Twenty-eight months progression-free survival after pyrotinib therapy for HER2-positive recurrent ovarian clear cell carcinoma: a case report

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Background: Ovarian cancer (OC) is the seventh most common newly diagnosed cancer in women worldwide. Ovarian clear cell carcinoma (OCCC) is a specific type of epithelial ovarian cancer with a poor prognosis. It has been revealed that human epidermal growth factor receptor 2 (HER2)-positive (2+/3+) has been observed in 14% to 45.6% of patients with OCCC. Anti-HER2 therapy has been demonstrated to be an effective strategy for the treatment of HER2-positive breast cancer. However, the role of anti-HER2 therapy in OC remains largely unknown. This case report is the first report suggesting a 28-month PFS of pyrotinib in HER2-positive OCCC.

Case Description: A 67-year-old female patient with HER2-positive OCCC was admitted to our hospital because of fever, who benefited greatly from treatment with pyrotinib, an irreversible HER2 antagonist conditionally approved for patients with advanced or metastatic HER2-positive breast cancer in China. The patient, who had previously been diagnosed with stage I_A OCCC [according to the International Federation of Gynecology and Obstetrics (FIGO)] and undergone radical surgery with standard adjuvant chemotherapy on May 15, 2017, was diagnosed with HER2-positive OCCC at FIGO stage III_C. She was treated with oral pyrotinib (400 mg/day in 21-day cycles) starting on November 27, 2018. Imaging assessments were conducted every 2 to 4 treatment cycles. Best response by response evaluation criteria in solid tumors (RECIST) 1.1 were partial response. However, on March 30, 2021, the patient was assessed using contrast-enhance CT and found to have progressive disease with liver metastases. Subsequently, on April 26, 2021, the patient underwent liver microwave ablation and ultrasound-guided liver biopsy. The immunohistochemistry results of the liver biopsy showed the origin of the disease to be ovarian. Therefore, the disease was identified as HER2-positive OCCC at FIGO stage IV_B.

Conclusions: Progression-free survival (PFS) in second-line chemotherapy for patients with recurrent OC ranges from 3.8 to 11.3 months. In the case of this patient, treatment with pyrotinib yielded a PFS of 28 months, which was a promising result for the use of pyrotinib in treating HER2-positive OC.

Keywords: Pyrotinib; ovarian clear cell carcinoma (OCCC); ovarian cancer (OC); human epidermal growth factor receptor 2 positive (HER2-positive); case report

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Introduction

Ovarian cancer (OC) is the seventh most common newly diagnosed cancer in women worldwide. Ovarian clear cell carcinoma (OCCC) accounts for approximately 10% of epithelial ovarian carcinomas, which comprises approximately 90% of all ovarian carcinomas. The incidence of OCCC varies considerably in different ethnicities with 4.8% in Whites and 11.1% in Asians (1). OCCC has a poorer prognosis than serous or endometrioid ovarian cancer. Recurrence rates of OCCC have been reported as 29% (stage I), 30% (stage II), 62% (stage III), and 73% (stage IV), while the 5-year survival rate has been reported as 13.2%, and the median survival time as 10 months after recurrence (2). Human epidermal growth factor receptor 2 (HER2) is a 185-kDa glycoprotein and transmembrane receptor with tyrosine kinase activity that plays an important role in regulating cell functions, such as proliferation, immigration, and differentiation. HER2 overexpression (2+/3+) has been observed in 14% to 45.6% cases of OCCC in small patient cohorts (3,4). Controversial conclusions have been reached in several studies assessing the prognostic value of HER2 overexpression in OC (4-7).

Pyrotinib is an orally administered irreversible dual pan-ErbB tyrosine kinase inhibitor (TKI), which inhibits the members of EGFR family, including HER1, HER2, and HER4, and demonstrates antitumor activity in the treatment of HER2-positive advanced solid tumors (8). Based on the results of pyrotinib plus capecitabine for HER2-positive metastatic breast cancer in a phase II clinical study, pyrotinib combined with capecitabine was conditionally approved in China for use in patients with HER2-positive, advanced, or metastatic breast cancer that had previously been treated with anthracycline or taxane chemotherapy. When compared with lapatinib plus capecitabine, pyrotinib plus capecitabine demonstrated a superior ability to prolong progression-free survival (PFS) in the phase III HER2-positive metastatic breast cancer (PHOEBE) trial (9), which aimed to explore the efficacy of pyrotinib in the treatment of HER2-overexpressed breast cancer. Because targeting HER2 has been a pivotal treatment strategy for HER2-positive breast cancer, the strategy has potential promise for treating HER2-positive OC.

The treatment strategy for OCCC has been very similar to that of other histologic types of epithelial ovarian cancers. OCCC, especially recrudescent OCCC, is a chemo-resistant carcinoma with a response rate to chemotherapy that is much lower than other epithelial ovarian cancers (less than 10% even among patients sensitive to platinum) (10). The median PFS and median (OS) after combination chemotherapy in women with recurrent/relapsed ovarian cancer have been reported as between 3.8 and 11.3 months and between 17.4 and 29 months, respectively (11-13). Anti-HER2 targeted therapy may be an effective way to ameliorate the unsatisfactory PFS and OS for patients with HER2-positive OC. The present case study discusses the case of a patient with advanced HER2-positive OCCC, who was treated with pyrotinib and achieved a PFS of 28 months. To our knowledge, this is the first report of pyrotinib in HER2-positive OCCC achieving clinical benefits beyond expectation. We present the following case in accordance with the CARE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-1045/rc).

Case presentation

A 67-year-old female patient presented with fever without obvious discomfort in early May 2017 (*Figure 1*). On May 4, 2017, positron emission tomography/computed tomography (PET/CT) showed the possibility of a malignant tumor arising from the ovary (cystadenocarcinoma), with multiple renal and hepatic cyst formations (*Figure 2*). In addition, she had a medical history of hypertension for 30 years, controlled by amlodipine besylate and irbesartan hydrochlorothiazide; type 2 diabetes mellitus for 7 years, controlled by acarbose capsules and metformin; and coronary heart disease for 17 years. No family history of cancer was noted.

On May 15, 2017, the patient was diagnosed with stage I_A OCCC [according to the International Federation of Gynecology and Obstetrics (FIGO)] and underwent radical surgery for OC under general anesthesia. Postoperative histopathology suggested OCCC (Grade II) in the right ovary and the right fallopian tube was not involved. Immunohistochemistry (IHC) results showed Ki-67 (30%+), p53 (+), estrogen receptor (ER) (–), and HER2 (–). The patient was administered with 6 cycles of TcP regimen (paclitaxel liposome, 150 mg/m^2 on day 1, and carboplatin, area under the time *vs.* concentration curve (AUC) 5 on day 1, every 3 weeks) as adjuvant chemotherapy from June 14, 2017, to September 28, 2017.

On June 12, 2018, a PET-CT scan was carried out. When the scan was compared with PET-CT images from May 15, 2017, new metastases were observed in the left iliac fossa and right mid-abdomen (*Figure 3*). On August

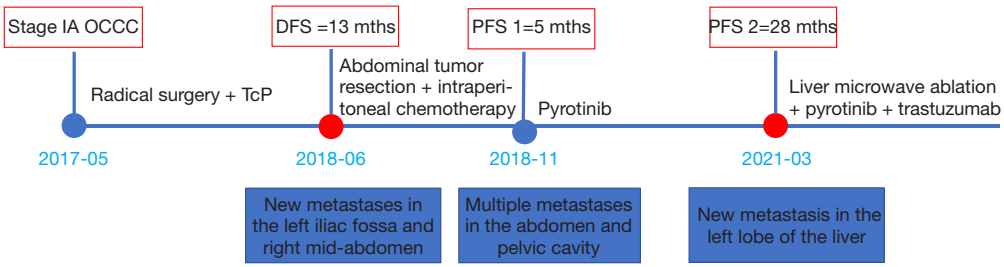

Figure 1 Treatment timeline. Illustration of the treatment regimen and the corresponding PFS in months. DFS, disease-free survival; PFS, progression-free survival; mths, months.

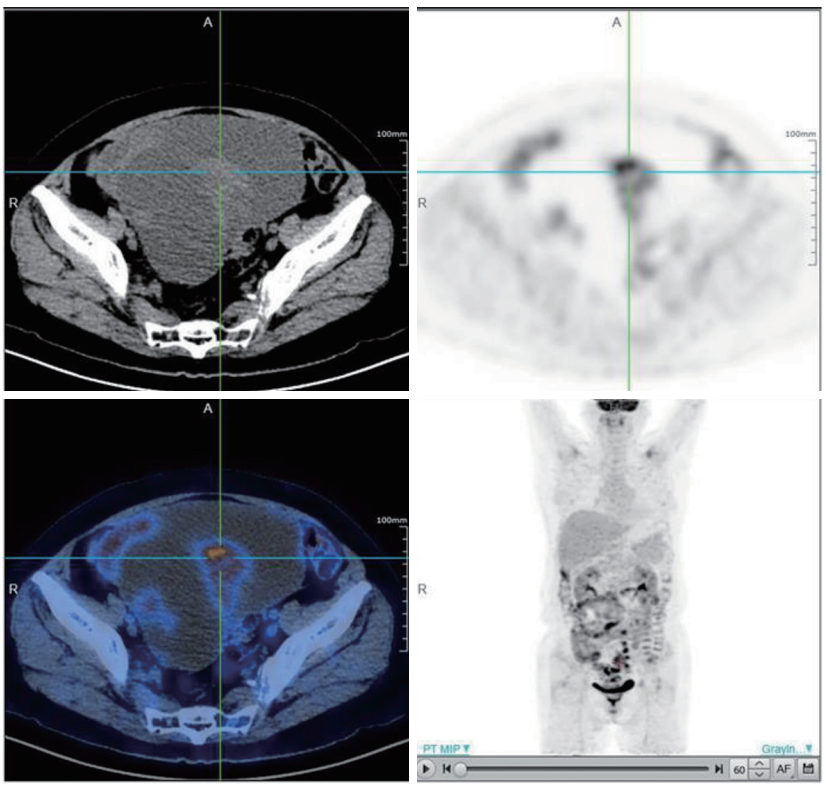

Figure 2 PET-CT images on May 4, 2017. A massive cystic, solid mass (about 155.0 mm × 129.8 mm) were shown above the uterus in the pelvic cavity. Multiple compartments within the lesion were observed. Nodules in the abdominal wall were accompanied by abnormally increased glucose metabolism, with a maximum SUV value of 9.5. Glucose metabolism in the cystic part was defective. The lesion could not be separated from the bilateral appendages. PET-CT, positron emission tomography/computed tomography; SUV, standardized uptake value; A, anterior; R, right.

29, 2018, the patient underwent abdominal tumor resection combined with hernioplasty for incisional hernia and intraoperative hyperthermic intraperitoneal chemotherapy. The postoperative pathology suggested the recurrence of OCCC with IHC results showing Ki-67 (20%+) and HER2 (3+), and fluorescence *in situ* hybridization (FISH) results showing HER2-positive with a HER2:CEP17 ratio of 10.6. No BRCA alterations were found in the laboratory examination. The patient received no further treatment.

On November 26, 2018, contrast-enhanced CT images showed multiple metastases in the abdomen and pelvic cavity (*Figure 4A*). Laboratory examinations,

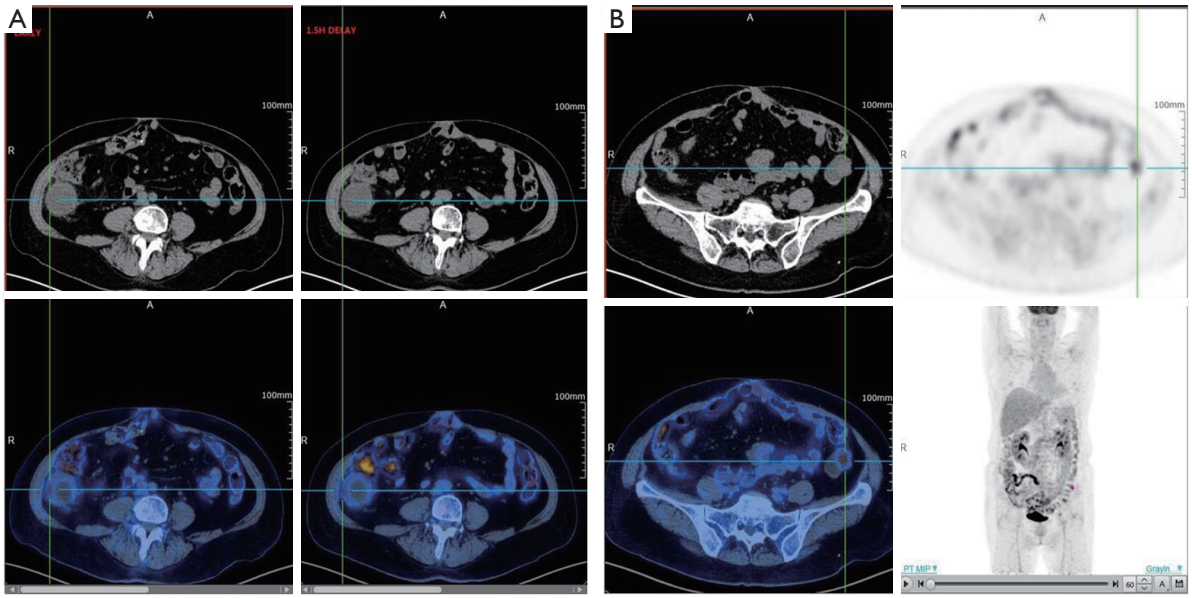

Figure 3 PET-CT images on June 12, 2018. (A) Cystic foci, about 45.5 mm × 42.3 mm, were shown in the paracolic sulcus in the right middle abdominal cavity. There was increased glucose metabolism in the marginal area, with a maximum SUV of 4.4. (B) A cystic-solid space-occupying lesion of approximately 33.1 mm × 30.3 mm was seen in the left iliac fossa. The solid area showed increased glucose metabolism, with a maximum SUV of 6.2. PET-CT, positron emission tomography/computed tomography; SUV, standardized uptake value; A, anterior; R, right.

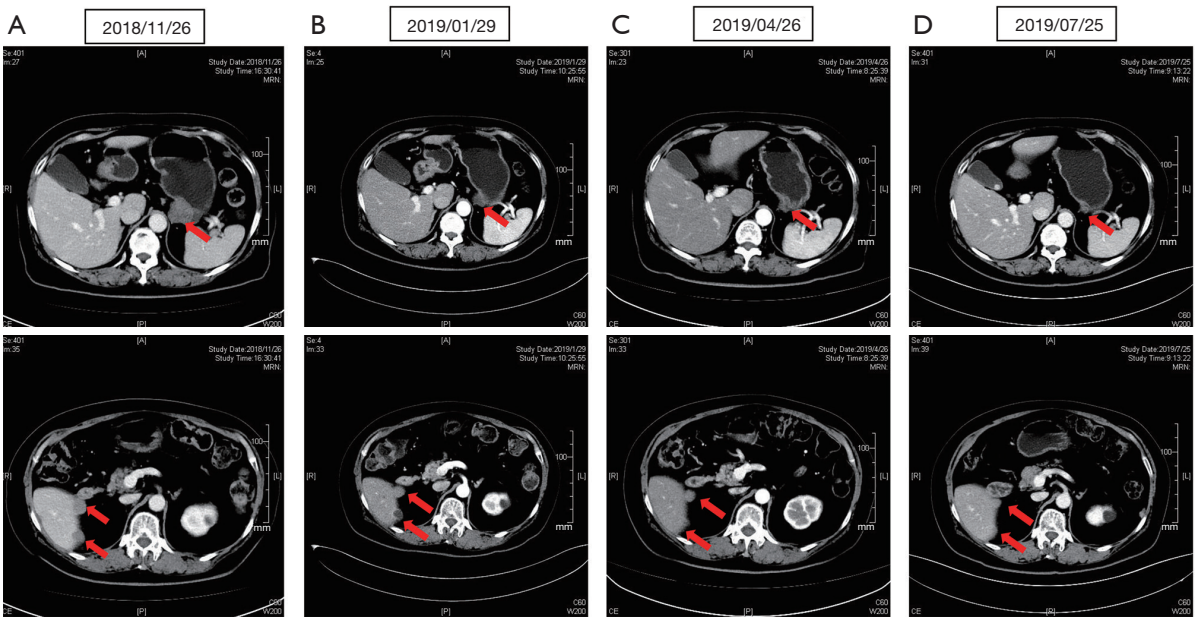

Figure 4 Contrast-enhanced CT images of the abdomen showing nodules and a mass inside the left side of the greater omentum and between the stomach and abdominal aorta. (A) Nodule with a diameter of about 3.5 cm with inhomogeneous reinforcement seen in contrast-enhanced CT; (B) nodule with a diameter of about 2.4 cm not obvious in contrast-enhanced CT; (C) nodule with a diameter of about 1.8 cm not obvious in contrast-enhanced CT; (D) nodule with a diameter of about 1.5 cm with slight reinforcement seen in contrast-enhanced CT. Two small nodules appeared outside the liver outline in the capsule of the right posterior lobe of the liver. CT, computed tomography; A, anterior; R, right; L, left; P, posterior.

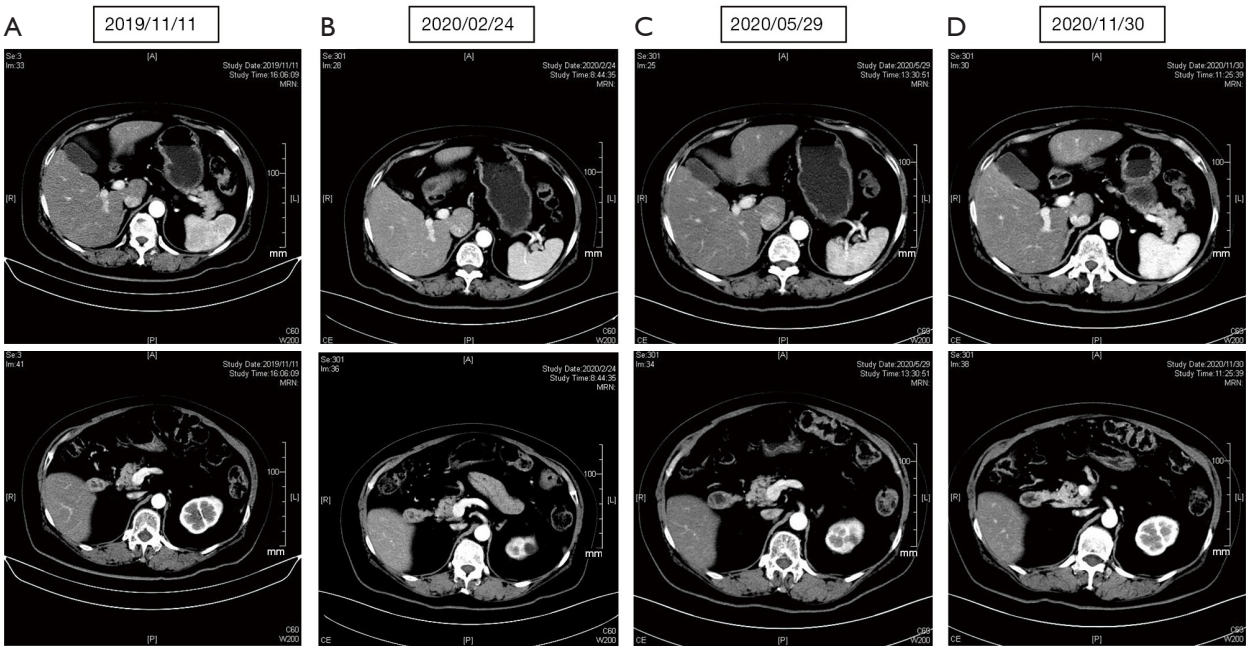

Figure 5 Contrast-enhanced CT images of the abdomen. (A-D) Nodules and mass inside the left side of the greater omentum and between the stomach and abdominal aorta were not obvious. Two small nodules almost disappeared outside the liver outline in the capsule of the right posterior lobe of the liver. CT, computed tomography; A, anterior; R, right; L, left; P, posterior.

including blood routine indicators, liver and kidney function, electrocardiogram, and echocardiography, were unremarkable. The patient was ultimately diagnosed with recurrent FIGO stage III_C OCCC with HER2 overexpression. Because of the HER2-positive signature, pyrotinib (400 mg daily in 21-day cycles) was prescribed on November 27, 2018. During treatment with pyrotinib, contrast-enhanced CT imaging assessments were conducted every 2 to 4 cycles (*Figures 4,5*). Best response by response evaluation criteria in solid tumors (RECIST) 1.1 were PR (partial response). On March 30, 2021, contrast-enhanced CT images of the abdomen and pelvic cavity showed multiple metastases with partial new lesions and partial shrinkage. Possible new metastasis (3.3 cm × 2.2 cm) was observed in the left lobe of the liver. Given these results, the patient was diagnosed with progressive disease (PD), following the RECIST v1.1 method (*Figure 6*). On April 26, 2021, the patient underwent liver microwave ablation and ultrasound-guided liver biopsy (*Figure 7*). Postoperative histopathological examination confirmed diagnostic consistency between metastatic OCCC and the IHC results of Ki-67 (60%+) and HER2 (2+/3+). FISH examination results showed HER2-positive with a HER2:CEP17 ratio of 8.6. The patient was ultimately diagnosed with FIGO stage IV_B OCCC.

Pending the IHC results and decisions regarding the next treatment, the dose of pyrotinib was reduced to 320 mg daily from the contrast-enhanced CT assessment on March 30, 2021. Once found to be HER2-positive as before, the patient was administered dual anti-HER2 therapy by adding trastuzumab (440 mg every 3 weeks) to pyrotinib (320 mg daily) on June 23, 2021. No grade 3 to 4 adverse events occurred during the treatment with pyrotinib.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

We present a case of a patient with HER2-positive recurrent OCCC, diagnosed as FIGO stage III_C, who

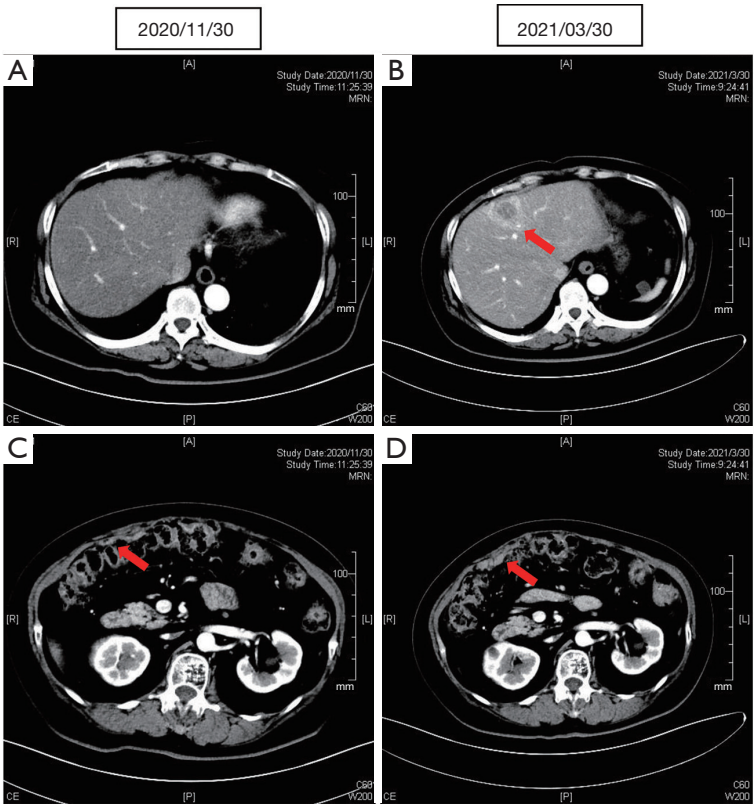

Figure 6 Contrast-enhanced CT imaging of the abdomen imaging after 22 (A) and 26 (B) cycles of treatment. Compared with *Figure 6A*, *Figure 6B* shows abnormal mass density in the left lobe of the liver (red arrows; about 3.3 cm × 2.2 cm). (C) Slightly thickened right peritoneum (red arrow); (D) multiple nodular thickening with enhancement, especially in the lower right abdomen, with the largest nodule (red arrow; 1.8 cm in diameter). CT, computed tomography; A, anterior; R, right; L, left; P, posterior.

achieved a significantly longer PFS than expected (28 months) through anti-HER2 target therapy with pyrotinib. The patient exhibited PR during the treatment, demonstrating the promising efficacy of pyrotinib as an anti-HER2 targeted therapy in the treatment of OCCC. Pyrotinib, in combination with capecitabine, has been approved by the National Medical Products Administration (NMPA) of China for treating HER2-positive, advanced, or metastatic breast cancer in patients previously treated with anthracycline or taxane chemotherapy. This case study was an exploratory study of the use of pyrotinib in HER2-positive OCCC. The efficacy of pyrotinib in HER2-positive OC needs to be further elucidated in large-scale clinical trials.

Therapy targeting HER2 in HER2-positive OC has been developed since targeted agents, including humanized antibodies and their combinations, emerged. Trastuzumab, a monoclonal antibody, binds to the extracellular domain IV of HER2. Nevertheless, it has demonstrated a disappointing response rate of 7.3% and an additional disease stability rate of 39% in patients with recurrent or refractory HER2-positive OC (14,15). Pertuzumab, another HER2 monoclonal antibody that interacts with the subdomain II of the HER2 extracellular domain and sterically blocks the dimerization of HER2, has been assessed in the treatment of OC. Not only has pertuzumab monotherapy yielded a response rate of 4.3% and a rate of 6.8% with stable disease (SD) lasting at least 6 months in OC (16), it has also enhanced gemcitabine activity for the treatment of platinum-resistant ovarian, peritoneal, and tubal carcinomas (17). The combination of pertuzumab and gemcitabine, along with pertuzumab and paclitaxel, has demonstrated favorable tendencies in improving the PFS in patients with low HER-3 mRNA expression, with hazard of progression results of 0.63 and 0.56, respectively, in the subgroup analyses of the PENELOPE trial (18).

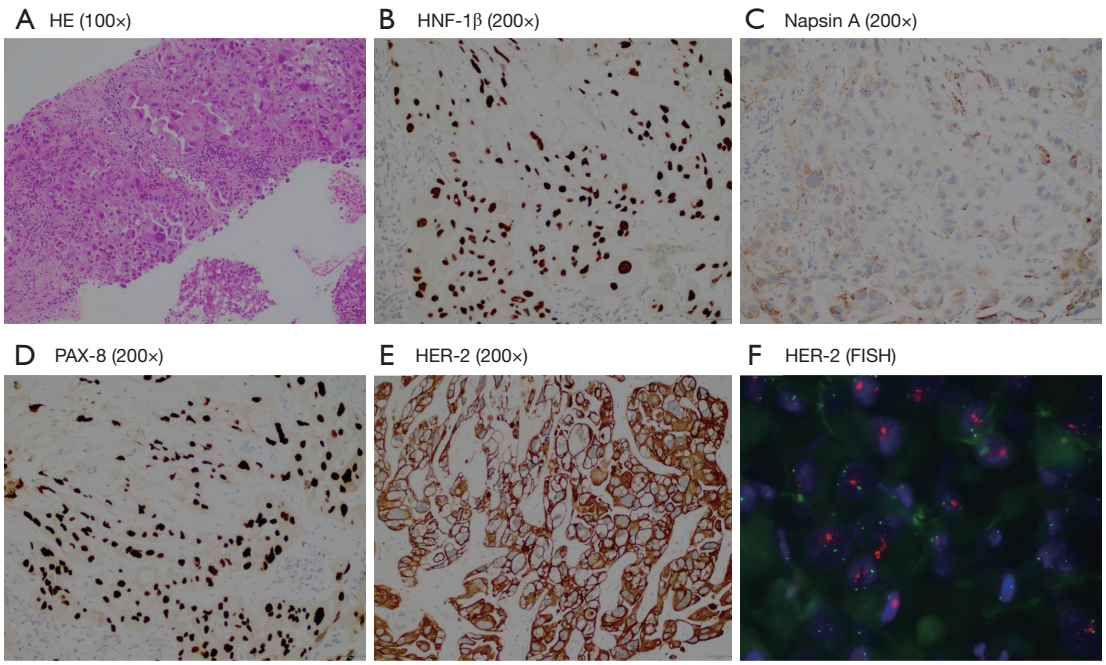

Figure 7 The pathological results of ultrasound-guided liver biopsy. (A) The poor differentiation in H&E staining; (B-E) positive IHC result of HNF-1β, Napsin A, PAX-8, and HER2 (100% 2+/3+), respectively; (F) FISH result of HER2-positive (1,000×). HE, hematoxylin-eosin; IHC, immunohistochemistry; HNF-1β, hepatocyte nuclear factor-1β; HER2, the human epidermal growth factor receptor 2; FISH, fluorescence in situ hybridization.

However, the addition of pertuzumab to carboplatin-based chemotherapy failed to substantially prolong PFS in patients with unselected platinum-sensitive OC. Few TKIs have been reported to benefit patients with OC via the signaling pathway associated with HER2.

In a randomized phase II study, the objective response rate (ORR) for pyrotinib plus capecitabine was 78.5% *vs.* 57.1% for lapatinib plus capecitabine (P=0.01). The study also recorded a median PFS of 18.1 months for pyrotinib plus capecitabine *vs.* 7.0 months for lapatinib plus capecitabine [hazard ratio (HR) 0.36, P<0.001] in patients with previously treated metastatic breast cancer in the (19). In an interim analysis of PHOEBE trial, pyrotinib plus capecitabine significantly prolonged the median PFS compared to lapatinib plus capecitabine (12.5 *vs.* 6.8 months, HR 0.39 (95% CI: 0.27–0.56); one-sided P<0.0001) in patients with HER2-positive metastatic breast cancer (5). Moreover, a study showed that pyrotinib achieved an independent review committee (IRC)-assessed ORR of 30.3% and a median response duration of 6.9 months in patients with HER2-mutated non-small-cell lung cancer (NSCLC), who had previously been treated with platinum-based chemotherapy. The median PFS and OS in the same study were 6.9 months and 14.4 months, respectively (20).

In the present case, HER2-positive was observed with disease progression after surgical resection and adjuvant chemotherapy. Pyrotinib was used to treat the patient, and she achieved a PFS of 28 months, which is significantly longer than the reported PFS of 3.8–11.3 months in patients with ovarian cancer recurred/relapsed from second-line chemotherapy (11,13). Pyrotinib may provide a new treatment option for patients with HER2-positive OC, who could benefit from the effects of pyrotinib treatments. However, further research with larger-scale trials is required, and there is still an important question challenging the clinical practice: how should we manage the treatment of HER2-positive OC after progression on anti-HER2 monotherapies.

Pyrotinib, as a dual antagonist of EGFR and HER2, has a different mechanism to trastuzumab. Due to the synergistic effects of trastuzumab plus pertuzumab and lapatinib plus trastuzumab in patients with HER2-positive breast cancer, it has been suggested that pyrotinib combined with trastuzumab may have a synergistic anti-

HER2 effect (21,22). Dual anti-HER2 blockade has shown superiority to mono-blockade in HER2-positive breast cancer. A randomized controlled trial (NCT03910712), evaluating the efficacy of pyrotinib plus trastuzumab and aromatase inhibitors as first-line treatment for HER2-positive and hormone receptor-positive metastatic or locally advanced breast cancer, are currently underway (23). It could be favourable to add trastuzumab to pyrotinib in treating HER2-positive OC, taking advantage of their synergistic effect. In the case of our patient, the attending doctor decided to adopt the combined therapy of pyrotinib (320 mg daily) and trastuzumab (440 mg every 3 weeks) until disease progression.

The patient and her family were satisfied with the entire diagnosis and treatment process. In addition, they still hope for benefit from the subsequent treatment with pyrotinib (320 mg daily) and trastuzumab (440 mg every 3 weeks).

Our study proves that pyrotinib can be considered a potentially effective strategy for treatment of patients with HER2-positive recurrent OCCC. The limitations of our study were only one case report and lack of mechanism investigation. Thus, further studies are needed to elucidate the potential molecular mechanisms underlying this phenomenon, and clinical trials or large-scale cohort studies are conducted to confirm the efficacy and safety of this strategy.

Conclusions

This case study has presented the case of a patient who received pyrotinib treatment for HER2-positive OCCC and benefitted from this anti-HER2 therapy. Drawing on the results of previous studies of HER2-positive breast cancer, pyrotinib plus trastuzumab is likely to prove beneficial for patients. Ours is a case of successful treatment with pyrotinib for HER2-positive OCCC. However, the efficacy of pyrotinib in OC needs to be further evaluated in large-scale clinical trials.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-1045/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-1045/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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