Case Report

The reversal of anti-HER2 resistance in advanced HER2-positive breast cancer using apatinib: two cases reports and literature review

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Background: Human epidermal growth factor receptor 2 (HER2)-targeted treatment has yielded a notable clinical benefit in patients with HER2-positive breast cancer. However, nearly 50% of patients still suffer disease progression due to resistance to HER2-targeted therapy. After the failure of macromolecular monoclonal antibodies (mAbs) therapy, we can choose small molecule tyrosine kinase inhibitors (TKIs) to reverse HER2 resistance. When small molecule TKIs resistance, we can use mAb combined with small molecule TKI, or antibody-drug conjugates (ADCs) to reverse HER2 resistance. However, then due to the availability and price of ADCs, patients may not use them. Consequently, new therapeutic approaches are required to overcome HER2-targeted therapy resistance. Vascular endothelial growth factor and its receptors (VEGF/VEGFRs) promote tumor angiogenesis. They can also activate downstream signaling pathways to promote tumorigenesis. VEGFR is a key regulator of the tyrosine kinase signaling pathway and may be a potential target in HER2-positive breast cancer. Apatinib is a small molecule TKI that specifically binds to VEGFR2 and thus exerts an antitumor effect. Although there is no definite indication for apatinib in breast cancer, it has a good benefit in advanced gastric cancer.

Case Description: The two patients we reported were both HER2-positive breast cancer who we followed for more than 10 years. After the failure of multi-line anti-HER2 treatment, apatinib combined with anti-HER2 treatment had PFS of 8.4 months and 10.6 months, respectively. One patient had grade 2 hand-foot syndrome. The other had grade 2 leukopenia and grade 2 thrombocytopenia, both of them improved after control. And the best response of them were PR and SD, respectively.

Conclusions: Our cases demonstrate that, in HER2-positive breast cancer patients with HER2-targeted resistance, apatinib may be able to reverse HER2 resistance. These two cases suggest an alternative method for clinical HER2-targeted treatment of drug-resistant breast cancer patients and provide new insights for future research.

Keywords: Advanced human epidermal growth factor receptor 2-positive breast cancer (advanced HER2-positive breast cancer); apatinib; case report

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Introduction

Breast carcinoma is one of the most common malignant tumors globally and is responsible for a high mortality rate in females. Human epidermal growth factor receptor 2 (HER2)-positive breast cancer accounts for roughly 15–20% of all types of breast cancer and has a more aggressive phenotype and worse prognosis (1). Although anti-HER2 targeted therapy has shown promising clinical benefits for patients with advanced HER2-positive breast cancer, disease progression occurs in a large proportion of patients due to inherent and acquired resistance to trastuzumab and other HER2-targeted drugs (2). Therefore, new therapeutic options are needed to overcome resistance to anti-HER2 therapy that could be applied clinically to optimize treatment benefits.

HER2 resistance may be due to the mutation of the target itself after anti-HER2 treatment, which leads to changes in drug binding. Another possibility is that HER2 downstream intracellular signaling pathways are activated, which promote tumorigenesis (3). After the failure of macromolecular mAbs therapy, we can choose small molecule tyrosine kinase inhibitors (TKIs) to reverse HER2 resistance. When small molecule TKIs resistance, we can use mAb combined with small molecule TKI, or an antibody-drug conjugates (ADCs) to reverse HER2 resistance. However then due to the availability and price of ADCs, patients may not use them (4-6). Therefore, new strategies are needed to reverse HER2 resistance.

Tumor angiogenesis is one of the most important mechanisms for the occurrence and development of malignant tumors, contributing to tumor growth and metastasis. Vascular endothelial growth factor (VEGF) is known to play an essential role in angiogenesis. Therefore, anti-angiogenesis therapy has become an important type of antitumor therapy (7). Apatinib is a highly selective vascular endothelial growth factor receptor 2 (VEGFR2) small-molecule TKI that blocks the transmission of downstream signaling pathways, significantly inhibiting the proliferation of tumors (8). Now apatinib has not been approved for breast cancer, but it has good efficacy and safety in advance gastric cancer (9). To date, there are few reports on the efficacy of apatinib in reversing HER2-resistant advanced breast cancer. It has been reported that apatinib monotherapy has a good benefit in HER2 targeted therapy resistant advanced HER2-positive breast cancer (10). We consider whether apatinib combined with anti-HER2 therapy can reverse HER2 resistance.

In this report, we discuss two cases of advanced HER2-positive breast cancer treated with apatinib in combination with anti-HER2 therapy after multi-line therapy. These two case reports may provide a new direction for reversing HER2-targeted therapy resistance by using apatinib in clinical practice. We present the following article in accordance with the CARE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-2483/rc).

Highlight box

Key findings

- We reported two advanced HER2-positive breast cancer patients. After the failure of multi-line anti-HER2 treatment, apatinib combined with anti-HER2 treatment had PFS of 8.4 and 10.6 months, respectively. And the best response of them were PR and SD, respectively.

What is known and what is new?

- In a preclinical mouse model of HER2-amplified breast cancer brain metastasis, combined targeted anti-HER2 and anti-VEGFR2 therapy can significantly inhibit tumor growth and prolong survival. Our cases demonstrate that, in HER2-positive breast cancer patients with HER2-targeted resistance, apatinib may be able to reverse HER2 resistance.

What is the implication, and what should change now?

- The antitumor mechanism of apatinib needs further study to achieve targeted treatment. Exploring the combination of apatinib and other anti-HER2 targeted drugs may bring better survival benefits and a higher quality of life for patients.

Case presentation

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 Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patients for publication of this case

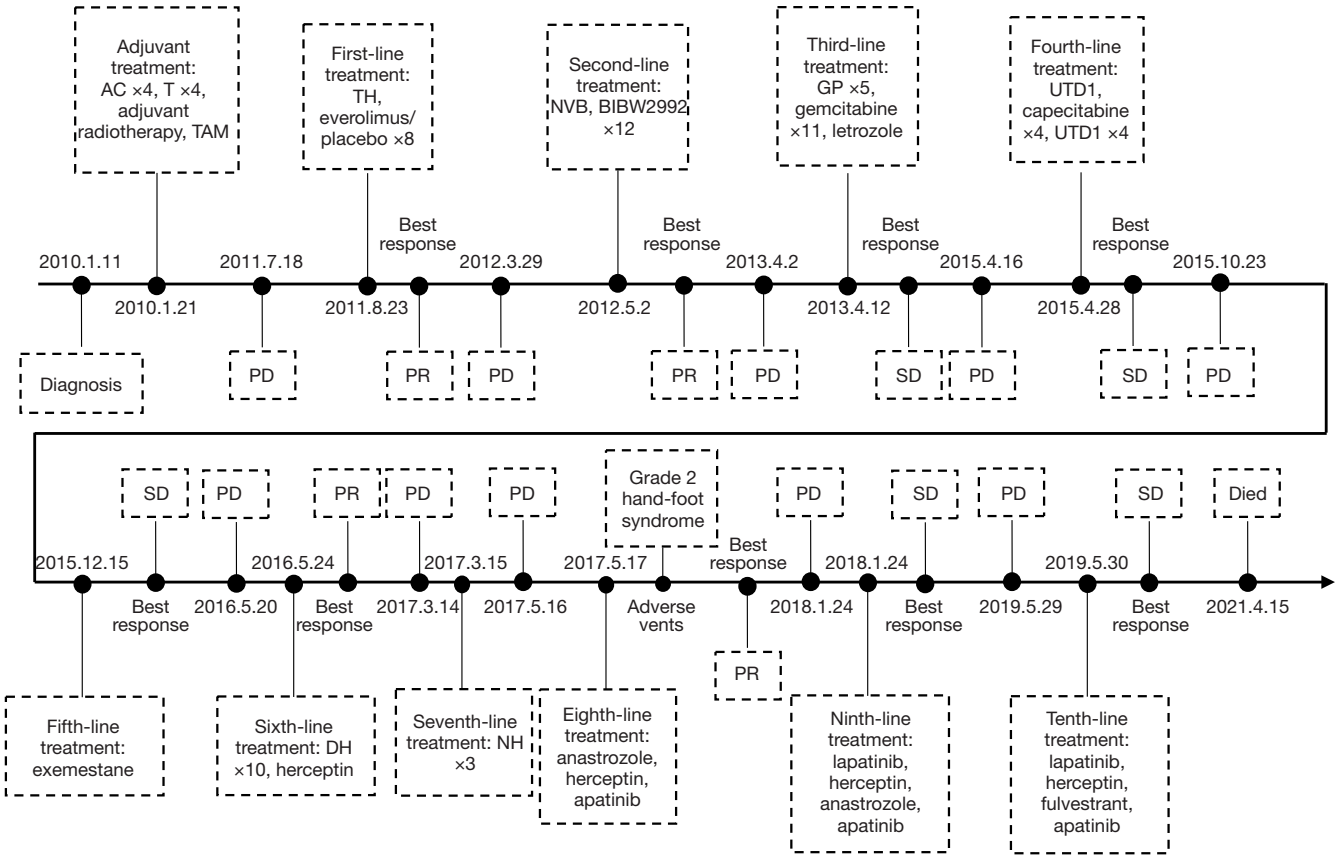

Figure 1 Timeline of the patient management for Case 1. AC, CTX, THP; CTX, cyclophosphamide; THP, pirarubicin; T, paclitaxel; TAM, tamoxifen; TH, taxol, herceptin; NVB, vinorelbine; GP, gemcitabine, DDP; DDP, cisplatin; UTD1, utidelone; DH, docetaxel, herceptin; NH, NVB, herceptin; NA, not applicable; PR, partial response; SD, stable disease; PD, progressive disease; PFS, progression-free survival.

report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Case 1

The patient management is described in *Figure 1*. A 52-year-old female patient underwent a modified radical mastectomy for right breast cancer on January 11, 2010. The postoperative pathological report revealed a right breast invasive ductal carcinoma. The tumor was 5.2 cm × 3.5 cm × 3.5 cm in size and classified histologically as grade III with 15/29 right axilla lymph nodes involved. The nipple, skin incision, and basal margin were negative. Immunohistochemistry (IHC) showed estrogen receptor (ER) (+), progesterone receptor (+), HER2 (+++), and Ki-67 (+). After surgery, she received "AC" regimen chemotherapy for four cycles [cyclophosphamide (CTX) 500 mg/m^2 d1 + pirarubicin (THP) 60 mg/m^2 d1 q3w] and was sequenced to four cycles of "T" chemotherapy (paclitaxel 175 mg/m^2 d1 q2w). From July 14, 2010, to August 19, 2010, adjuvant radiotherapy was performed. After that, the patient started endocrine therapy with "tamoxifen (TAM) 10 mg bid" from August 20, 2010, until July 27, 2011. However, on July 11, 2011, a computed tomography (CT) scan showed intrahepatic space occupation, suspected to be metastases. On July 18, 2011, CT results from another hospital showed progressive disease (PD) had occurred in the liver. On August 4, 2011, the patient was enrolled in a clinical trial (CRAD001J2301/TRIO-CIRG019) of everolimus combined with trastuzumab and paclitaxel as first-line therapy. From August 23, 2011, to March 28, 2012, eight cycles of "taxol + herceptin (TH) + everolimus/placebo" chemotherapy were performed. After six cycles, the therapeutic evaluation was partial response (PR). However, CT showed PD on March 29, 2012, indicating a

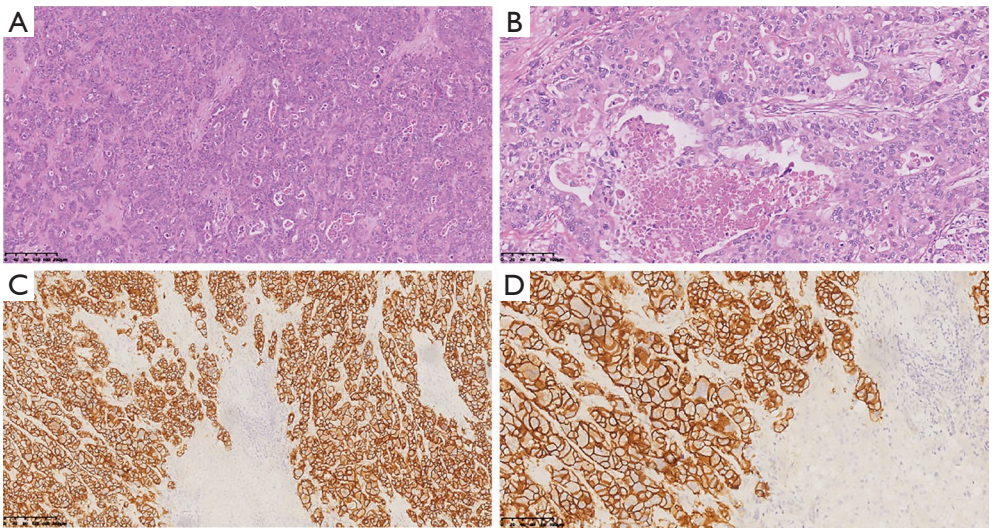

Figure 2 Pathological images for Case 1. The major histological type was (right liver) poorly differentiated adenocarcinoma with degeneration. (A) Hematoxylin and eosin staining. Magnification, ×10. (B) Hematoxylin and eosin staining. Magnification, ×20. IHC grading is 3+. (C) Immunohistochemical staining for HER2 in the adenocarcinoma. Magnification, ×10. (D) Immunohistochemical staining for HER2 in the adenocarcinoma. Magnification, ×20. IHC, immunohistochemistry; HER2, human epidermal growth factor receptor 2.

progression-free survival (PFS) of 7.3 months. On May 2, 2012, the patient participated in a clinical trial (LUX-BREAST 1) of BIBW2992 + vinorelbine (NVB) *vs.* trastuzumab + NVB in the treatment of metastatic HER2 overexpressed breast cancer patients who had failed previous trastuzumab treatment. Our patient was randomized to the NVB + BIBW2992 group. The patient received second-line chemotherapy from May 2, 2012, to March 7, 2013, with a best response of PR. Unfortunately, after 12 cycles of chemotherapy, the CT examination on April 2, 2013, revealed that PD persisted in the liver, with a PFS of 11.1 months. Anti-HER2-targeted therapy was refused by the patient due to economic concerns. Subsequently, five cycles of "gemcitabine and cisplatin (DDP) (GP)" chemotherapy were performed from April 12, 2013, to July 10, 2013. A gemcitabine needle (1.8 g d1, 8 + DDP 40 mg d1–2/50 mg d3) was used intravenously. Subsequently, the reexamination of the patient's condition indicated stable disease (SD). Due to the decreased tolerance to chemotherapy, "DDP" chemotherapy was suspended from August 2, 2013, to May 13, 2014, and 11 cycles of "gemcitabine needle 1.8 g d1, 8" chemotherapy was resumed. The re-inspection after seven cycles of chemotherapy suggested SD. After that, she received sequenced maintenance endocrine therapy with "letrozole tablets 2.5 mg qd" from June 11, 2014. On April 16, 2015, the reexamination showed that the liver lesions were enlarged (low-density lesions in the anterior segment of the right liver were larger than before), and her condition was considered PD, producing a PFS of 24.5 months. She again refused anti-HER2-targeted therapy due to economic reasons and enrolled in the "phase III clinical study of utidelone (UTD1) injection combined with capecitabine in the treatment of patients with advanced metastatic breast cancer" on April 27, 2015. She was randomized to the UTD1 combined with capecitabine treatment group. From April 28, 2015, to July 03, 2015, the patient received four cycles of "capecitabine 1.5 g in the morning and 2 g in the evening, d1–14, or capecitabine 1.5 g, bid d1–14, and UTD1 56.9 mg/44.93 mg/35.1 mg, intravenous injection, d1–15". After two cycles, the reexamination indicated SD. From July 22, 2015, to September 24, 2015, chemotherapy of "UTD1 35.1 mg d1–5 intravenous injection" was given in the 5th, 6th, 7th, and 8th cycles. On October 23, 2015, after eight cycles of chemotherapy, the reexamination indicated that the metastatic lesion in the liver was enlarged. The therapeutic evaluation was PD, and the PFS was 5.9 months. Subsequently, the patient underwent "laparotomy resection of liver cancer + cholecystectomy" on October 30, 2015. Postoperative pathology showed a poorly differentiated adenocarcinoma of the right liver with degeneration. IHC suggested ER (local lesion+), hepa/

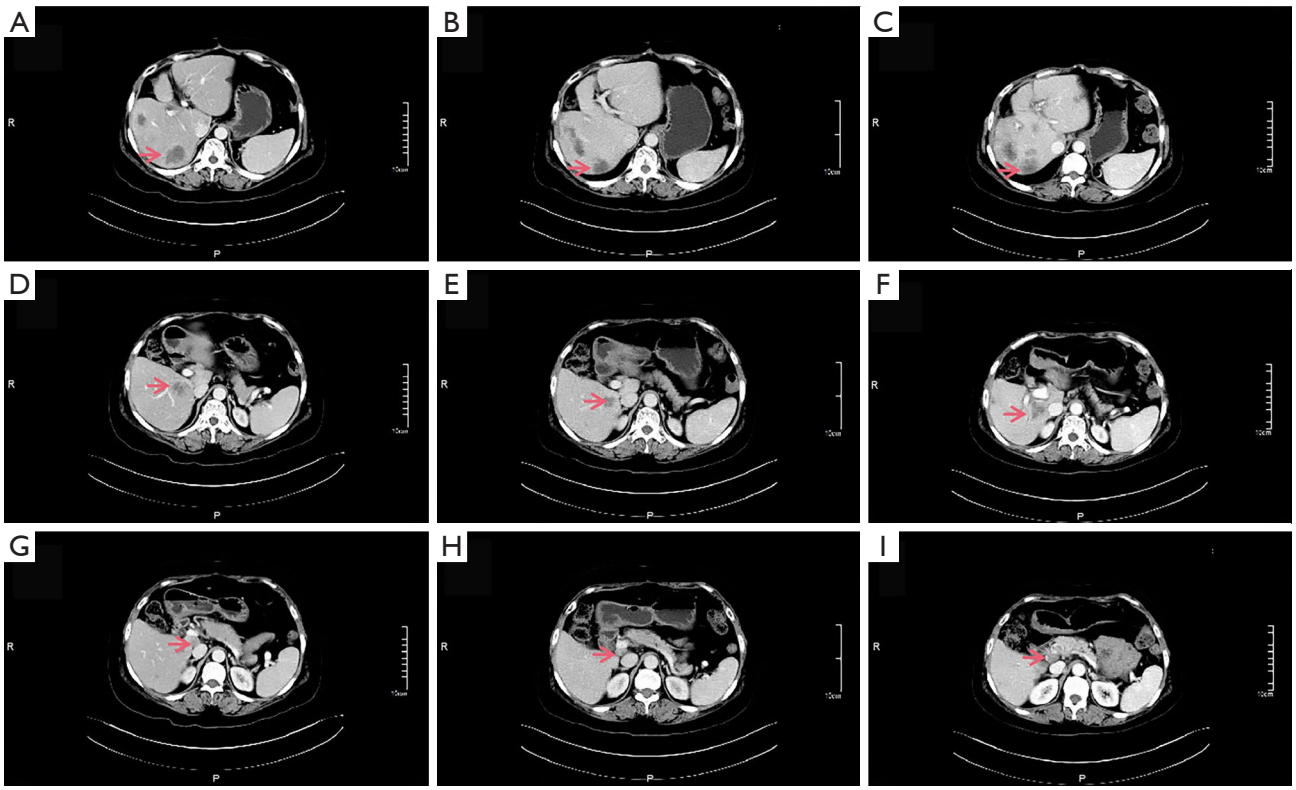

Figure 3 Case 1. On May 16, 2017, before "anastrozole, herceptin, apatinib" treatment. (A) Liver lesion (4.1×3.0 cm^2); (D) liver lesion (3.0×2.0 cm^2); (G) retroperitoneal lymph node lesion (2.7×1.8 cm^2). On July 18, 2017, after "anastrozole, herceptin, apatinib" treatment, CT showed partial response. (B) Liver lesion reduced to 2.6×1.7 cm^2; (E) liver lesion reduced to 2.0×1.8 cm^2; (H) retroperitoneal lymph node lesion reduced to 2.0×1.1 cm^2. On January 24, 2018, disease progressed. (C) Liver lesion increased to 2.9×2.3 cm^2; (F) liver lesion increased to 3.0×2.3 cm^2; (I) retroperitoneal lymph node lesion reduced to 2.1×1.7 cm^2. The arrows indicate lesions in the liver and retroperitoneal lymph nodes. CT, computed tomography.

hepatocyte (–), alpha fetoprotein (AFP) (–), progesterone receptor (–), HER2 (3+), and GATA-3 (+) (*Figure 2*). On December 12, 2015, a CT scan indicated PD. Anti-HER2 targeted therapy was recommended, but the patient was temporarily unable to accept the treatment due to financial difficulties. She received sequenced maintenance endocrine therapy with "exemestane 25 mg qd" from December 15, 2015, to May 20, 2016. However, on May 20, 2016, the CT results showed PD was present in the liver and retroperitoneal lymph nodes, producing a PFS of 5.2 months. Later, the patient was treated with ten cycles of a DH regimen (docetaxel 130 mg d1, herceptin) from May 24, 2016, to November 30, 2016. The best response was PR. She subsequently received sequenced maintenance targeted therapy with "herceptin 6 mg/kg q3w" until February 23, 2017. Unfortunately, PD was detected on March 14, 2017, with a PFS of 9.8 months. She started a new chemotherapy regimen of NH (NVB 47 mg d1, 8, herceptin) for three cycles from March 15, 2017, to May 3, 2017. A CT scan on May 16, 2017, showed multiple hepatic metastases with most lesions more progressed than before, but the left liver lesion was smaller. The hepatic portal and retroperitoneal lymph nodes were enlarged, similar to the previous investigations. The results indicated PD, with a PFS of 2.1 months (*Figure 3*). The patient refused further chemotherapy and lapatinib treatment. In accordance with the patient's wishes, she was treated with "anastrozole tablets 1 mg qd + herceptin 6 mg/kg q3w d1 + apatinib 250 mg qd" from May 17, 2017. After 3 weeks of treatment, the patient developed grade 2 hand-foot syndrome related to the apatinib treatment, and apatinib was suspended for 1 week. On June 7, 2017, the hand-foot syndrome improved, and the patient continued treatment with the original protocol. Surprisingly, a CT reexamination on July

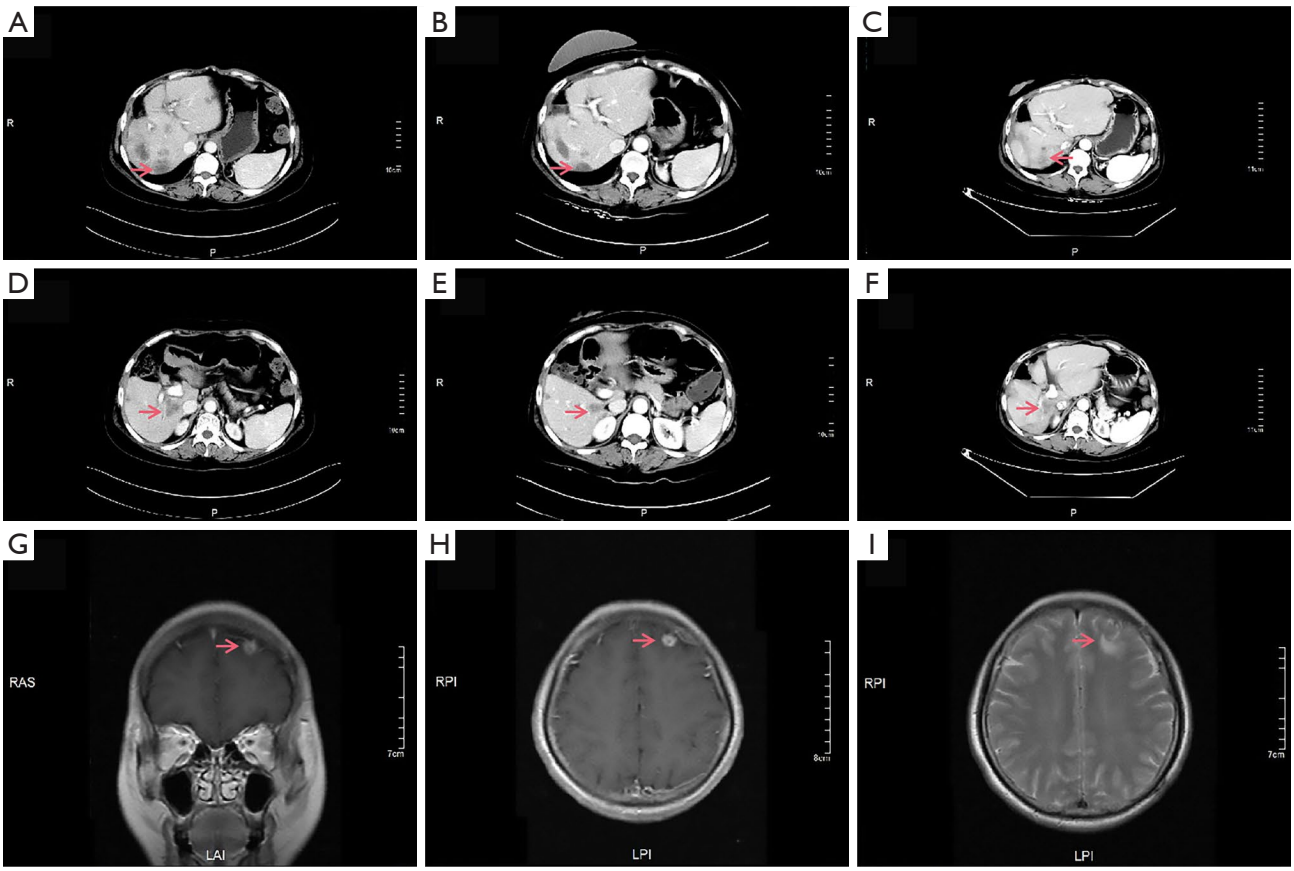

Figure 4 Case 1. On January 24, 2018, before "anastrozole, lapatinib, herceptin and apatinib" treatment. (A) Liver lesion increased to 2.9×2.3 cm^2; (D) liver lesion (3.0×2.3 cm^2). On April 17, 2018, after "anastrozole, lapatinib, herceptin and apatinib", SD. (B) Liver lesion (2.5×1.6 cm^2); (E) liver lesion (2.3×1.7 cm^2). On May 29, 2019, the disease progressed. (C) Liver lesion (2.8×2.1 cm^2); (F) liver lesion (2.5×1.7 cm^2); (G-I) brain lesion (1.0×0.9 cm^2). The arrows indicate lesions in the liver and brain. SD, stable disease.

18, 2017, showed that the liver and retroperitoneal lymph node lesions were smaller than before. The best response was PR (*Figure 3*). She continued to receive this endocrine and targeted therapy until January 24, 2018. However, on January 24, 2018, due to the discovery of increased liver lesions, the patient was changed to a therapy regimen of "anastrozole tablets 1 mg qd, lapatinib, herceptin, and apatinib 250 mg qd" until May 29, 2019, producing a PFS of 8.4 months (*Figures 3*,*4*). A recheck on April 17, 2018, suggested that the liver lesion was slightly smaller than before, and the therapeutic evaluation was SD (*Figure 4*). Unfortunately, a CT on May 29, 2019, showed further enlargement of the liver lesions, and a magnetic resonance imaging (MRI) scan found a lesion in the brain. These indicated that the disease had progressed, and the PFS was 16.3 months (*Figure 4*). Later, the patient underwent targeted therapy combined with endocrine therapy of "lapatinib, herceptin, fulvestrant 500 mg q4w, and apatinib 250 mg qd" from May 30, 2019, to September 10, 2019. The disease was stable during this period. On September 10, 2019, a CT scan showed that the lesions remained similar in size to the previous examination, indicating SD. Abnormal liver function occurred on September 10, 2019. The patient complained of right upper abdominal pain with an NRS score of 2 points, diarrhea, and watery stools 2–3 times a day. The patient was treated with liver protection and jaundice reduction in the Department of Hepatopathy. Later, the patient took Chinese medicine orally at home by herself, but the details were unknown. Unfortunately, our follow-up found that the patient passed

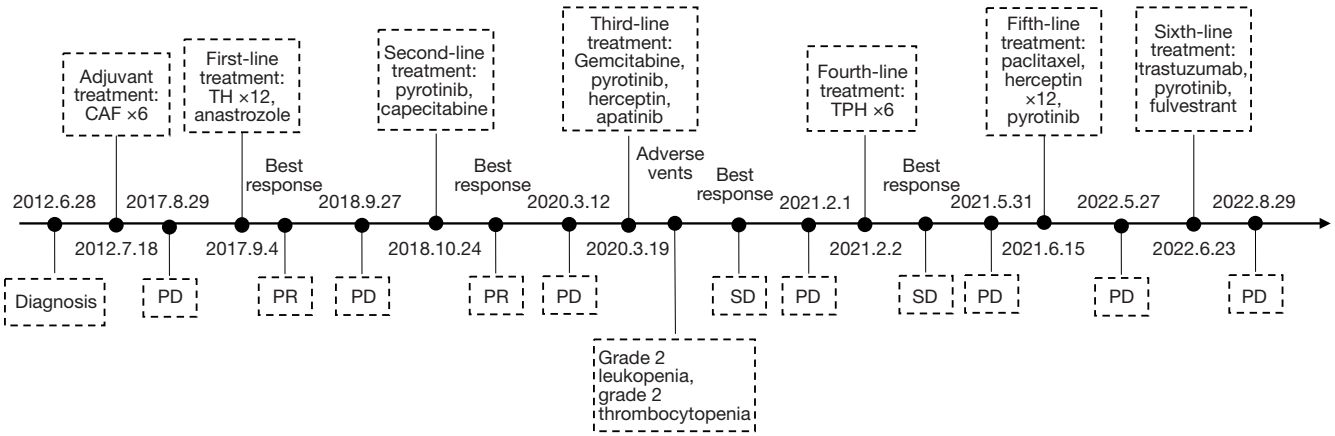

Figure 5 Timeline of the patient management for Case 2. CAF, CTX, THP, fluorourail; CTX, cyclophosphvnamide; THP, pirarubicin; TH, taxol, herceptin; TPH, paclitaxel, pertuzumab, trastuzumab; PR, partial response; SD, stable disease; PFS, progression-free survival.

away on April 15, 2021, and the PFS was 22.9 months.

Case 2

The patient management is described in *Figure 5*. A 64-year-old female patient underwent modified radical mastectomy for left breast cancer on June 28, 2012. The pathological diagnosis was invasive ductal carcinoma of the left breast, grade II. None of the 17 left axillary lymph nodes or 5 axillary lymph nodes showed metastasis. The results of IHC suggested ER (–), progesterone receptor (–), HER2 (2+), and Ki-67 (+20%). A fluorescence in situ hybridization (FISH) test revealed HER2/CEP17 >2.2, and the HER2 gene ratio was positive. The diagnosis showed postoperative left breast cancer, pT2N0M0, stage IIA, and HER2 positive type. From July 18 to November 13, 2012, six cycles of CAF regimen were administered [CTX 0.8 g d1 + THP 40 mg d1 + fluorouracil 0.5 g d1, 2.0 g continuous intravenous infusion (CIV) 48 h]. After chemotherapy, the patient did not receive herceptin, radiotherapy, or endocrine therapy, preferring to take Chinese medicine for more than 2 years by herself with breast and abdominal ultrasound checks every 6 months. A CT plain chest scan in her local hospital on August 12, 2017, revealed multiple metastases in both lungs. Moreover, there were multiple hypodense patchy shadows of varying sizes with unclear borders in the liver, indicative of metastases. Pathological consultation in our hospital on August 22, 2017, showed left invasive ductal carcinoma of the breast, grade II, and 19 lymph nodes (left axilla) with chronic inflammation. The nipple and base were negative. IHC showed HER2 (3+), ER (–), progesterone receptor (–), epidermal growth factor receptor (EGFR) (–), and Ki-67 (individual+). On August 29, 2017, a CT scan of her chest and abdomen indicated PD. Pathology of the left liver puncture performed on September 1, 2017, showed poorly differentiated carcinoma with degeneration and necrosis in the fibrous tissue. IHC showed HER2 (3+), ER (++, 80 %), progesterone receptor (++, 70%), EGFR (+), Ki-67 (+, 30 %), AFP (–), hepa/hepatocyte (–), and GATA-3 (+) (*Figure 6*). From September 4, 2017, to May 3, 2018, 12 cycles of TH regimen (paclitaxel 116 mg d1, 8 + herceptin 300 mg d1) chemotherapy were given. Reexamination showed the response was continuous PR. Due to poor chemotherapy tolerance after the 12 cycles of chemotherapy, she received sequenced maintenance endocrine therapy with "anastrozole 1 mg qd" from May 11, 2018, to September 27, 2018. Reexamination with an enhanced brain MRI on September 27, 2018, suggested PD, producing a PFS of 12.9 months. From October 8, 2018, to October 19, 2018, whole-brain radiotherapy was performed. On October 23, 2018, a CT scan showed PD. On October 24, 2018, "pyrotinib (400 mg qd) + capecitabine 1.50 g BID d1–14, discontinued for 1 week" were administered. On November 15, 2018, reexamination with an enhanced brain MRI showed multiple metastases in the brain parenchyma, some of which were smaller than the last time. The best response was PR. However, a recheck with an enhanced brain MRI on March 12, 2020, showed that the intracranial metastases were larger than before. Both CT and enhanced MRI revealed PD, producing a PFS of 16.8 months (*Figure 7*). From March 19, 2020, the patient was switched to gemcitabine (1.4 g d1) chemotherapy combined with

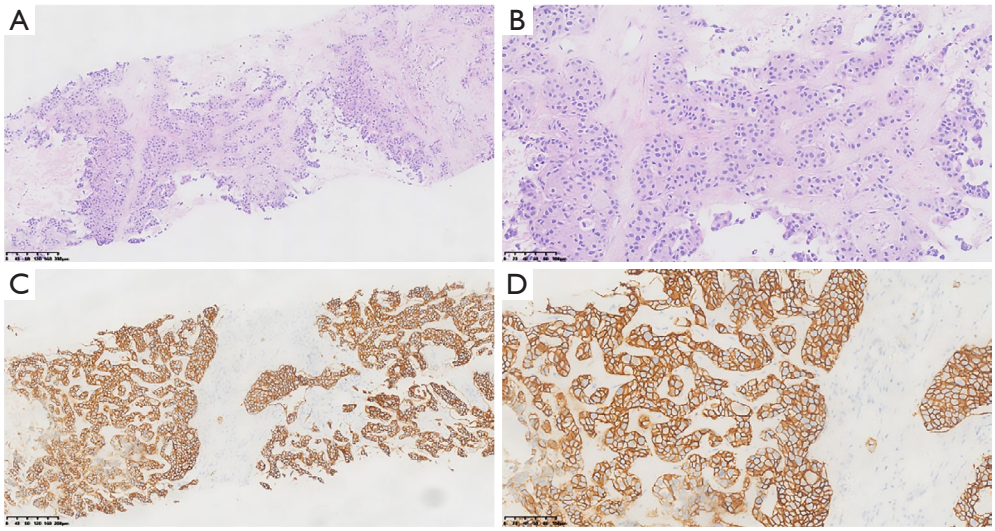

Figure 6 Pathological images for Case 2. The major histological type is (left) invasive ductal carcinoma of the breast. (A) Hematoxylin and eosin staining. Magnification, ×10. (B) Hematoxylin and eosin staining. Magnification, ×20. IHC grading is 3+. (C) Immunohistochemical staining for HER2 in the invasive ductal carcinoma. Magnification, ×10. (D) Immunohistochemical staining for HER2 in the invasive ductal carcinoma. Magnification, ×20. IHC, immunohistochemistry; HER2, human epidermal growth factor receptor 2.

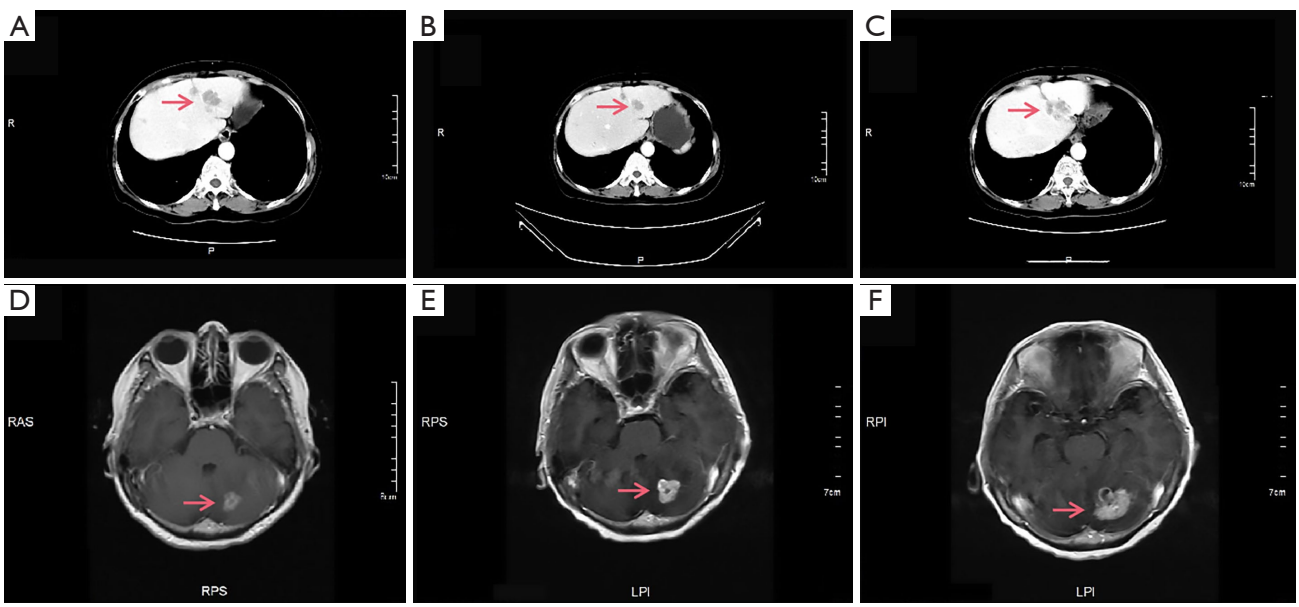

Figure 7 Case 2. On March 12, 2020, before "gemcitabine, pyrotinib, herceptin, apatinib" treatment. (A) Liver lesion (2.5×1.9 cm^2); (D) brain lesion (1.6×1.4 cm^2). On July 30, 2020, after "gemcitabine, pyrotinib, herceptin, apatinib" treatment, SD. (B) Liver lesion (2.5×1.8 cm^2); (E) brain lesion (1.8×1.5 cm^2). On February 1, 2021, the disease progressed. (C) The liver lesion increased to 3.5×2.5 cm^2; (F) the brain lesion increased to 2.7×2.5 cm^2. The arrows indicate lesions in the brain and liver. SD, stable disease.

targeted therapy of pyrotinib (400 mg qd), apatinib (250 mg qd), and herceptin (376 mg d1). Grade 2 leukopenia and grade 2 thrombocytopenia occurred after chemotherapy, the patient discontinued chemotherapy on the 8th day of the first cycle and blood picture recovered after symptomatic treatment. Both curative effects after the 2nd and 4th cycles

of reexamination were SD. The patient was rechecked on July 30, 2020, with both CT and MRI showing SD (*Figure* 7). On February 1, 2021, an abdominal CT and enhanced brain MRI showed PD, with a PFS of about 10.6 months (*Figure* 7). After that, six cycles of a TPH regimen (paclitaxel injection 180 mg d1, 8, pertuzumab 420 mg d1 + herceptin 300 mg d1) were given from February 2, 2021, to May 31, 2021. After two cycles, the therapeutic evaluation was SD. Because the CT showed PD, a new targeted therapy (paclitaxel 180 mg d1, herceptin 300 mg d1, pyrotinib 400 mg qd) was administered from June 15, 2021, to April 11, 2022 Unfortunately, on May 27,2022, a subsequent MRI showed PD. We changed the therapy to trastuzumab 372 mg + pyrotinib 400 mg qd + fulvestrant 500 mg d1, 14 from June 23, 2022, to August 29, 2022. A recheck on August 29, 2022, showed PD, with a PFS of 2.2 months.

Discussion

HER2 is a transmembrane tyrosine kinase molecule of the HER family, encoded by the HER2 gene. HER2 forms homo- or heterodimer together with other members of the HER family, such as EGFR, HER3, and HER4, to activate downstream signaling pathways that lead to cell proliferation and angiogenesis (11,12). It has been found that HER2 overexpression is associated with VEGF upregulation and may activate downstream angiogenic signaling pathways, such as the PI3K-AKT and Ras-MAPK pathways (13-15). In addition, HER2 amplification may positively correlate with the expression of VEGF protein and mRNA (14). In this way, VEGF expression may be increased with the continuous growth of the tumor vasculature (16). It is well-established that angiogenesis plays a significant role in the growth and metastasis of breast carcinoma (17,18), and VEGF/VEGFRs serve as regulating effects during angiogenesis (10). The clinical application of anti-angiogenesis therapies in breast cancer is likely to be a promising option (19,20).

Trastuzumab (herceptin) is a humanized HER2-targeted monoclonal antibody (mAb) that is approved for the treatment of HER2-overexpressed breast cancer. Trastuzumab has more than one antitumor mechanism. Trastuzumab may achieve anti-HER2 therapy by inhibiting HER2 shedding (13). Bevacizumab is a mAb that blocks the VEGF axis (21). It has been suggested that bevacizumab combined with chemotherapy provides a benefit in prolonging PFS in metastatic breast cancer (22). Lapatinib was the first TKI approved for use in HER2-positive advanced breast cancer (2,23). Lapatinib is a reversible TKI capable of blocking both EGFR and HER2. It also prevents the activation of phosphorylation and receptor actions (11). By preventing the activation of HER2-dependent downstream signaling pathways, such as MAPK and PI3K/AKT, it thereby reduces cancer cell growth and proliferation (13). Apatinib is a new oral TKI that selectively inhibits VEGFR2. It also can reduce the density of tumor microvessels and the proliferation level of vascular endothelial cells, thus inhibiting tumor angiogenesis (24,25). Studies have shown that apatinib has a good antitumor effect and controllable toxicity in metastatic breast cancer (26,27).

Although anti-HER2 targeted therapy has had a good effect on patients with HER2-positive breast cancer, disease progression can occur because of drug resistance (28). We speculated that the patient developed disease progression due to HER2 resistance. VEGFR is a key regulator of the tyrosine kinase signaling pathway. The patient received anti-angiogenic therapy, blocking VEGFR2, which inhibited the migration and proliferation of vascular endothelial cells to achieve the antitumor effects (20). It has been showed that dual blockade of VEGFR1 and VEGFR2 can prevent VEGF-driven metastasis by regulating PI3K/AKT and MAPK/ERK1/2 signaling pathways. In trastuzumab-resistant HER2-positive breast cancer, the resistance pathway includes the PI3K/AKT pathway, similar to the angiogenic blocking pathway (5,29). In a preclinical mouse model of HER2-amplified breast cancer brain metastasis, combined targeted anti-HER2 and anti-VEGFR2 therapy can significantly inhibit tumor growth and prolong survival (30). Study suggested anti-angiogenesis may have better value in metastatic breast cancer patients treated with trastuzumab. The expression of VEGFR may be a useful predictor of survival in HER2-positive breast cancer patients (31). Moreover, it has been shown that in HER2-positive breast cancer, chemotherapy combined with trastuzumab followed by bevacizumab has a higher overall survival (OS) and recurrence-free survival (RFS) compared with chemotherapy combined with trastuzumab, and they had similar pathologic complete response (pCR) rates. This suggests a synergistic antitumor effect of bevacizumab and trastuzumab (32). Studies have confirmed that anti-VEGF therapy can enhance antitumor activity (33). One study showed that apatinib reversed acquired resistance to pyrotinib in advanced HER2-positive

gastric cancer. Furthermore, pyrotinib and apatinib have synergistic antitumor effects (34).

In Case 1, the disease progressed after multi-line treatment, and the patient was administered apatinib combined with anti-HER2 therapy. A CT reexamination revealed that the lesion was smaller than before, and the best efficacy evaluation was PR. Similarly, our Case 2 patient was given apatinib combined with anti-HER2 treatment after multi-line therapy, and the best curative effect was SD. During apatinib treatment, both patients suffered adverse reactions, such as hand-foot syndrome, thrombocytopenia, and leukopenia, and the dosage was adjusted according to the symptoms. Adverse events were improved after control. Thus, apatinib may still provide a good clinical benefit in patients who develop HER2 resistance after multi-line therapy.

These two cases were both advanced HER2-positive patients who demonstrated resistance to multi-line anti-HER2 therapy. Apatinib combined with anti-HER2-targeted therapy achieved good clinical benefits. We speculate that apatinib may reverse HER2 resistance and benefit patients. However, further research is needed to verify these findings.

Conclusions

Apatinib may effectively inhibits tumor neovascularization by the highly selective inhibition of VEGFR2, thereby reversing HER2 resistance. The antitumor mechanism of apatinib needs further study to achieve targeted treatment. Exploring the combination of apatinib and other anti-HER2 targeted drugs may bring better survival benefits and a higher quality of life for patients.

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Footnote

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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 Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patients 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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