A rapid reduction in tumor size by cyclin-dependent kinase inhibition in hormone receptor-positive postpartum breast cancer: a case report of two patients and a review of the literature

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Background: Postpartum breast cancer (PPBC) as an independent entity different from PABC. PPBC is defined as breast cancer (BC) diagnosed within 5 years after delivery in many relevant literatures and is associated with a poor prognosis and a decrease in overall survival. PPBC patients commonly present with inflammatory breast cancer (IBC) phenotype, multifocal lesions, and lymph node metastasis. Hormone receptor-positive (HR+) PPBC is an under-investigated subtype. In PPBC, the risk of death of HR+ subtype significantly increased two-fold, while that was only modestly increased for triple-negative breast cancer (TNBC) subtype, and was not significant in human epidermal growth factor receptor 2-positive (HER2+) subtype. HR+ PPBC is a subtype associating with enhanced signatures of cell cycle control, T-cell activation and exhaustion, decreased HR signaling, and altered P53 signaling. The recommended treatment for HR+ PPBC patients is still lacking. Cyclin-dependent kinase (CDK) 4/6 inhibitors are used as a novel treatment standard not only in pretreated patients but also in the first-line setting of HR+ metastatic breast cancer (MBC). However, there is no clinical case report on the application and efficacy of CDK4/6 inhibitors in HR+ PPBC patients.

Case Description: This article describes the clinical cases of two patients with advanced HR+ PPBC who were rapidly relieved after receiving leuprorelin combined with letrozole combined with dalpiciclib. We reviewed the related literature of PPBC, and found that HR+ PPBC has not been clinically classified as a BC subtype, and only some basic studies suggested that HR+ PPBC may be sensitive to CDK4/6 inhibitors. The purpose of this study is to provide the basis for the related research on the therapeutic effect of CDK4/6 inhibitors in HR+ PPBC through the report of clinical cases.

Conclusions: This article reports for the first time the good therapeutic effects of CDK4/6 inhibitors on HR+ PPBC patients. Based on our findings, we suggest that dalpiciclib combined with endocrine therapy can be considered as the first-line treatment for patients with advanced HR+ PPBC. Our case report provides new clinical evidence for the related research on the role of CDK4/6 inhibitors in HR+ PPBC therapy.

Keywords: postpartum breast cancer (PPBC); cyclin-dependent kinase (CDK) 4/6 inhibitors; mammary stem cell (MaSC); hormone receptor-positive (HR+) breast cancer; case report

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Introduction

Previously, pregnancy-associated breast cancer (PABC) was defined as a cancer of the breast detected during pregnancy or within a year of delivery (1). Compared to non-PABC cases, young premenopausal women who are pregnant or have been pregnant have poor survival rates, and the risk of metastasis is more than 2-fold. The factors associated with a poor prognosis are age at time of diagnosis, stage, histological grade, and hormone receptor status (2). However, the definition of PABC is insufficient to meet the clinical needs for accurate diagnosis and treatment of breast cancer (BC) (3). Pregnancy and the postpartum period are intertwined. There is increasing evidence that postpartum breast cancer (PPBC) is an independent entity different to BC that occurs during pregnancy. According to the latest data, the postpartum stage can last up to 5–10 years after birth, and each type has unique biological attributes and prognosis (4,5).

In women, the postpartum window coincides with a developmental process called weaner-induced breast relapse, which has been shown to promote the development and metastasis of BC in rodent models (6,7). A meta-analysis of 41 studies showed that women diagnosed with BC after childbirth had a higher risk of death (hazard ratio 1.79; 95% confidence interval is 1.39–2.29) (8). In addition, PPBC is an independent risk factor associated with death from hormone receptor-positive (HR+) BC, which increases mortality by 2–3 times. Around the world and among all age groups, HR+ BC represents the most common subtype of BC (9). And of all metastatic BC cases, women with HR+, human epidermal growth factor receptor 2-negative (HER2–) metastatic BC represent about 60% (10). Previously, hormonal treatment consisted only of the estrogen receptor modulator tamoxifen, luteinizing hormone-releasing hormone (LHRH) agonists and aromatase inhibitors (AIs) (9). Cancer progression is typified by the loss of cell cycle control and subsequent uncontrolled growth of cancer cells (11). More recently, cyclin-dependent kinase (CDK) 4/6 inhibitors have come into widespread use in the treatment of HR+/HER2– BC patients (12). CDK4/6 inhibitors represent a paradigm shift in the treatment of advanced BC HR+/HER2–, given the clinically and statistically significant gain in overall survival associated with this new class of medications (13). However, the report on the application and efficacy of CDK4/6 inhibitors in HR+ PPBC patients is still blank.

In this article, we report 2 cases of HR+ BC patients with overwhelming tumor burdens. Both the patients received treatments containing leuprorelin, letrozole and dalpiciclib, and achieved a rapid treatment response with a remarkable disease-free time (DFS). Our findings suggest that the CDK4/6 inhibitors may have good potential as a treatment option for the HR+ PPBC patients. We present the following article in accordance with the CARE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-5201/rc).

Highlight box

Key findings

- This article reports for the first time the good therapeutic effects of Cyclin-dependent kinase (CDK) 4/6 inhibitors on Hormone receptor-positive (HR+) postpartum breast cancer (PPBC) patients.

What is known and what is new?

- CDK4/6 inhibitors are used as a novel treatment standard in the first-line setting of HR+ metastatic breast cancer (MBC) now.
- This is the first clinical case report on the application and efficacy of CDK4/6 inhibitors in HR+ PPBC patients.

What is the implication, and what should change now?

- We should attach importance to the therapeutic role of CDK4/6 inhibitors in HR+ PPBC patients and design rigorous prospective clinical trials to verify this.

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

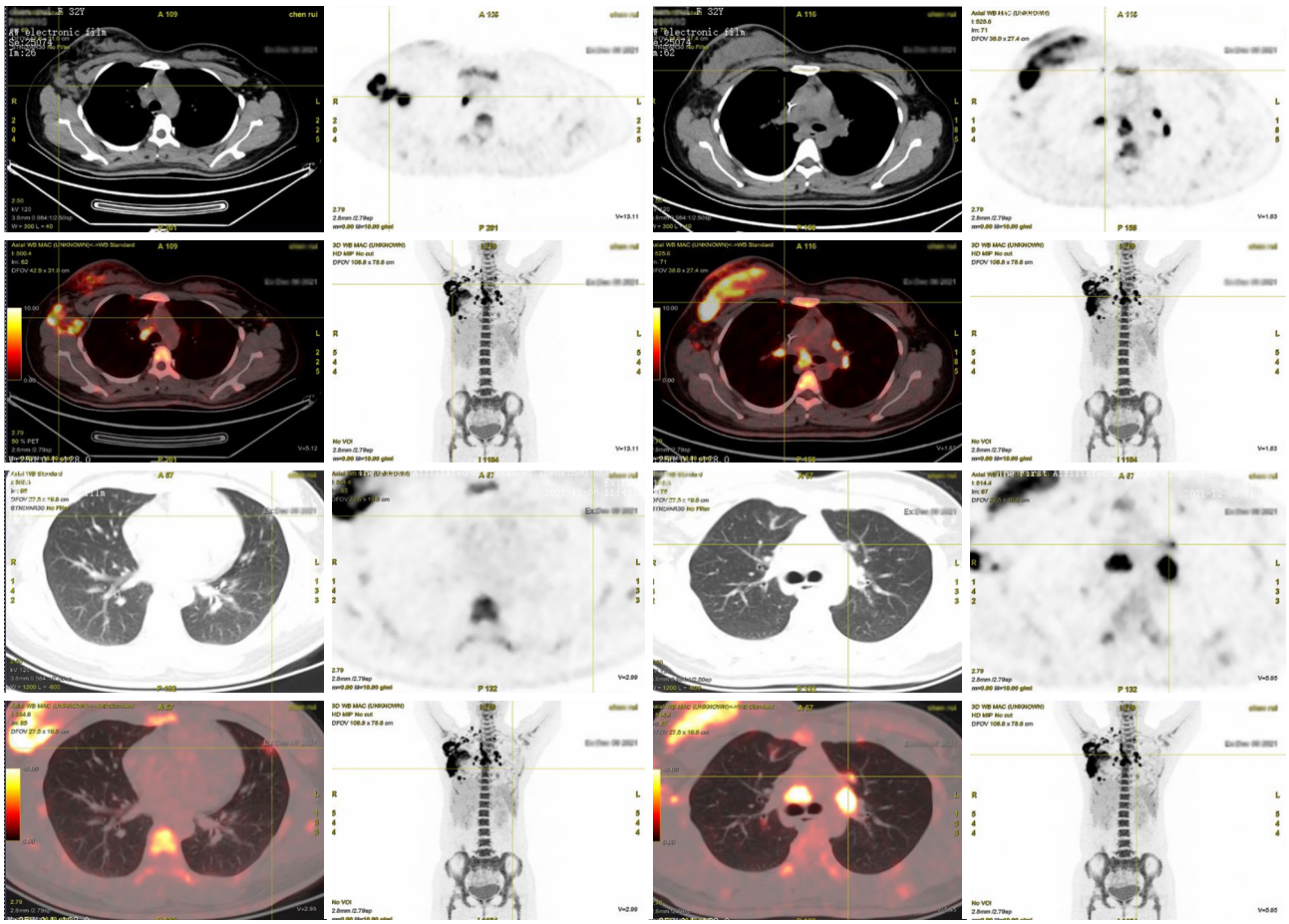

Figure 1 PET-CT examination at the baseline for the patient in case 1. The results showed that this patient had large tumor burdens. PET-CT, positron emission tomography/computed tomography.

Case 1

On November 25, 2021, a 32-year-old woman was admitted to our department with a chief complaint of a self-detected right breast tumor for 1 month. At this time, her lactation period had just ended. After admission to evaluate her condition, she was diagnosed with right breast invasive cancer. Her immunohistochemistry results were as follows: estrogen receptor-positive (ER+) (60%), progesterone receptor-positive (PR+) (80%), HER2 (0), and Ki-67 (approximately 30%+). On admission, the patient appeared to be in a good clinical condition, and had a performance status (PS) score of 0. She had no smoking or drinking habits and no other chronic diseases.

On physical examination, there was a palpable hard mass measuring about 8.0 cm × 6.0 cm in the right breast. The swollen hard lymph nodes could be reached under the right axilla, were about 3 cm × 2 cm in size, and had poor mobility, an unclear boundary, and no tenderness. Edema and hardening were observed on her right breast skin. The results of further examinations, including computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET)-CT showed that her BC had metastasized to the lymph nodes in the right neck (region IV–V), right supraclavicular region, infraclavicular region, mediastinum (region 1–8), bilateral hilum, right armpit, right internal mammary region, hepatogastric region, and retroperitoneum. In addition, her BC had metastasized to her lung and the cutaneous of her right breast (*Figure 1*).

We performed biopsies of her lymph nodes in the right supraclavicular region, lymph nodes in the infraclavicular region, her right breast cutaneous metastatic lesions, and her lung metastatic lesions. The pathologic results

showed that these lesions all had luminal B subtype BC metastasis. Based on these findings and in combination with the National Comprehensive Cancer Network (NCCN) guidelines (V2022.2), we confirmed that the patient had a stage IV HR(+), HER2(–) BC.

Due to her large tumor load, we developed a chemotherapy regimen containing nab-paclitaxel, doxorubicin (DOX) and cyclophosphamide for her. She started chemotherapy on December 1, 2021, and after 2 cycles, her response was assessed as stable disease (SD). After her 4th chemotherapy cycle, her response was assessed as progressive disease (PD) because of the rapidly spreading redness of the skin on her right breast (*Figure 2*). Combined with her immunohistochemical status, we finally recommend that she take LHRH agonists combined with AIs and CDK4/6 inhibitors for treatment, which she happily accepted.

A program of leuprorelin (3.75 mg, monthly injection), tamoxifen (20 mg, qd, po) followed by letrozole (2.5 mg qd, po) and dalpiciclib (125 mg, qd, po,3 weeks on/1 week off) was formulated for the patient, and she started her treatment on March 1, 2022 (tamoxifen was administered for the first 2 weeks after the patient was first treated with leuprorelin). After 3 days of treatment with leuprorelin, tamoxifen, and dalpiciclib, the firmness of her right breast tumor was relieved, and her bone pain entered remission (*Figure 2*). Additionally, we administered denosumab therapy with oral calcium supplements and calcitriol. The treatment process, the time of disease progression, and the factors that affected our decision-making process are shown in Figure S1. She suffered from grade 3 neutropenia after the second cycle of dalpiciclib. Considering that COVID-19 is still in epidemic, 300 μg dose of granulocyte colony stimulating factor was selected to correct her grade 3 neutropenia after full communication with the patient, and traditional Chinese medicine was used for supportive treatment when grade 1–2 neutropenia was present (Table S1). No other significant side effects were observed. As the treatment continued, her symptoms were rapidly relieved, and her last follow-up was November 21, 2022.

Case 2

On February 9, 2022, a 36-year-old woman was admitted to our department with a complaint of a self-detected a left breast tumor for 11 months. Some 11 months ago, the patient had found a left breast mass during lactation, and had been diagnosed with mastitis caused by milk accumulation at many hospitals. She had accepted symptomatic treatment, including an infusion of antibiotics and an external application of magnesium sulfate solution, but her tumor continued to grow. After admission to evaluate her condition, she was diagnosed with left breast invasive cancer, accompanied by left breast skin edema. Her immunohistochemistry results were as follows: ER+ (70%), PR+ (15%), HER2 (0), and Ki-67 (approximately 70%+).

On admission, the patient appeared to be in a good clinical condition, and she had a PS score of 1. She suffered from genetically related polycystic liver disease (PLD) and polycystic kidney disease (PKD), but her liver and kidney function indicators were normal. Her father and grandfather had also suffered from these 2 diseases, but their causes of death were not related to these 2 diseases, and they were both over the age of 70 years when they died. She had no smoking and drinking habits and no other chronic diseases.

On physical examination, a palpable mass measuring about 5.0 cm was found in the upper left breast and the skin on her left breast was edematous and sclerotic. The mass in the upper part of the areola had caused the edema and a bulge of the skin in the areola. The results of a further examination including CT, PET-CT, and MRI showed that she had metastasis to the left axillary lymph nodes, left supraclavicular lymph nodes, internal breast lymph nodes, and retroperitoneal lymph nodes, and multiple bone metastases (*Figure 3*).

We performed genetic testing and found that the patient had a copy number amplification (7-fold higher than normal) of *CCND1* gene, a p.R282W missense mutation of *TP53* gene (abundance, 52.3%), and the *KMT2C* gene exon 14 p.L804V mutation (abundance, 3.9%). Based on the clinical history, pathological findings, and the Clinical Practice Guidelines in Oncology of the NCCN (V2022.2), we confirmed that she had stage IV HR(+), HER2(–) BC.

Despite there being no reports of hepatic or renal dysfunction, we still had concerns about the potential damage of chemotherapy drugs to liver and kidney function. Combined with her immunohistochemical status, we ultimately recommend that she take LHRH agonists combined with AIs and CDK4/6 inhibitors for treatment, which she happily accepted. A program of leuprorelin (3.75 mg, monthly injection), tamoxifen (20 mg, qd, po) followed by letrozole (2.5 mg qd, po) and dalpiciclib (125 mg, qd, po, 3 weeks on/1 week off) was formulated for the patient (tamoxifen was administered for the 1st 2 weeks after the patient was first treated with leuprorelin). She started treatment on February 15, 2022. During the 3 days

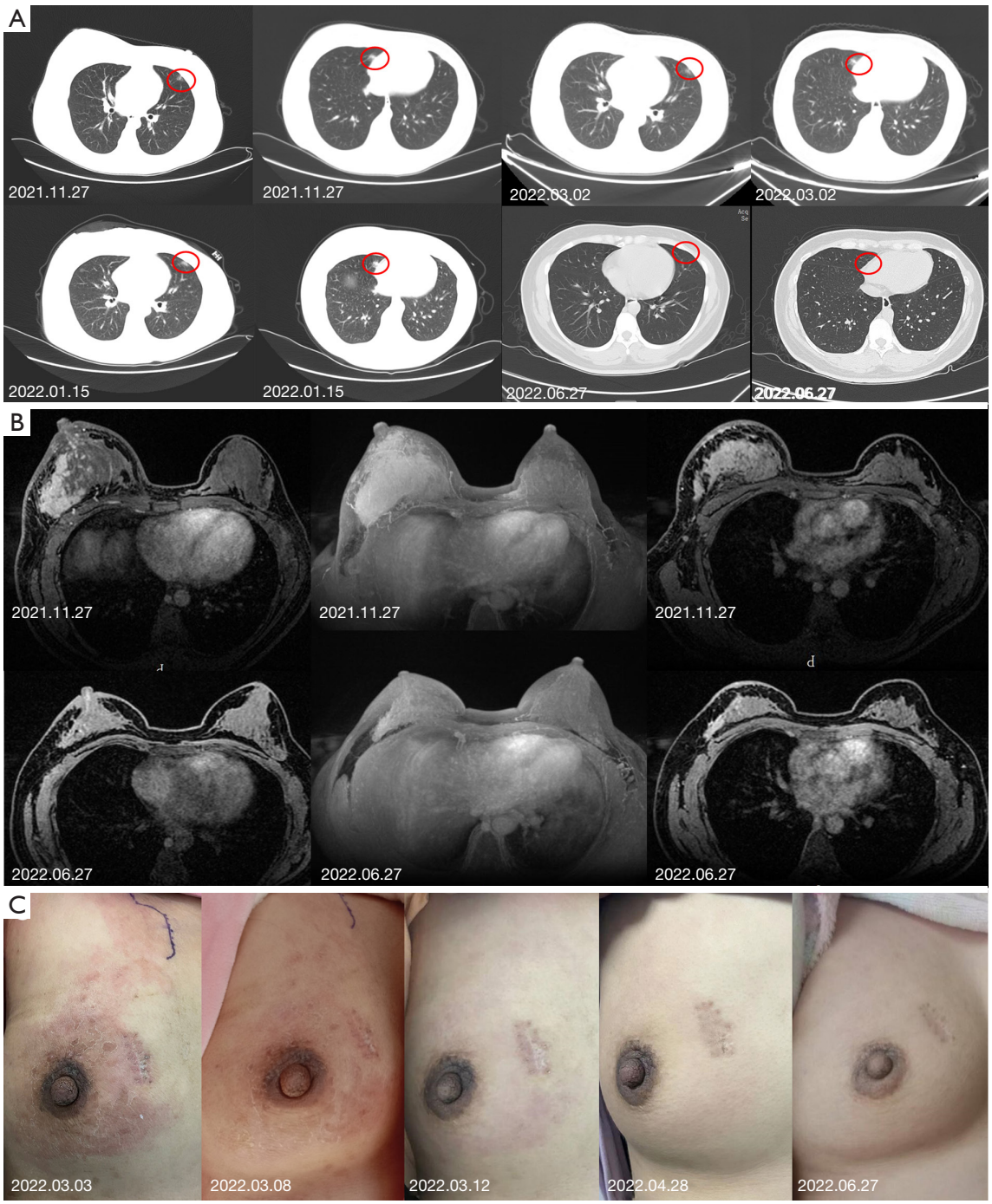

Figure 2 Response of the metastases to treatment of the patient in case 1. (A) Photograph showing that her pulmonary lesions change very little during the chemotherapy, but were controlled well after treatment with leuprorelin, tamoxifen followed by letrozole (tamoxifen was administered for the first 2 weeks after the patient was first treated with leuprorelin) and dalpiciclib. The breast cancer metastases on the lung of this patient are circled in red. (B) Breast MRI at the baseline and the last follow-up of the patient in case 1; her symptoms continued to improve. (C) Response of the cutaneous tumor metastases to treatment of dalpiciclib combined with endocrine therapy: The redness and hard nodules of the skin had obviously subsided. MRI, magnetic resonance imaging.

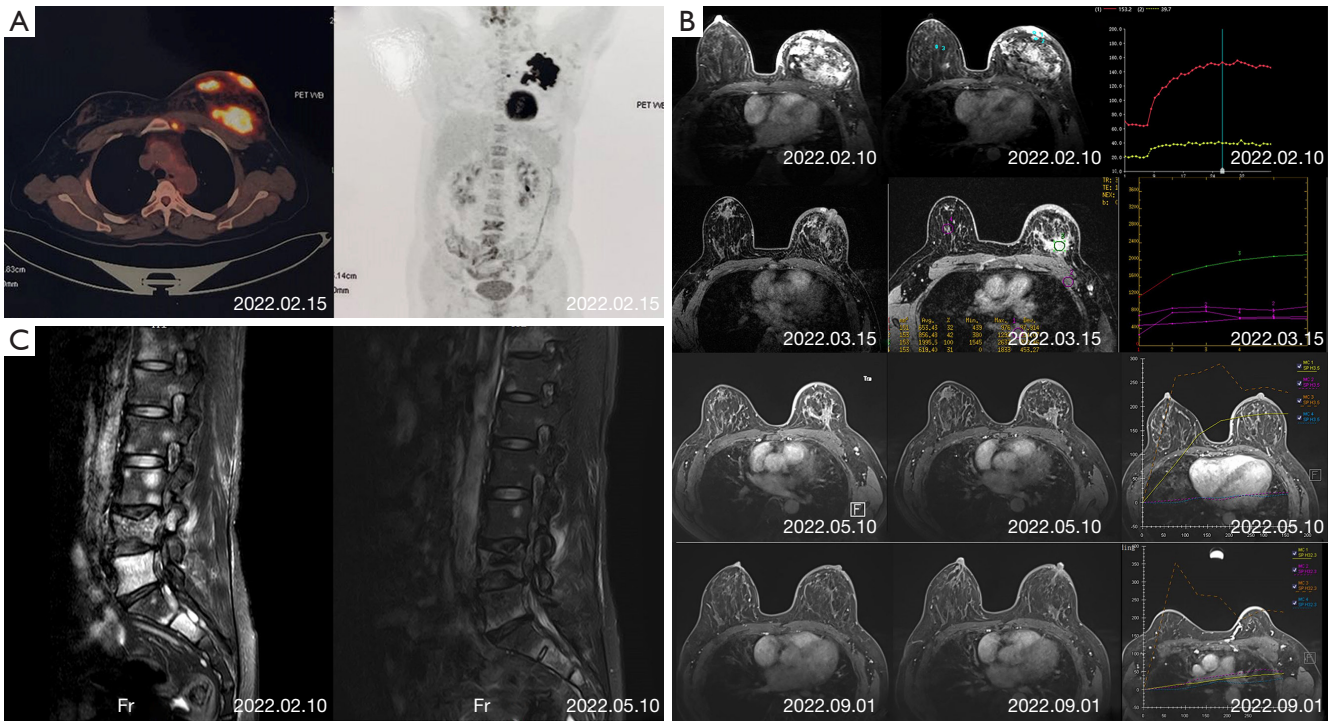

Figure 3 Response of the metastases to treatment of the patient in case 2. (A) PET-CT examination at the baseline of the patient in case 2. The results showed that this patient had large tumor burdens. (B) Breast MRI at the baseline and during follow-up; her symptoms gradually improved during the follow-up periods. (C) Response of the bone tumor metastases to the treatment of dalpiciclib combined with endocrine therapy; The bone destruction improved significantly. PET-CT, positron emission tomography/computed tomography; MRI, magnetic resonance imaging.

of treatment with leuprorelin, tamoxifen, and dalpiciclib, the firmness of the mass was relieved (*Figure 4*). She suffered from grade 3 neutropenia after the first cycle of dalpiciclib. 300 μg dose of granulocyte colony stimulating factor was selected to correct her grade 3 neutropenia after full communication with the patient, and traditional Chinese medicine was used for supportive treatment when grade 1–2 neutropenia was present (Table S2). Both her liver and kidney function detection and Urinary β2-microglobulin detection were within the normal range. No other significant side effects were observed. As the treatment continued, her symptoms were rapidly relieved, and her last follow-up was November 27, 2022.

Discussion

In 2022, there were more than 4 million female invasive BC survivors in the United States (US) (14). Among these than 4 million survivors, more than 2.7 million (i.e., about 2/3 of the female BC survivors) were aged ≥65 years, and only about 6% were aged <50 years (14). According to the Surveillance, Epidemiology, and End Results study in the US, young women's breast cancer (YWBC) has increased 1.62-fold since 2000. The increase in the incidence rate is entirely due to ER+ BC diseases (15). Given that the incidence of BC is influenced by a reproductive age of 25–30 years, a possible explanation for the poor prognosis of YWBC patients is that cancer outcomes may be related to delivery (16,17).

Previously, postnatal BC was often studied together with BC diagnosed during pregnancy as "pregnancy-related breast cancer", with conflicting clinical data (18-20). Numerous epidemiological studies and recent meta-analyses have shown that BC patients diagnosed 10 years after giving birth have a significantly poorer prognosis, while women diagnosed and treated for BC during pregnancy have no increased risk of disease metastasis and death (21-24). A meta-analysis investigating whether the time of diagnosis of BC during pregnancy or postpartum affected the survival outcome of YWBC patients showed that patients diagnosed

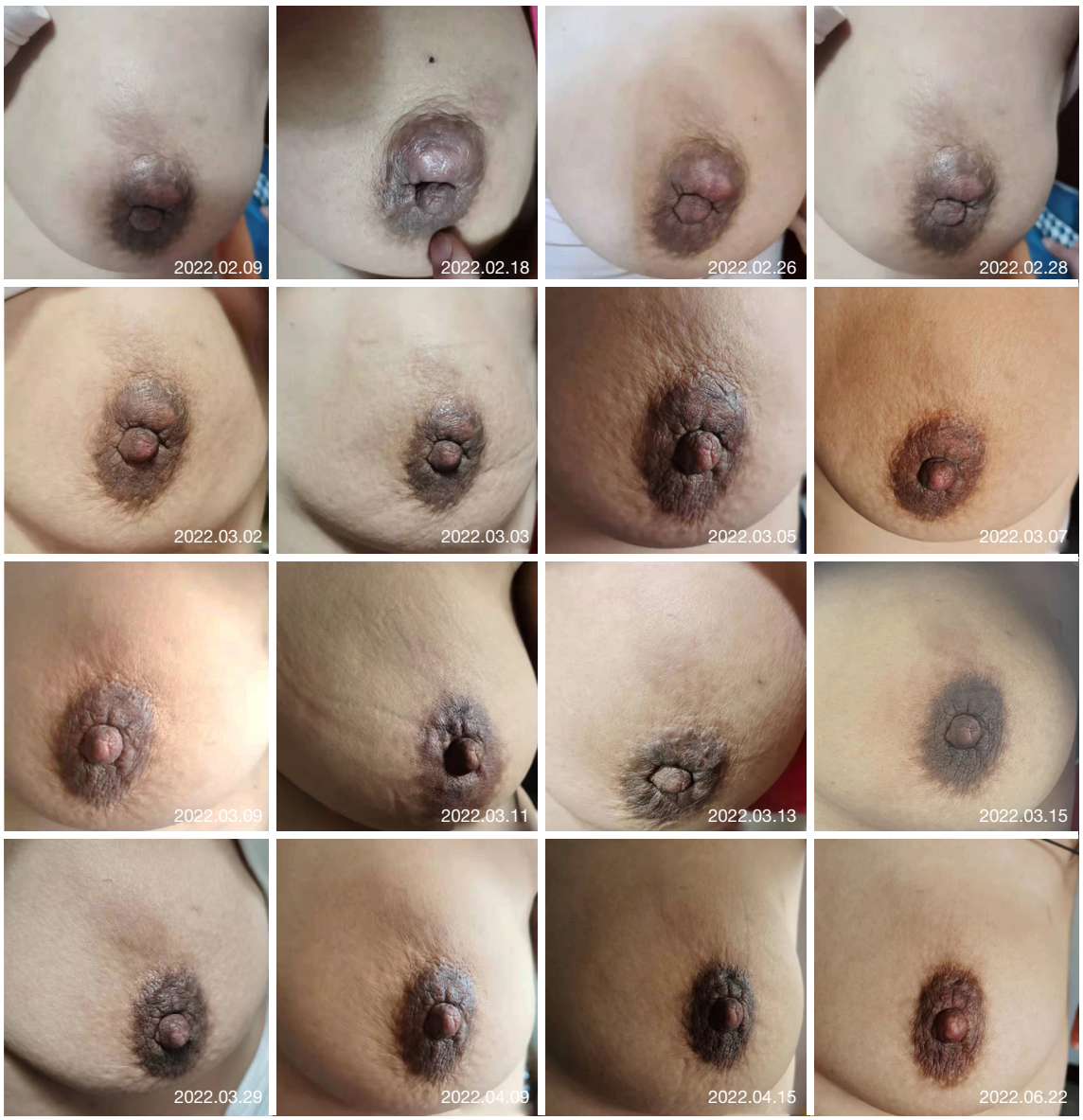

Figure 4 Response of the cutaneous tumor metastases to the treatment for the patient in case 2. Form the day of her initial visit (2022-02-09) to 2022-06-22, photographs of her left breast taken throughout the treatment process.

with BC during postpartum had a higher risk of death (hazard ratio 1.79; 95%, confidence interval 1.39–2.29) (8). Further, some studies have found that PPBC is independently associated with a 2- to 3-fold increased risk of death in HR+ BC patients (21,22).

Hyperactivity of CDK4/6 pathway was associated with resistance to endocrine therapy of HR+/HER2– BC (25). The combination of CDK4/6 inhibitors and endocrine therapy as first-line or second-line therapy has been proved to improve the survival results of HR+/HER2 metastatic breast cancer (MBC) patients. The clinical trial evidence includes MONARCH (26-28), MONALESSA (29-31), PALOMA (1,18,32,33) and DAWNA series (34,35). However, there has been no relevant case report or clinical research on the application of CDK4/6 inhibitors in HR+/HER2– PPBC patients, and the relevant basic research is also very insufficient.

Both the patients in this study (i.e., case 1 and case 2) presented with advanced stage (stage IV) BC at their 1st visits to the doctor, and their molecular subtype of

BC was HR+/HER2–. The HR+/HER2– subtype has the best prognosis among the 4 molecular subtypes of BC; however, the diagnosis of BC during lactation is an independent risk factor (2,36) for poor prognosis. Callihan demonstrated that BC patients diagnosed within 5 years postpartum have a significantly higher risk of metastasis and mortality than nulliparous BC patients (21). Even though immunohistochemical evaluation showed that the tumor HR expression was highly positive in more PPBC cases, the tumor HR signal transduction was still insufficient compared with NPBC. It was found that in HR+ BC patients, the downstream HR signaling pathway in tumor tissue of PPBC patients was more similar to the pathway of HR negative BC patients (37,38). Therefore, further studies should be conducted to identify potential therapeutic strategies for PPBC by combining existing efficacy evaluations and outcome data, and to determine whether existing agents, such as CDK4/6 inhibitors, can reverse resistance to HR+ PPBC endocrine therapy (13).

In case 1, the progression of the cutaneous lesions of the patient during chemotherapy indicated that she was resistant to anthracycline and taxane regimens. Because of her disease progression during chemotherapy, we were of the view that a combination of CDK4/6 inhibitors and endocrine therapy may be a more appropriate treatment for this patient. Clinical trials have confirmed that patients with HR+ may respond well to endocrine therapy after chemotherapy fails (39,40). A combination of CDK4/6 inhibitors and endocrine therapy is becoming the preferred treatment for advanced BC (41). During the treatment of case 1, the rapid improvement of her cutaneous metastatic lesions not only highlights the sensitivity of ER+ PPBC to dalpiciclib-containing therapy, but also suggested that the combination of CDK4/6 inhibitors and AIs might have a synergistic effect on cell apoptosis. Thus, endocrine therapy combined with dalpiciclib may be an effective treatment for HR+/HER2– advanced PPBC patients. As Case 2 had PLD and PKD, chemotherapy represented a great risk for her. Therefore, a LHRH agonists combined with AIs and CDK4/6 inhibitors regimen was developed for this patient, and her cutaneous metastases disappeared after she received 2 courses of treatment. Her last follow-up was on November 27, 2022, and as of that date, her disease was still well under control.

There is increasing evidence that PABC and PPBC should be treated as separate and distinct entities (21). PPBC has unique biological properties and a unique prognosis and can occur up to 5–10 years after delivery (4,42). During pregnancy, mammary epithelial cells proliferate and differentiate in preparation for lactation. After delivery, in the absence of lactation, or during weaning, glands are remodeled to a state similar in shape and function to that before pregnancy through a process called involution (43,44). In female rodents, where the process of involution has been extensively studied, more than 80% of lactating mammary epithelial cells die during developmentally regulated tissue remodeling (45). Jindal *et al.* (46) found that ER+ PPBC was a molecular specific subtype with a poor prognosis, with a high p53 gene mutation, and was insensitive to chemotherapy drugs. They also believed that cell-cycle inhibitors, such as CDK4/6 inhibitors, may have better efficacy in treating PPBC than conventional treatment. The 2 cases in this report also verified to some extent that CDK4/6 inhibitors have considerable potential in the treatment of PPBC.

It has been shown that both mammary stem cells (MaSCs) and receptor activator of NF kappa B-ligands (31) are highly expressed and highly correlated in BC in young women (aged <40 years) (47,48). MaSCs are also known to express high levels of growth hormone (GH) receptors. Given that GH is highly expressed during pregnancy and lactation, it is plausible to assume that GH acts on GH receptors in the MaSCs, resulting in an increase in their number and potentially promoting the aggressiveness of PPBC (49,50). Some studies have shown that MaSCs are normally regulated by steroid hormones, presumably via paracrine signals from ER+ luminal cells (6). The hormonal control of MaSCs function has significant implications for understanding the decreased BC risk associated with ovariectomy and chemoprevention (51,52). Research has shown that the levels of cyclin D1 (CCND1) and cyclin D2 (CCND2) are decreased in the cells of ovariectomized mice, and treatment with the AI letrozole reduces the MaSC pool (48). CCND1 and CDK6 are direct transcription targets of the transcriptional coactivator (TAZ), and the chemoprevention of BC may be achieved by suppressing MaSC function (48). CCND1 activation promotes cell-cycle progression through the phosphorylation of substrates, such as retinoblastoma (Rb) protein and transcription factors, which play roles in proliferation and differentiation. Shen *et al.* (53) found that the CDK4/6 inhibitors could target TAZ-driven cellular processes and preferentially inhibit cell proliferation in HR+ and HER2– BC. Based on the above literature analysis and the significant curative effects of these 2 cases, we conclude that HR+ PPBC should be studied as a separate BC subtype, and that the combination

of CDK4/6 inhibitors with endocrine therapy may have the potential to be the first-line treatment for patients with HR+/HER2– advanced PPBC.

Conclusions

HR+/HER2– PPBC should be explored and studied as a separate BC subtype. The good therapeutic effect of CDK4/6 inhibitors combined with endocrine therapy may be based on the triple inhibitory effect of this regimen on MaSCs in HR+ and HER2– PPBC patients; that is, the CDK4/6 inhibitors may block the TAZ-driven cell proliferation process and the AIs combined with LHRH not only inhibit the growth-promoting effects to BC cells of estrogen via ERs but also the cell proliferation process of MaSCs via CCND1. For patients with HR+/HER2– advanced PPBC, CDK4/6 inhibitors combined with endocrine therapy has the potential to be the first-line treatment, and further research is necessary.

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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-22-5201/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-5201/coif). NW reports this study was supported by the Department of Education of Henan Province, Key University Science Research Project of Henan Province, Award (No. 23A320016); and Health Commission of Henan Province, Youth Project of Medical Science and Technology Project of Henan Province, Award (No. SBGJ202103070). The other 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 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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