA125 level decreased from 431.0 U/mL to 143.0 U/mL, but no CT examination was performed, and it was therefore impossible to evaluate the efficacy accurately.

The patient was readmitted to our hospital on November 21, 2019. Disease progression was determined by CT scans and serum tumor markers. Thoracoabdominal CT (Figure 1) demonstrated that the original metastatic lesions had increased in size compared with the previous evaluation and new metastatic lesions had appeared, with extensive metastases in the armpit, right breast, right diaphragm, liver, spleen, abdominal cavity, pelvic cavity, and groin (Figure 1, a1-f1). Her serum CA125 level had increased to 1832.7 U/mL and her Karnofsky performance status (KPS) score was approximately 60. Considering her poor physical condition and chemotherapy-related toxicities, anlotinib was administered as subsequent-line treatment from November 24, 2019.

Anlotinib was administered orally at 12 mg/day for 2 weeks, followed by 1 week off treatment. After one cycle of anlotinib treatment, her serum CA125 level decreased from 1832.7 U/mL to 496.2 U/mL. She remained on anlotinib targeted therapy for five cycles from December 11, 2019 to March 28, 2020. During this period, her serum CA125 level continued to decrease to 118.7 U/mL (Figure 2). A CT scan after six cycles of anlotinib treatment (March 28, 2020) showed that most of the metastases had reduced in size (Figure 1, a2-f2), with about a 39% decrease in tumor sizes according to RECIST 1.1. The patient's general condition also improved after anlotinib treatment, and her KPS score improved to around 80. The overall efficacy evaluation was PR. The patient continued to take anlotinib, with a progression-free survival (PFS) time of more than 4 months. The most recent CA125 value was 144.6 U/mL, detected on August 27, 2020, but no further CT examinations were performed. The main adverse event during anlotinib treatment was grade 1 hypertension, with no asthenia, hand-foot skin reaction, or gastrointestinal reaction.

The patient provided signed informed consent for treatment and for publication of this report.

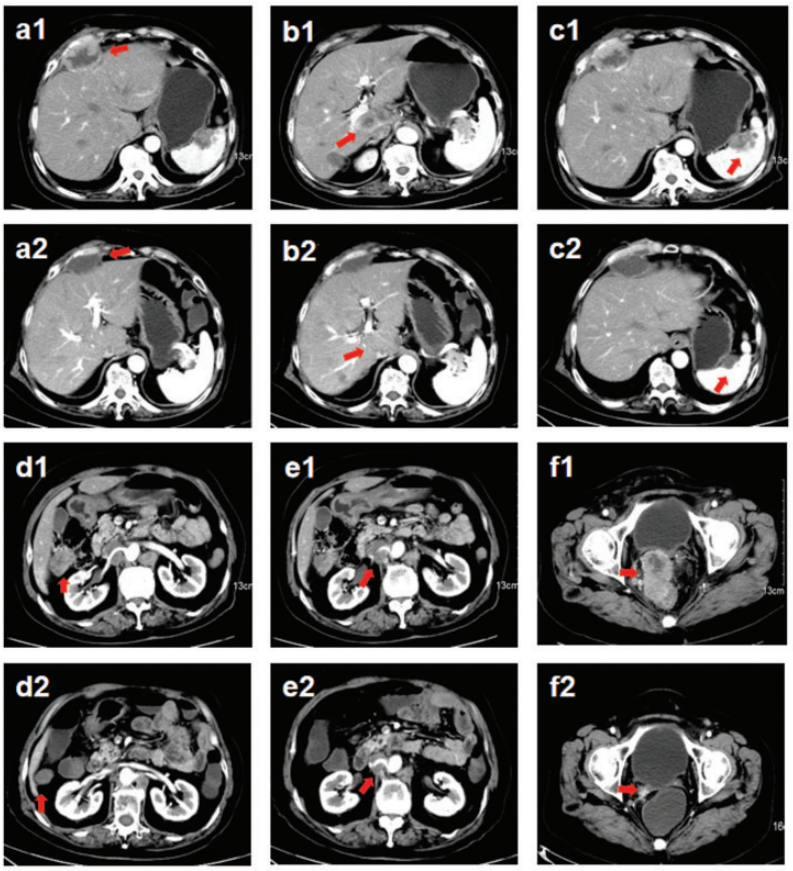

Figure 1. Computed tomography (CT) scans before and after anlotinib treatment. (a1-f1) Extensive metastases (arrows) were evident on CT scans before anlotinib treatment (November 21, 2019). (a2-f2) Metastatic lesions were reduced on CT scans after six cycles of anlotinib treatment (March 28, 2020).

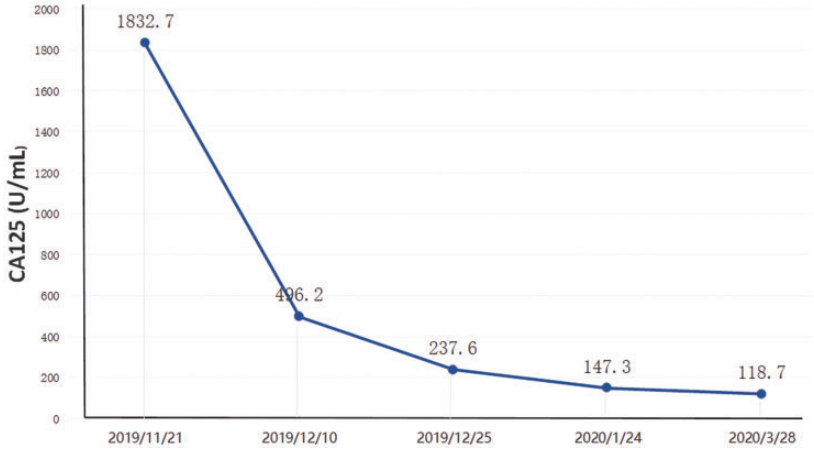

Figure 2. Serum CA125 levels during anlotinib therapy.

Discussion

Anlotinib might be a novel therapeutic option for patients with advanced ovarian cancer. Surgery and chemotherapy are currently the standard treatments for ovarian cancer.[3] However, although most patients achieve a favorable response to first-line chemotherapy, many soon relapse.[4] The NCCN guidelines recommend cytoreductive surgery combined with platinum-containing chemotherapy for patients with platinum-sensitive relapse. Most patients with relapsed ovarian cancer eventually develop platinum resistance and succumb to the disease, and the therapeutic options for platinum-resistant relapse remain limited and the response rates are low. Treatment regimens for platinum-resistant ovarian cancer thus aim to slow the progression of the disease and improve the patient's quality of life.

Recent progress has been made in terms of targeted therapy for ovarian cancer. Targeted agents mainly include angiogenesis inhibitors and poly-ADP ribose polymerase (PARP) inhibitors. Bevacizumab was the first targeted agent approved for treatment of ovarian cancer worldwide.[5] It functions as a monoclonal VEGF antibody, preventing the VEGF–VEGF receptor interaction, which in turn suppresses tumor angiogenesis. Other angiogenesis inhibitors, such as cediranib, pazopanib, nintedanib, and trebananib, were also confirmed to improve PFS in patients with recurrent ovarian cancer.[4] PARP inhibitors can block the DNA repair process in tumor cells by binding to PARP, causing tumor cell death. Although PARP inhibitors such as olaparib, niraparib, and rucaparib have been approved by the US Food and Drug Administration for the treatment of ovarian cancer,[6] further studies are needed to explore targeted agents for ovarian cancer.

Anlotinib is an oral tyrosine kinase inhibitor that targets VEGFR, FGFR, PDGFR, rearranged during transfection (RET), and c-Kit, exerting anti-angiogenic and anti-proliferative effects. A previous study showed that anlotinib had stronger anti-angiogenic activity than three other angiogenesis inhibitors, sorafenib, sunitinib, and nintedanib.[7] Anlotinib has also demonstrated effective antitumor efficacy both i*n vitro* and *in vivo*.[7] In the ALTER 0303 trial,[8] anlotinib significantly prolonged the median PFS and overall survival (OS) compared with placebo in patients with advanced NSCLC who had failed at least two previous lines of treatment. Based on the results of this study, anlotinib was approved for third- or further-line treatment in China by the China Food and Drug Administration.[7] The updated OS results for the ALTER 1202 study indicated that, in addition to the PFS benefit, median OS was significantly prolonged by about 2.4 months in the anlotinib group compared with the placebo group in patients with SCLC who had failed at least two lines of chemotherapy.[9] Other studies, including ALTER 1102, NCT02586350, ALTER 0802, and ALTER 0203, confirmed that anlotinib was also efficacious in patients with esophageal squamous cell carcinoma,[10] medullary thyroid carcinoma,[11] hepatocellular carcinoma,[12] and soft tissue sarcoma.[13] Overall, these results suggest that anlotinib is a promising treatment option for patients with various solid tumors.

Some studies have explored the efficacy and safety of anlotinib in ovarian cancer. An ongoing prospective phase II clinical study of anlotinib monotherapy in patients with recurrent or refractory ovarian cancer by Shan et al.[14] has reported on 14 evaluable patients, including two cases of partial response (14.3%), eight stable disease (57.1%), and four progressive disease (28.6%). All the AEs were mild (grade 1 or 2), including hypertension (57.1%), fatigue (50.0%), hand–foot syndrome

(35.7%), hoarseness (14.3%), diarrhea (7.1%), gum pain (7.1%), decreased leukocyte count (6.7%), urine protein (7.1%), and cancer pain (7.1%), but no serious AEs were reported.[14] Sun et al.[15] reported a case of platinum-resistant ovarian cancer treated with anlotinib and etoposide. The patient remained progression-free for at least 18 weeks, and grade 2 hand–foot skin reaction was the only AE.[15] In addition, a phase II trial (NCT03924882) evaluating the efficacy and toxicity of anlotinib in patients with platinum-resistant or refractory ovarian cancer is currently ongoing.

Anlotinib exhibits efficacy in various cancers; however, predictive biomarkers for anlotinib remain unclear. Liu et al.[16] performed follow-up research to the ALTER 0303 trial and concluded that a decline in CD31-positive activated circulating endothelial cells (aCECs) after anlotinib treatment indicated a longer PFS in patients with NSCLC, suggesting that CD31-labeled aCECs may be a sensitive marker for predicting the efficacy of anlotinib. Furthermore, Lu et al.[17] found that an anlotinib-induced decrease in serum C–C motif chemokine ligand 2 was related to PFS and OS benefits in NSCLC patients. It is necessary to find ideal biomarkers for predicting efficacy in order to screen the patient population.

In the current case, the patient received multiple cycles of chemotherapy, which were terminated because of poor tolerance to the side effects (primarily gastrointestinal reactions and myelosuppression). Because of the patient's poor physical condition and older age, anlotinib monotherapy was selected, with a relatively good response and no AEs apart from mild hypertension. Unfortunately, the patient's BRCA/homologous recombination deficiency status and other molecular characteristics were not determined, and their role in the favorable treatment response and in guiding treatment selection remain unknown.

In conclusion, anlotinib could represent a good treatment option in patients with advanced ovarian cancer who have poor physical condition and poor chemotherapy tolerance. Further studies are needed to confirm to role of anlotinib in the treatment of ovarian cancer.

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Declaration of conflicting interest

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References

1. Zhang J, Song X, Li C, et al. Expression and clinical significance of SLP-2 in ovarian tumors. *Oncol Lett* 2019; 17: 4626–4632.
2. Sun Y, Niu W, Du F, et al. Safety, pharmacokinetics, and antitumor properties of anlotinib, an oral multi-target tyrosine kinase inhibitor, in patients with advanced refractory solid tumors. *J Hematol Oncol* 2016; 9: 105.
3. Zou H and Li H. Knockdown of long noncoding RNA LINC00152 increases cisplatin sensitivity in ovarian cancer cells. *Exp Ther Med* 2019; 18: 4510–4516.
4. Cortez AJ, Tudrej P, Kujawa KA, et al. Advances in ovarian cancer therapy. *Cancer Chemother Pharmacol* 2018; 81: 17–38.
5. Monk BJ, Sill MW, Walker JL, et al. Randomized phase II evaluation of

bevacizumab versus bevacizumab plus fosbretabulin in recurrent ovarian, tubal, or peritoneal carcinoma: An NRG Oncology/Gynecologic Oncology Group study. *J Clin Oncol* 2016; 34: 2279–2286.
6. Liu Y, Song H, Song H, et al. Targeting autophagy potentiates the anti-tumor effect of PARP inhibitor in pediatric chronic myeloid leukemia. *AMB Express* 2019; 9: 108.
7. Shen G, Zheng F, Ren D, et al. Anlotinib: a novel multi-targeting tyrosine kinase inhibitor in clinical development. *J Hematol Oncol* 2018; 11: 120.
8. Zhou M, Chen X, Zhang H, et al. China National Medical Products Administration approval summary: anlotinib for the treatment of advanced non-small cell lung cancer after two lines of chemotherapy. *Cancer Commun (Lond)* 2019; 39: 36.
9. Cheng Y, Wang Q, Li K, et al. 1738O – Overall survival (OS) update in ALTER 1202: Anlotinib as third-line or further-line treatment in relapsed small-cell lung cancer (SCLC). *Ann Oncol* 2019; 30: v711.
10. Huang J, Xiao J, Fang W, et al. Anlotinib in chemotherapy-refractory metastatic esophageal squamous cell carcinoma (ESCC): A randomized, double-blind, multicenter phase II trial. *J Clin Oncol* 2019; 37: 95.
11. Li D, Tang PZ, Chen X, et al. Anlotinib treatment in locally advanced or metastatic medullary thyroid carcinoma: A multicenter, randomized, double-blind, placebo-controlled phase IIB trial. *J Clin Oncol* 2019; 37: 6019.
12. Zhou A, Sun Y, Zhang W, et al. 751P – Anlotinib for advanced hepatocellular carcinoma: Interim results from the phase II ALTER0802 study. *Ann Oncol* 2019; 30: v288–v289.
13. Chi Y, Yao Y, Fang Z, et al. 1693P – Efficacy and safety of anlotinib in advanced leiomyosarcoma: Subgroup analysis of a phase IIB trial (ALTER0203). *Ann Oncol* 2019; 30: v694.
14. Shan B, Shen W and Wang H. Anlotinib in patients with recurrent platinum-resistant or refractory ovarian carcinoma: A prospective, single-arm, single-center, phase II clinical study. *J Clin Oncol* 2020; 38: 6061.
15. Sun L, Yang M, Zhang X, et al. Anlotinib combined with etoposide for platinum-resistant recurrent ovarian cancer: A case report. *Medicine (Baltimore)* 2020; 99: e20053.
16. Liu Z, Wang J, Meng Z, et al. CD31-labeled circulating endothelial cells as predictor in anlotinib-treated non-small-cell lung cancer: Analysis on ALTER-0303 study. *Cancer Med* 2018; 7: 3011–3021.
17. Lu J, Zhong H, Chu T, et al. Role of anlotinib-induced CCL2 decrease in anti-angiogenesis and response prediction for nonsmall cell lung cancer therapy. *Eur Respir J* 2019; 53: 1801562.