Patient with hormone receptor-positive Her2-negative metastatic breast cancer with visceral crisis with good response to abemaciclib and letrozole: A case report and review of the literature

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Abstract. Combined chemotherapy is typically the preferred treatment for patients with hormone receptor-positive (HR+)/human epidermal growth factor receptor 2-negative (HER2-) metastatic breast cancer (MBC) experiencing a visceral crisis. However, the emergence of cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) has introduced a potential alternative: The combination of CDK4/6i with endocrine therapy (ET). The present study reported a case of HR+/HER2-MBC with extensive liver and bone metastases who responded well to abemaciclib and letrozole. The patient achieved a rapid partial response and continuous clinical stabilization and the progression-free survival of this patient reaches 30 months and counting. Furthermore, the side effects were manageable and no dose reductions were necessary during treatment. These findings suggest that the combination of CDK4/6i and ET in the treatment of HR+/HER2-advanced breast cancer cannot be underestimated.

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Abbreviations: ABC, advanced breast cancer; CA125, carbohydrate antigen 125; CDK4/6i, cyclin-dependent kinase 4/6 inhibitors; CEA, carcinoembryonic antigen; CT, computed tomography; DFS, disease-free survival; ER, estrogen receptor; ET, endocrine therapy; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemical; MBC, metastatic breast cancer; OS, overall survival; PFS, progression-free survival; PR, progesterone receptor; TTR, time to response

Key words: case report, breast cancer, visceral crisis, CDK4/6 inhibitor, endocrine therapy

Introduction

Hormone receptor-positive (HR+)/human epidermal growth factor receptor 2-negative (HER2-) breast cancer is the most common subtype of metastatic breast cancer (MBC), accounting for ~65% of all cases (1). The development of cyclin-dependent kinase 4/6 (CDK4/6) is crucial in HR+ breast cancer onset, survival and progression, facilitating the G1-to-S phase cell cycle transition (2,3). CDK4/6 inhibitors (CDK4/6i) block this pathway by inhibiting phosphorylation of tumor suppressor retinoblastoma protein, preventing tumor cell proliferation and inducing G1 phase arrest (4,5). In combination with endocrine therapy (ET), CDK4/6i have demonstrated benefits in terms of overall survival (OS) and progression-free survival (PFS) in several clinical trials, both as the first- and second-line therapies (6-14). As a result, CDK4/6i combined with ET has become the standard treatment for HR+/HER2-advanced breast cancer (ABC) (15-17).

However, chemotherapy remains the preferred option for patients with HR+/HER2-MBC experiencing rapid tumor progression or a high tumor burden, such as visceral crisis (15-18). Visceral crisis is defined as severe organ dysfunction characterized by rapid symptom progression, complaints and laboratory abnormalities. Chemotherapy is often required to achieve a quick response and provide relief within a limited timeframe. However, the side effects of chemotherapy can be significant. Meanwhile, the time-to-response (TTR) for CDK4/6i combined with ET has become much shorter than for hormone monotherapy, presenting a treatment dilemma for cases of metastatic HR+/HER2-breast cancer with visceral crisis (8-14).

The present study reported the case of a patient with HR+/HER2-MBC diagnosed in 2021 who presented with multiple lymph node, liver and bone metastases. The patient had a disease-free survival (DFS) period of 11 years before relapse occurred 3 years after the discontinuation of adjuvant ET. Due to severe liver function and a poor general condition, chemotherapy was deemed to likely worsen the patient's condition. Given the patient's prior positive response to ET, CDK4/6i combined with ET was chosen as the first-line treatment, even in the presence of visceral crisis. Considering drug

availability, abemaciclib plus letrozole were administered. The patient's condition improved rapidly and remained stable for >30 months. At the same time, side effects were well-tolerated and the patient's quality of life was enhanced.

Case presentation

A 37-year-old woman underwent a left breast-modified radical mastectomy for breast cancer in February 2010 at the Affiliated Hospital of Qingdao University (Qingdao, China). Pathological examination revealed invasive ductal carcinoma (histological grade II; tumor size, 1.2x1.0x1.0 cm) with no axillary lymph node metastasis. The pathological stage was pT1cN0M0, stage IA, based on the eighth edition of the Cancer Staging Manual for Breast Cancer by the American Joint Committee on Cancer (19). The pathological assessments were performed in the Affiliated Hospital of Qingdao University (Qingdao, China). Immunohistochemical analysis was performed on formalin-fixed, paraffin-embedded tissue sections using standard procedures for tumor specimens. ER, PR and HER2 status and the Ki-67 index were evaluated by two experienced pathologists from the Department of Pathology independently. Immunohistochemical (IHC) results showed estrogen receptor (ER) (+), progesterone receptor (PR) (+), HER2 (0) and Ki67 (25%) (IHC antibody information and images are not available due to the interval of more than 13 years). The patient received four cycles of adjuvant chemotherapy with docetaxel and epirubicin and ET with tamoxifen (from March 2010 to December 2018). Radiotherapy was not administered postoperatively and ET had been discontinued for >3 years before relapse occurred.

In December 2021, the patient presented to the emergency department of the Affiliated Hospital of Qingdao University (Qingdao, China) with abdominal pain, distension, mild dyspnea and joint pain, accompanied by significant physical weakness, with an Eastern Cooperative Oncology Group performance score of 2 (20). Physical examination revealed hepatomegaly. Computed tomography (CT) scans showed pleural effusion, lymphangitis carcinomatosis, bone metastases and liver metastases (Fig. 1A). Multiple suspected enlarged lymph nodes were detected in the mediastinum, as well as supraclavicular and infraclavicular fossae. Laboratory tests indicated elevated serum levels of carbohydrate antigen 125 (CA125; 151.00 U/ml; normal range, 0-35 U/ml), carcinoembryonic antigen (CEA; 216.00 U/ml; normal range, 0-3.4 U/ml), aminotransferase and bilirubin. Glutamic oxaloacetic transaminase was 477.00 U/l (normal range, 14-36 U/l) and alanine aminotransferase was 433.00 U/l (normal range, 9-52 U/l). Bilirubin was 119.73 μmol/l (normal range, 3-22 μmol/l), with no biliary obstruction evident on CT. No metastasis was detected in other organs. A CT-guided liver biopsy was performed in December 2021, confirming metastatic breast invasive ductal carcinoma. IHC results showed ER (+) (cat. no. 790-4325, sp1), PR (+) (cat. no. 790-4296, IE2), HER2 (1+) (cat. no. 790-4493, 4B5) and Ki67 (20%) (cat. no. 790-4286, 30-9; all from Roche Diagnostics).

Given the patient's DFS of >10 years and poor liver function precluding chemotherapy, abemaciclib plus letrozole was set as the first-line treatment, despite the patient's visceral crisis. Abemaciclib 100 mg was administered twice daily and letrozole was added ~2 weeks after a slight improvement in liver function. Zoladex (a goserelin implant) was administered for ovarian function suppression and denosumab for bone protection.

After 21 days of treatment, the patient's chest tightness and shortness of breath improved, and CT scans showed decreased pleural effusion and volume-reduced lymph nodes (Fig. S1). From the second treatment cycle, the abemaciclib dose was increased to 150 mg twice daily. After two treatment cycles, the number and volume of multiple hepatic metastases decreased significantly (Fig. 1B). The patient's serum glutamic oxaloacetic transaminase and alanine aminotransferase levels normalized within 10 days, and elevated bilirubin levels returned to normal within 40 days (Table SI). Serum CA-125 levels normalized after 2 months of treatment and have since then remained within the normal range. The patient's serum CEA levels continued to decrease slightly throughout the treatment (Fig. 2), indicating ongoing therapeutic efficacy. Regular enhanced CT examination of the neck, chest, upper abdomen, lower abdomen and pelvic cavity was performed every 2-3 months (Fig. 1C). Pleural effusion decreased and resolved within 3 months, and multiple enlarged lymph nodes shrunk significantly. No signs of lymphangitis carcinomatosis were seen on a recent CT scan (June 2024). Regular whole-body scans every 12 months showed that bone metastasis remained stable and no signs of brain metastasis were observed on craniocerebral MRI. In addition, the patient's general condition improved significantly shortly after the start of treatment, and the patient's self-described quality of life (as determined from patient self-statements at the average monthly outpatient visit) was maintained. The toxicity of abemaciclib plus letrozole was tolerable and mild neutropenia occurred. Mild diarrhea occurred in February 2022 and was controlled with drugs. No dose reduction of abemaciclib was required throughout the treatment. Recent examinations (April 2024) indicated stable liver metastases (Fig. 1D) and normal glutamic oxaloacetic transaminase, alanine aminotransferase and bilirubin. The patient's PFS has reached 30 months (Fig. 3).

Discussion

ET is generally recommended for patients with HR+/HER2-MBC unless hormonal resistance is suspected or visceral crisis is present. Visceral crisis is characterized by rapid disease progression and severe organ dysfunction due to multiple metastases, such as in the liver, bone marrow or lungs. Almost all guidelines for the diagnosis and treatment of breast cancer recommend chemotherapy as the preferred choice for ABC in the presence of visceral crisis (17,18,21). Chemotherapy is expected to provide more timely disease relief and higher response rates (RR) than ET. However, higher toxicity and other adverse effects are unavoidable.

CDK4/6i have achieved promising therapeutic outcomes in patients with HR+/HER2-ABC, offering new potential treatment strategies (22). Furthermore, CDK4/6i-based therapy elicits an objective response within 3 months of treatment initiation in most responders (23,24). However, the lack of head-to-head studies comparing first-line CDK4/6i plus ET with combined chemotherapy in patients with HR+/HER2-breast cancer with visceral crisis hinders its application in this context.

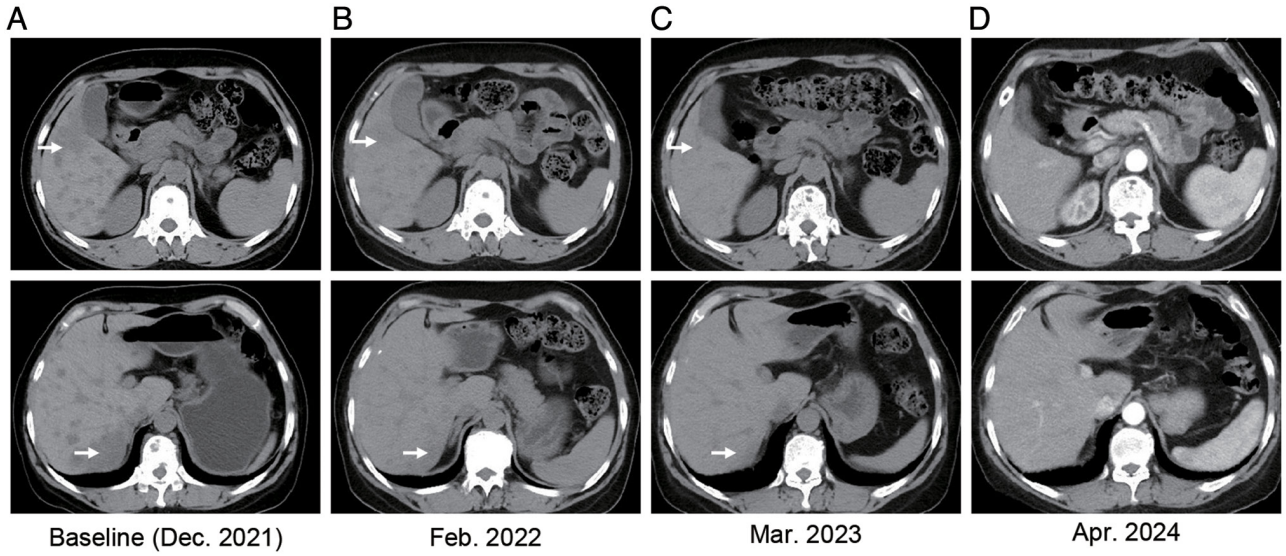

Figure 1. Changes of liver metastases in CT scanning images during the treatment of abemaciclib plus letrozole. Arrows indicate two main areas of liver metastases at different scan levels (upper and lower panels). (A) The baseline of liver metastases at the beginning of abemaciclib and letrozole (December 2021). (B) After two cycles of treatments, both the number and volume of multiple hepatic metastases exhibited marked decreases (February 2022). (C) Liver metastasis in March 2023. (D) Liver metastasis in April 2024.

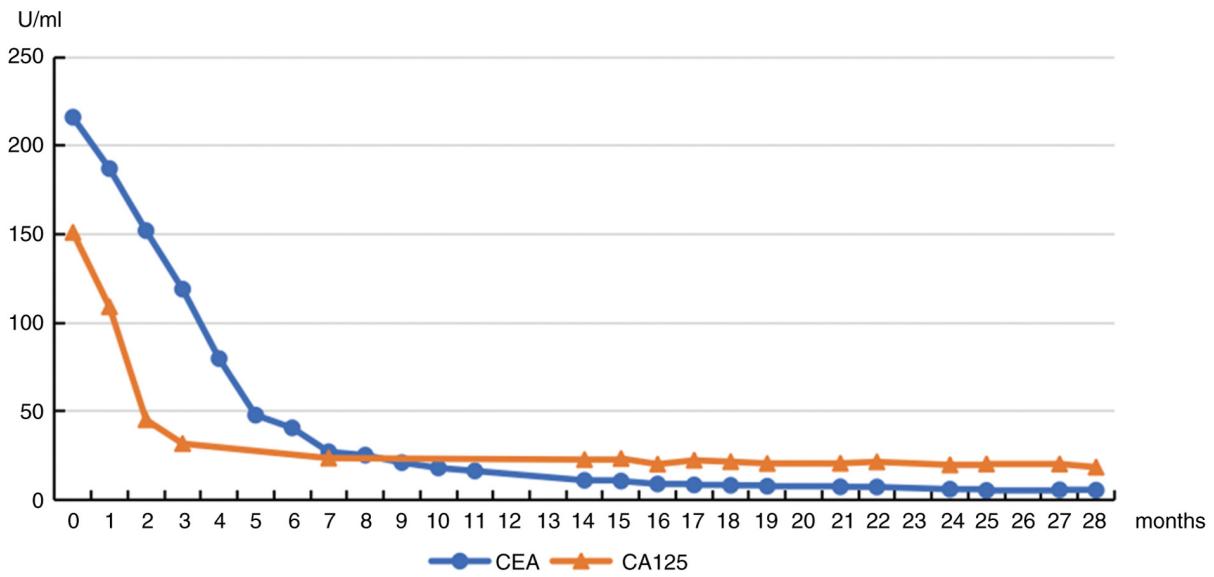

Figure 2. Serum CEA and CA125 (U/ml) at different time-points from the start of treatment with abemaciclib plus letrozole.

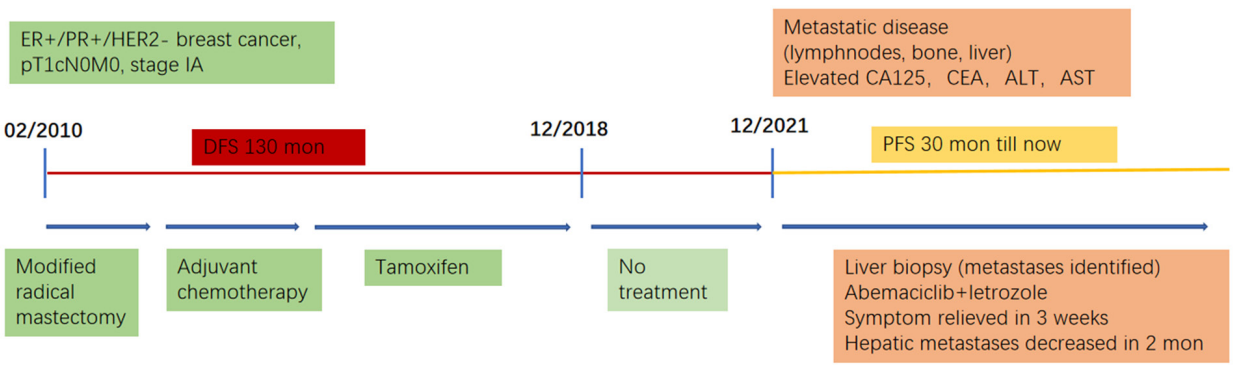

Figure 3. Treatment history of the patient with hormone receptor+/HER2-breast cancer with visceral crisis receiving abemaciclib plus letrozole as first-line treatment. HER2, human epidermal growth factor receptor 2; ER, estrogen receptor; PR, progesterone receptor; ALT, alanine aminotransferase; AST, glutamic oxaloacetic transaminase; PFS, progression-free survival; DFS, disease-free survival; mon, months.

Three CDK4/6i have been approved by the Food and Drug Administration for treating MBC: Palbociclib, abemaciclib and ribociclib (15). Abemaciclib is also approved for adjuvant therapy in HR+/HER2-early breast cancer with a high risk of recurrence (25). In addition to halting cell-cycle progression of cancer cells in the G1 phase, which is expected for all three CDK4/6i, abemaciclib can also induce G2-phase arrest by suppressing CDK1 and CDK2, which are critical for cell-cycle progression through the S-phase and mitosis (26).

In the MONARCH 3 trial, a double-blinded, randomized phase III study, abemaciclib combined with an aromatase inhibitor showed significant clinical benefits in postmenopausal patients with HR+/HER2-ABC. After a median follow-up of ~8 years, the median OS was 66.8 months for abemaciclib *vs*. 53.7 months for placebo, which is clinically meaningful but without statistical significance. In a subgroup analysis of patients with visceral disease, the median OS was 63.7 months for abemaciclib *vs*. 48.8 months for placebo (27). The addition of abemaciclib also prolonged PFS and chemotherapy-free survival with no new safety concerns. The PFS was 29 months for abemaciclib *vs*. 14.8 months for placebo. The proportion of patients who achieved PFS of >6 years was significantly higher in the abemaciclib group (23.3 *vs*. 4.3%). The addition of abemaciclib resulted in a higher objective response rate in all subgroups, particularly in patients with liver metastases, PR-tumors and high-grade tumors (28).

An exploratory analysis of the MONALEESA series III studies (Monaleesa-2, -3 and -7) in patients with visceral metastases was presented at the 2022 European Society of Medical Oncology meeting (Yardley DA, et al, abs. 205P). It showed that CDK4/6i plus ET as a first-line treatment for patients with visceral metastases (including liver and multiple metastases) extended the median PFS (mPFS) by nearly 15 months compared with placebo (29.6 *vs*. 14.7 months; hazard ratio, 0.56; 95% CI, 0.47 to 0.67), and extended the median OS by nearly 12 months (63.4 *vs*. 51.8 months; hazard ratio, 0.78; 95% CI, 0.64-0.96).

The RIGHT Choice study was the first prospective, randomized, controlled, head-to-head clinical study to compare CDK4/6i plus endocrine regimens with combination chemotherapy regimens in pre/perimenopausal patients with highly invasive HR+/HER2-ABC. The study included 222 patients, with 112 in the first-line ribociclib plus ET group and 110 in the combination chemotherapy group, including 47.7% of patients with investigator-assessed visceral crisis (29). After a median follow-up of 37.0 months, the median PFS was 21.8 months for ribociclib plus ET (17.4-26.7 months) and 12.8 months for combination chemotherapy (10.1-18.4 months) with statistical significance. The overall RR was 66.1 and 61.8% in the ribociclib and the chemotherapy group, respectively. The median TTR was 4.9 months in the ribociclib group *vs*. 3.2 months in the chemotherapy group. The study demonstrates that first-line treatment with ribociclib plus ET offers significant PFS benefits, similar RRs and better tolerability compared to combination chemotherapy in patients with HR+/HER2-ABC (30). The subgroup PFS benefit was in consistency with the overall analysis, with the benefit being diminished in patients with visceral crisis and recurrent disease. CDK4/6i is highly effective in treating HR+/HER2-ABC, and the addition of CDK4/6i may result in rapid and deep remission (29,30). Although the TTR in the ribociclib group was prolonged by ~1.7 months, there was no statistically significant difference. In addition, the incidence of adverse effects decreased significantly in the ribociclib-treated group. No noticeable difference was observed in OS between the two groups, suggesting no meaningful difference in survival benefit. CDK4/6i plus endocrine regimens provide a more tolerated treatment option and are also effective for patients with HR+HER2-breast cancer who could only receive chemotherapy in the past.

The present study reported on a patient with HR+/HER2-MBC with visceral crisis. The patient showed a good response to Abemaciclib and letrozole and the PFS of this patient reached >30 months. Overall, clinical studies comparing combination chemotherapy and targeted therapy plus ET in the first-line treatment of HR+/HER2-ABC with visceral crisis have supported a shift in clinical practice, possibly establishing the dominant position of CDK4/6i and changing the status of chemotherapy in the treatment of patients with visceral crisis. While the contribution of chemotherapy regimens in managing HR+/HER2-ABC cannot be overstated, multiple factors should be considered to make treatment decisions in clinical practice. Individualized precision therapy that considers tumor biological characteristics is the key determinant of palliative pharmacological treatment. However, for patients with relatively high ER expression and expected endocrine sensitivity, CDK4/6i plus ET may be the better option, as supported by the findings of the RIGHT Choice study (30).

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

YW contributed to acquiring data and writing of the manuscript. XZ and YM were engaged in formal analysis and prepared the figures. ML interpreted the radiological images. WL treated the patient and contributed to the conceptualization of the study. All authors have read and approved the final version of the manuscript. YW and WL checked and confirmed the authenticity of the raw data.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

The patient consented to the publication of data and images in the case study.

Competing interests

The authors declare that they have no competing interests.

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