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CASE REPORT

Endostar Plus Apatinib Successfully Achieved Long Term Progression-Free Survival in Refractory Ovarian Cancer: A Case Report and Literature Review

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Background: Ovarian cancer (OC) is a common malignancy in the gynecological tumor. Standard treatment for ovarian cancer is surgery and chemotherapy based on paclitaxel and platinum. However, traditional chemotherapy for ovarian cancer is limited by drug resistance and systemic side effects. It is imperative to explore effective treatment options for refractory ovarian cancer.

Case Presentation: A 52-year-old female initially presented with lower abdominal distension and migratory pain. After the laparoscopic exploration and biopsy, immunohistochemistry showed poorly differentiated adenocarcinoma originated from ovarian (cT3NxM1, stage IV, peritoneal and abdominal wall metastasis). The next generation sequence detected ERRFI1 (T187A, exon4) mutation.

Results: The patient received first-line chemotherapy (paclitaxel, nedaplatin plus avastin), followed by maintenance therapy with gefitinib, achieving a 15-month progression-free survival (PFS). After disease progression and second-line treatment failure, endostar plus apatinib was administered for 14 cycles and she obtained a PFS of 14 months without long-term adverse events.

Conclusion: We believe that the ERRFI1 gene may be a potential target of gefitinib. Importantly, endostar combined with apatinib is worth recommending for maintenance treatment in refractory ovarian cancer.

Keywords: ovarian cancer, antiangiogenic therapy, endostar, apatinib, gefitinib

Background

Ovarian cancer is one of the most common malignant tumors in gynecology. In 2018 statistics indicate a burden of 225, 000 new cases and 140,200 deaths.[1] Due to the lack of early symptoms and effective screening strategies, approximately 70% of patients with ovarian cancer are usually diagnosed at a late stage, not to mention the even higher mortality.[2] According to previous studies, the 10-year progression-free survival (PFS) rate of patients with recurrent disease is only 15%, and the median overall survival (OS) is 12–24 months.[3] Standard treatment for ovarian cancer is surgery and chemotherapy based on paclitaxel and platinum. However, traditional chemotherapy for ovarian cancer is limited by drug resistance and systemic side-effects. Therefore, joint efforts are necessary to develop novel therapies for chemotherapy resistance and recurrent ovarian cancer, For patients with

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BRCA mutations, maintenance therapy with approved PARP inhibitors can significantly improve PFS.[4] Bevacizumab combined with platinum-based dual therapy, and PARP inhibitors combined with anti-angiogenesis drugs or immune checkpoint suppression are also under active research.[5] Based on the patient's genes and tumor molecular characteristics, targeted therapy allows for an individualized approach in the management of ovarian cancer. Both anti-angiogenic therapies alone and combined with chemotherapy have shown efficacy in ovarian cancer.[6–8] Here, we report an ovarian cancer patient who achieved partial response (PR) from antiangiogenic therapy with a PFS of 14 months after multiple-lines failure, and combine with a literature review to demonstrate the effectiveness of this novel combined regimen in ovarian cancer.

Case Presentation

A 52-year-old female was admitted to the hospital in January 29, 2018, initially presenting with lower abdominal distension and migratory pain. Her family history was unremarkable and she is a non-smoker with unknown allergic history. The Eastern Cooperative Oncology Group score was one point. The serum antigen-125 (CA-125) was 326.4 U/mL, and the abdominal enhanced CT (Figure 1A) showed an enlarged uterus, irregular soft tissue-like mass on the left posterior, and multiple nodules and masses in the peritoneum and omentum on both sides. Laparoscopic biopsy was performed and the histopathology confirmed poorly differentiated adenocarcinoma originating from the ovary (Figure 2). Immunohistochemical analysis of omentum tissue was positive for Pax2, PaX8, CK7, WT-1, ER, P53. According to pathology and immunohistochemistry, the clinical diagnosis was advanced ovarian cancer (FIGO stage IV, cT3NxM1). In April 2018, NGS detected ERRFI1 (T187A, exon4) mutation, but no "actionable" drugs have been approved by FDA (Table 1).

The patient received 6 cycles of paclitaxel, nidaplatin and avastin (intravenous paclitaxel 180 mg/m^2 d1; nidaplatin 50 mg/m^2 d1-d2; avastin 300mg/m^2 d1) every 21-day cycle starting in mid-March 2018. According to the literature, we found ERRFI1 is a regulatory factor in the EGFR pathway, and it has been reported that cases treated with gefitinib have a higher remission rate. Therefore, the patient began to receive oral targeted therapy of gefitinib 250mg qod combined with chemotherapy in May 2018. After 4 courses, a CT scan revealed a significant reduction of pelvic mass (Figure 1B) and achieved partial remission (SD) according to RECIST 1.1. Considering that the patient cannot continue to afford avastin, medical insurance cannot be reimbursed in our country. Since then, gefitinib monotherapy was given for ten months. CT scan was performed on May 27, 2019, and the treatment evaluation was PD. Currently, no data shows the survival benefit of secondary cell reduction. Considering the high risk of complications after cytoreductive surgery, the patient with peritoneal metastasis and splenic metastasis refused the second operation. Subsequently, the patient received a new chemotherapy regimen in September 2019 with docetaxel (90mg/m^2 d1) plus carboplatin (400mg/m^2 d1). However, the CT scan proved PD again and the therapy was unsuccessful (Figure 1C). Anti-VEGF therapy has been widely proven to be effective in the treatment of various malignant tumors in recent years. Since the patient has received multiple lines of chemotherapy, the patient could not tolerate the side-effects of chemotherapy and the inconvenience of chemotherapy administration. After full communication, the patient received a novel regimen with antiangiogenic drug endostar (30 mg, civ d1-4) plus apatinib (250 mg, po qod) from November 18, 2019. In consideration of the off-label use of endostar and apatinib, we communicated adequately with the patient before signing the off-label consent. Response evaluations after every two months during 10 cycles of treatment showed stable disease SD (Figure 1D). On December 2020, CT scan revealed that the mass on the right side was larger than before and accompanied by peritoneal metastasis, and simultaneously the CA-125 increased significantly. In view of the PFS of 13 months of this regimen, we advised the patient to continue endostar plus apatinib as maintenance therapy although the results showed a slight PD. However, her serum CA-125 level rose again one month and the therapeutic evaluation was PD. Generally speaking, PFS for apatinib combined with endostar therapy was 14 months. The patient was followed up for about 30 months and she is still alive now. During the treatment, CT and CA-125 (Figure 3) were reviewed every 2 months. The major adverse events observed were grade 1 hand-foot syndrome (HFS) and grade 2 gastrointestinal reactions. No hypertension or proteinuria occurred.

The patient and his family provided written informed consent for publication of this report and accompanying images. We confirmed with the institutional review board of the First Affiliated Hospital of Nanjing Medical

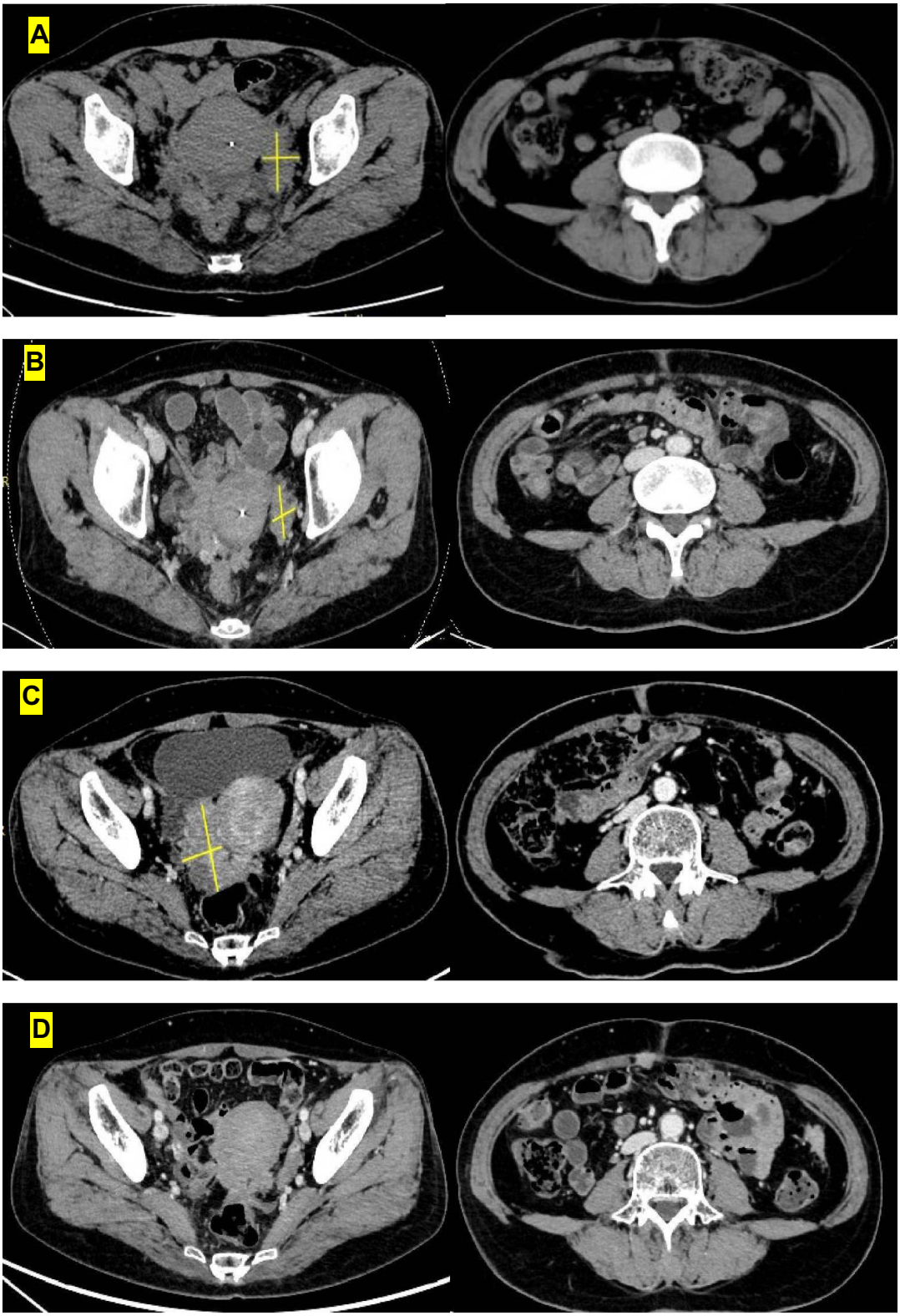

Figure 1 Changes on CT scans during treatment.
Notes: (**A**) Left posterior lesion of uterus (22.2mm/39.7mm) and Peritoneal metastasis (7.7mm) on February 19, 2018; (**B**) Left posterior lesion of uterus (19.5mm/32.1mm) and Peritoneal metastasis (5.4mm) on August 27, 2018; Changes on CT scans before and after endostar combined with apatinib treatment. (**C**) Left posterior lesion of uterus (42.2mm\36.6mm) and Peritoneal metastasis (11.1mm) on October 28, 2019; (**D**) Left posterior lesion of uterus (23.4mm\19.0mm) and Peritoneal metastasis (9.7mm) on August 31, 2020.
Abbreviation: CT, computed tomography.

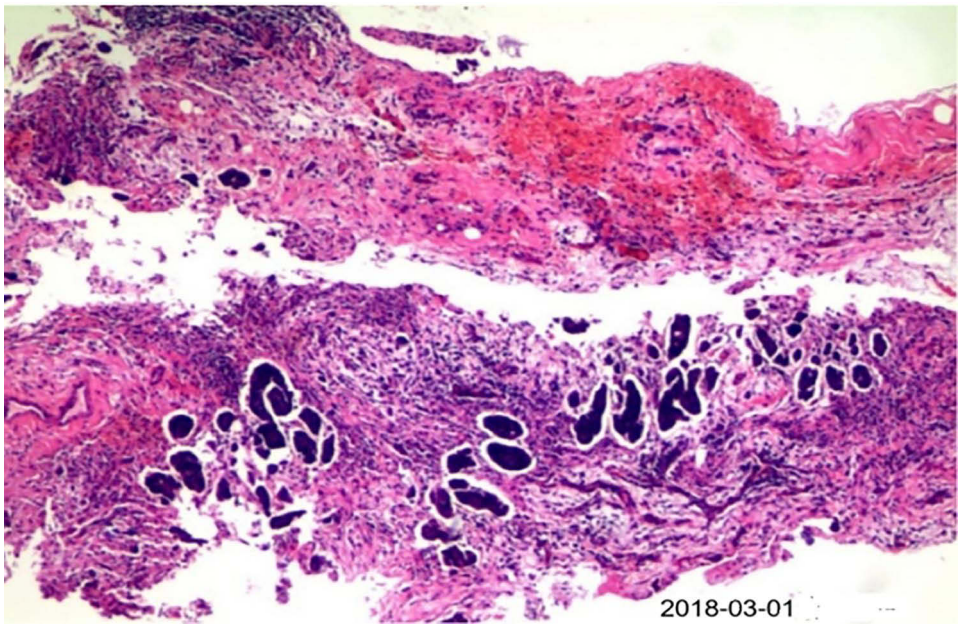

Figure 2 H&E staining with surgical specimens of the patient.

University that institutional approval was not required to publish this case report.

Discussion

In recent decades, the incidence and mortality of ovarian cancer in China have been increasing rapidly.[9,10] Despite numerous improvements in surgery, chemotherapy, and postoperative adjuvant chemotherapy, only about 30% of platinum-sensitive relapsed patients respond to second-line chemotherapy. Approximately 75% of women with advanced-stage ovarian cancer will relapse and die, and the 5-year overall survival rate is only 40–50%.[11] In view of the widespread adoption of primary surgical cytopenias, secondary cytoreductive surgery is also considered for patients with recurrent disease. In most cases, repetitive or secondary cytoreductive surgery for recurrent ovarian cancer refers to surgery performed within a certain period of time after the completion of primary treatment (the disease-free interval exceeds 6 to 12 months), with the goal of reducing tumors. Many single-institution and multi-institution retrospective reviews and meta-analysis support the procedure.[12] However, in a trial of platinum-sensitive patients with recurrent ovarian cancer, chemotherapy after the second surgery for cell reduction did not lead to a longer overall survival than chemotherapy alone.[13] Therefore, whether to choose surgery is based on the patient's age, general health, and patient's wishes. The individualized decision is to carefully weigh the potential benefits. Most ovarian cancers are sporadic, and about 15% of cases are considered to be genetically related to BRCA mutations.[14] Latest studies have shown that BRCA1 patients have an increased risk of morbidity after age 40, while BRCA2 patients have an increased risk of morbidity after age 50.[15] Since the discovery of BRCA in 1990, more and more researchers have realized the vital role of BRCA in ovarian tumorigenesis and applied it as a therapeutic target and a potential screening method. Germline mutations of BRCA1 and BRCA2 genes, which encode proteins necessary for double-strand DNA repair, break through homologous recombination and lead to increased cancer susceptibility.[16] BRCA1 can develop resistance to platinum-based chemotherapy through involvement in the FA/

Table 1 DNA Sequencing Tumor Tissue Genetic Variation, 450 Gene DNA Sequencing Detected 1 Tumor-Related Gene Mutation of 1 Gene

Gene Name	Mutation Information	Tumor Mutation Burden	Microsatellite Instability Results
ERRFI1	T187A exon4	3.2 Muts/Mb (<75%)	MSS

Note: Variation form: Threonine at position 187 of the ERRFI1 gene is changed to alanine.

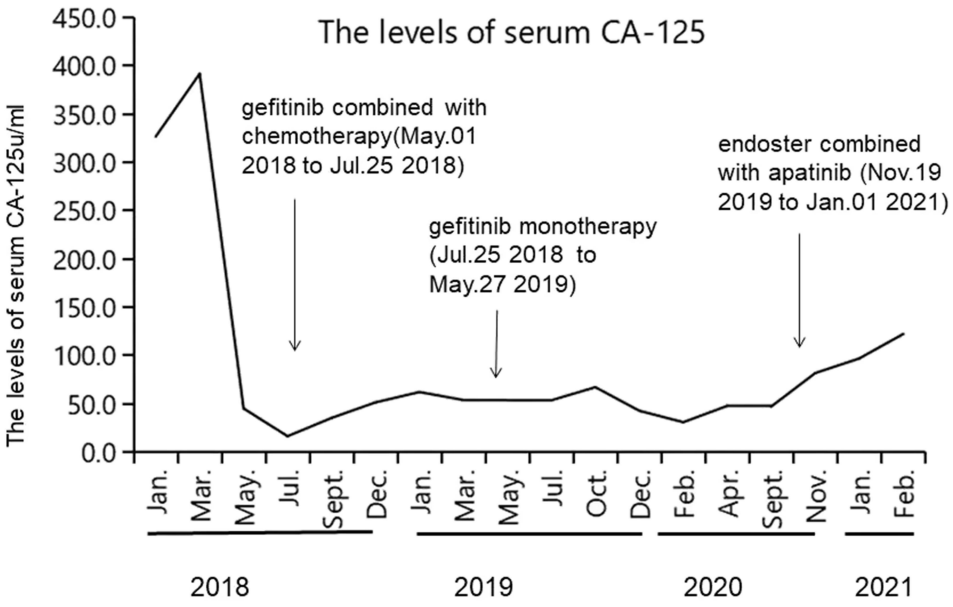

Figure 3 CA-125 levels change during treatment. After gefitinib maintenance treatment started in May 2018, the level of CA-125 remained stable at about 50 U/mL In October 2019, the CA-125 increased to 67.2U/mL. Endostar combined with apatinib treatment started in November 2019, and the CA-125 level was maintained within 50 U/mL again and entered a more stable state.

BRCA1, HR, and NER repair pathways.[17] Treatment after first-line therapy in EOC depends on the platinum-free interval (PFI) and the side-effects of the previous therapy. Unfortunately, the results of BRCA1/2 carriers challenge the traditional definition of platinum resistance. Researches have confirmed that patients with BRCA mutations have a better response to platinum therapy.[18–20] Recently, BRCA1/2 mutation screening has become routine examination in clinical practice, becoming one of the few successful clinical interventions for ovarian cancer. In 2005, two research groups respectively discovered that PARP inhibition induces synthetic lethality of mutant BRCA1 or BRCA2 cancer.[21] In 2009, the first trial of PARP inhibitors (PARPi) was published in solid tumors patients with BRCA mutations.[22] Currently, multiple PARPi have been approved by the FDA for advanced ovarian cancer and/or breast cancer, such as olaparib in 2014, rucaparib in 2016, niraparib in 2017, and talazoparib in 2018.[23] As molecularly targeted agents emerging, there are more options for the treatment of refractory ovarian cancer. Through genetic testing or circulating ctDNA, mutant genes can be effectively targeted for treatment. Our patient has no BRCA or other FDA-approved targeted mutations. The patient's NGS detected ERRFI1 mutation (the product of mitogen-inducible gene 6), located on the chromosome 1. Through the TCGA database, we learned the expression and survival curve of this gene in ovarian cancer (Figure 4). ERRFI1 is docked with the growth factor receptor (EGFR) kinase domain through its ERBB binding region,[24] inhibiting EGFR activation and downstream signal transduction. As ERRFI1 was identified as a feedback inhibitor of EGFR,[25] a high level of ERRFI1 can increase the resistance of cancer cells to EGFR tyrosine kinases (TKIs) and limit the therapeutic effects of EGFR TKIs, such as gefitinib or erlotinib. Gefitinib is an oral, competitive inhibitor of the EGFR TKI, also known as HER1 or ErbB-1, which can block EGFR mutations signal and overactive target cancer cell metastasis.[26] Several clinical studies have shown the obvious superiority of gefitinib in NSCLC patients with EGFR mutations for significant improvement in PFS and low incidence of adverse events. Interestingly, its effects are generally reversible.[27,28] Two cases have been reported, one with a low ERRFI1/EGFR ratio and the other one with ERRFI1 gene function-loss mutation. Gefitinib and erlotinib were respectively given and both patients achieved a higher remission rate.[29,30] In our case, the patient with mutation site ERRFI1 received conventional first-line chemotherapy combined with gefitinib maintenance treatment, achieving PFS for 15 months without obvious adverse reactions. These clinical cases suggest that the EEFI1 gene may be a potential cancer target of gefitinib.

Due to the lack of standardized therapy, treatment for refractory ovarian cancer is individualized based on patients' characteristics and previous treatment.

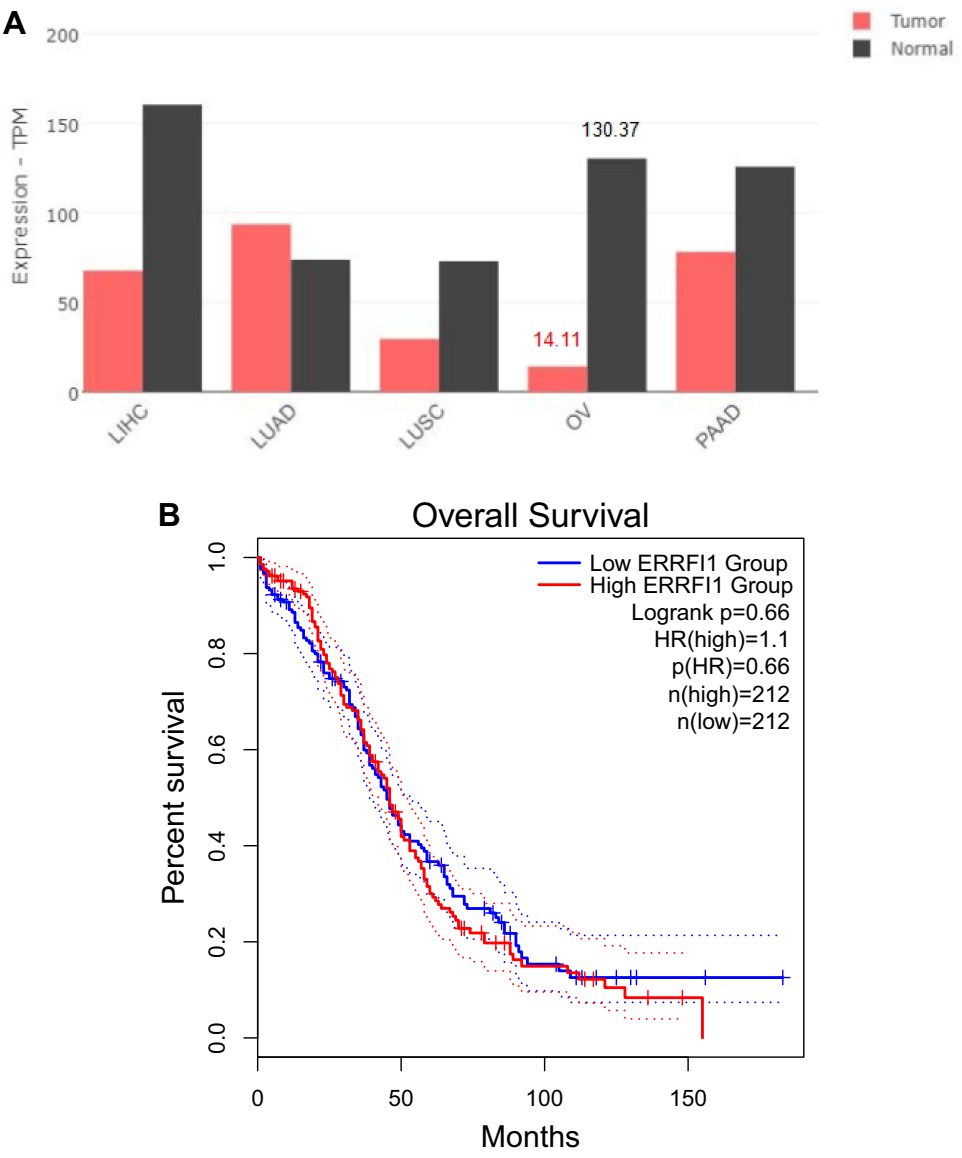

Figure 4 (**A**) The gene expression profile across some tumor samples and paired normal tissues. The height of bar represents the median expression of certain tumor type or normal tissue. (**B**) Expression of ERRFI1 and Survival Curve of Ovarian Cancer.

Abbreviations: LIHC, liver hepatocellular carcinoma; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; OV, ovarian serous cystadenocarcinoma; PAAD, pancreatic adenocarcinoma.

Increasing treatment options are emerging, including vascular endothelial growth factors (VEGF) inhibitors and TKI, such as bevacizumab, pazopanib, and nintedanib. Therefore, it is crucial to choose an appropriate treatment regimen. Up to now, endostar combined with apatinib has not been reported in EOC and both of them are new biological products for angiogenesis inhibition. Angiogenesis is a key factor in the growth of malignant tumors, and sustained angiogenesis is closely associated with tumor occurrence, development, and metastasis.[31] Studies have confirmed that anti-angiogenesis drugs have been beneficial for the treatment of many ovarian cancer patients who have failed in multi-line chemotherapy. Bevacizumab, one of the most studied target therapies, has been approved for first-line and second-line treatment of advanced EOC.[32] In addition, researches on apatinib and endostar has also been advancing. Bevacizumab mainly neutralizes VEGF-A and prevents binding to VEGFR-1, 2 to achieve angiogenesis inhibition while both apatinib and endostar not only are selective inhibitors of VEGFR-2 but also retain other anti-angiogenic activities. These three drugs have shown inhibitory effects on angiogenesis and tumors in the zebrafish model. Importantly, the effects of endostar and apatinib are

superior to bevacizumab.[33] Single antiangiogenic agents are prone to drug resistance and tumor recurrence. Jain published a paper in Science and proposed that the ideal tumor treatment requires the "cocktail therapy" of anti-angiogenesis therapy to normalize blood vessels.[34] Therefore, choosing a multi-target anti-angiogenic agent or a combination of anti-angiogenic agents may circumvent the anti-angiogenic drug resistance alone and obtain clinical benefit. An experimental study found that the combination of recombinant human endostatin and bevacizumab has an additive effect.[35] Our clinical team has previously achieved benefits in the treatment of a Merkel cell carcinoma patient who cannot tolerate chemotherapy and radiotherapy. The patient achieved partial remission after 2 months of treatment with endostar 30mg civ24h d1-4 plus apatinib 250mg qod PO, and achieved 6.5 months PFS with tolerable adverse reactions.[36] Thus, we selected an individualized treatment regimen with endostar plus apatinib for the patient in this case.

Apatinib, approved and marketed in China in 2014, is an oral new type of TKI. It could highly selectively compete for the ATP-binding site of intracellular VEGFR-2 and block its downstream signal transduction, thereby playing an antitumor part via robust inhibition of tumor angiogenesis.[37,38] In addition, apatinib can reverse multidrug resistance (MDR) of tumor cells mediated by multidrug transporter protein ABCB1 (p-glycoprotein) via suppressing its activity in pumping out chemotherapy drugs to improve chemotherapy efficacy.[7,39] Several cases showed that apatinib therapy significantly improves OS and PFS with acceptable safety although patients have previously received various chemotherapy regimens.[40] Apatinib may be a feasible option for recurrent platinum-resistant EOC and has good efficacy and controllable toxicity.[41,42] Further, apatinib is cheaper and easier to administer compared with bevacizumab.[43] According to the research of Scott et al, apatinib could reverse the P-glycoprotein ABCB1-and ABCG2-mediated multidrug resistance in drug-resistant solid tumor cells by inhibiting their transport function, to circumvents cancer cell resistance to other anti-tumor drugs.[44] Endostar is an anti-tumor angiogenesis drug developed in China and was approved by the China National Food and Drug Administration (CFDA) for NSCLC in September 2005. It's a modified human endostatin retaining endogenous endostatin function. Studies demonstrate endostar can not only down-regulate the expression of VEGFs and VEGF receptors (VEGFRs) but also inhibit the activation of ERK, p38 MAPK, and Akt,[45] which also up-regulate the level of SRCIN1 protein in vascular endothelial cells and affect the Src signaling pathway and restore blood vessel normalization.[46,47] Compared with anti-angiogenesis targeted therapies such as monoclonal antibodies and TKIs, endostar can regulate multiple signaling pathways, widely targeting signaling molecules, growth factors, and enzymes. Moreover, endostatin specifically binds to nucleolar proteins on the cell surface and inhibits tumor lymphangiogenesis and lymphatic metastasis by down-regulating VEGF-C levels and VEGFR-3 gene expression.[48] A large number of clinical data and experience have been obtained in the research of applying endostar to treat different cancers.[46] In recent years, endostar combined with chemotherapy has been effective in the treatment of ovarian cancer, and significantly improve PFS of ovarian cancer with the recurrent epithelial resistance of platinum.[46] Studies have analyzed that endostar can block the metastasis, invasion, and angiogenesis of ovarian cancer cells by inhibiting the activation of PD-L1 and STAT3.[49] Our patient, treated with endostar (30mg civ24h d1-4) plus apatinib (250mg qod PO) for 14 months, achieved stable disease with good safety, controllable adverse reactions, and no long-term adverse events. The recommended dosage of endostar's instructions is 7.5 mg and administrated by intermittent intravenous (IIV) infusion for 3–4 h per day during a 14-day period. Since 2010, the method of continuous intravenous (CIV) infusion via an infusion pump to increase the dose for short-term maintenance has been introduced and widely off-label used in clinical practice in China. This method is safe and effective and it can reduce toxicity, extend the retention time in the blood, and increase the active ingredient in the target tissue. Besides, it can improve the medical compliance and life treatment capacity of patients.[50] Hansma et al have studied the safety of CI at different doses and indicated that this method of administration is safe.[51] Chen et al have shown that there is a linear correlation between the exposure of the body to endostar and the administered dose between 7.5 and 30 mg/m^2/day.[52] Secondly, due to the small body surface area of our patient, and HFS was unbearable during the initial daily treatment with apatinib. Considering the study of Hu et al, the recommended dose was 500 mg daily and the rate of grade 3/4 toxicity was significantly decreased, whose efficacy was similar to that of the daily regimen of 850 mg in breast carcinoma.[53] In our case, we used apatinib at an initial dose of 250 mg/d, lower than the amount of apatinib applied in previous

clinical trials. Thus, common side effects such as high blood pressure and proteinuria were avoided.

In view of the clinical effectiveness of endostar plus apatinib and anti-angiogenesis treatment experience, endostar combined with apatinib might be a therapeutic option in refractory ovarian cancer to prolong survival. We have confirmed that the combination of two anti-angiogenic agents therapy is feasible in refractory ovarian cancer. Further studies and clinical data are needed to prove ovarian tumors with visceral metastasis or other cancers.

Conclusion

In conclusion, treatment for refractory ovarian cancer should be individualized. Our case indicated that the ERRFI1 gene may be a potential target of gefitinib and endostar plus apatinib is worth recommending for the maintenance treatment in refractory ovarian cancer. In addition, we confirmed that anti-angiogenic therapy is feasible in refractory ovarian cancer.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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