Long-term progression-free survival in HR+/HER2+ advanced breast cancer with combination therapy with a CDK4/6 inhibitor and first-line maintenance therapy: A case report

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Abstract. The current standard treatment for hormone receptor (HR)-positive and human epidermal growth factor receptor 2 (HER2)-positive advanced breast cancer (BC) involves the use of anti-HER2 monoclonal antibodies combined with chemotherapy, followed by sequential endocrine therapy. However, crosstalk between the HR and HER2 pathways may cause drug resistance. Combining therapies targeting both the HR and HER2 pathways may be a rational approach for patients with HR+/HER2+ tumors, as this strategy could counteract resistance by blocking crosstalk in the receptor pathway. However, clinical data in this field remain limited. The present report describes the case of a patient with HR+/HER2+ late-stage BC who achieved a long-term partial response rate after receiving anti-HER2 combination chemotherapy followed by sequential treatment with endocrine therapy and cyclin-dependent kinase 4/6 (CDK4/6) inhibitors. The present case provides additional evidence suggesting that incorporating CDK4/6 inhibitors into standard targeted chemotherapy regimens may be an effective treatment option for patients with HR+/HER2+ BC.

Introduction

Breast cancer (BC) is a highly heterogeneous disease comprising genetically and epigenetically distinct subtypes with varying clinical features (1). Based on the expression of estrogen receptor (ER), progesterone receptor (PR) expression and human epidermal growth factor receptor 2 (HER2), or HER2 amplification, BC is classified into five subtypes: Luminal A, Luminal B, HER2+, triple-positive and triple-negative subtypes (2).

A total of >50% of patients with HER2+ BC also express ER and/or PR (3). HR+/HER2+ BC can be categorized as HER2+ BC combined with ER+ or PR+, or both ER+ and PR+ [triple-positive BC (TPBC)]. There has been significant progress in the treatment of HER2+ BC, and combination chemotherapy with pertuzumab and trastuzumab improves the median survival time of metastatic HER2+ patients to >5 years (4). The biology of HER2+/HR+ BC differs from that of HER2+/HR- BC. For HER2+/HR+ tumors, the current consensus recommends endocrine therapy after the completion of targeted therapy and chemotherapy. However, patients with HER2+ advanced BC have few effective treatment options beyond anti-HER2 therapy and chemotherapy. The addition of a cyclin-dependent kinase (CDK)4/6 inhibitor (CDK4/6i) combined with endocrine therapy has been reported to have notable efficacy in the treatment of in HR+/HER2+ advanced BC (5). Preclinical studies have reported that CDK4/6is are effective against HER2+ cell lines (5,6). In animal models, the combination of anti-HER2 therapy and CDK4/6is has been reported to be more effective than either drug alone, and it re-sensitized resistant HER2+ BCs to anti-HER2 therapy (6). Furthermore, recent clinical trials have evaluated the clinical efficacy of administering CDK4/6is, aromatase inhibitors or fulvestrant to anti-HER2 therapy and chemotherapy to patients with HR+/HER2+ BC, showing improved median overall survival time in women with HR+/HER2+ advanced BC when compared with chemotherapy + trastuzumab (7,8).

CDKs are a family of serine-threonine kinases that serve an vital role in regulating cell cycle progression (8). Among the cyclin classes, D-type cyclins are important in cancer due to their role as the final recipients of many oncogenic pathways. This family consists of cyclins D1, D2 and D3, which are expressed in an overlapping and redundant manner in all proliferating cell types (9). D-cyclins bind to and activate CDK4 and CDK6, forming complexes that phosphorylate the retinoblastoma (RB) tumor suppressor protein (pRB) and pRB-like proteins (p107 and p130). This process activates E2F transcription factors, which induce target genes necessary for

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DNA synthesis during the S phase. Meanwhile, the cyclin D-CDK4/6 complex activates the CDK2 by sequestering the cell cycle inhibitors p27Kip1 and p21Cip1, facilitating G1 phase progression (10). The cyclin D/CDK4/6 complex is located downstream of the HER2 pathway. In mouse models, pharmaceutical inhibition of CDK4/6 has been reported to antagonize HER2-driven mammary tumor growth (11). Therefore, using CDK4/6is for the treatment of the HER2+ BC subtype is reasonable (12). Historically, cell cycle inhibitors have been used primarily for ER+/HER2- BC, and they have attracted much attention in the research of HER2+ BC. However, preclinical and clinical studies suggest that CDK4/6is may provide new therapeutic strategies for HER2+ BC in the future (13).

The present report describes the case of a 60-year-old female patient diagnosed with unresectable advanced HR+/HER2+ BC. The patient underwent systemic treatment with an aromatase inhibitor, CDK4/6is and anti-HER2 monoclonal antibodies, achieving a favorable clinical response to treatment. The present case highlights the potential of this therapeutic approach.

Case report

A 60-year-old female patient discovered a mass in the left breast and subsequently developed chest tightness in January 2021. The patient presented to the Affiliated Hospital of Nantong University (Nantong, China) for evaluation, and computed tomography (CT) revealed multiple nodules in both lungs, a mass in the left breast, multiple enlarged lymph nodes in the left axilla and an area of non-uniform density in the right sixth rib (data not shown). Given these findings and clinical characteristics, a positron emission tomography (PET)-CT scan was performed in February 2022, which indicated multiple metastases originating from left BC (Fig. 1). The next day, a needle biopsy was performed on the left breast mass and the left axillary lymph node. Pathological examination of the left breast mass revealed invasive ductal carcinoma. Moreover, immunohistochemical analysis was performed on 10% formalin-fixed (room temperature for ≤12 h) and paraffin-embedded tissue sections, with deaffinity and rehydration using alcohol xylene. Sections were heated in a microwave in a sodium citrate buffer (0.01 M, pH 6.0) for antigen retrieval. Thereafter, the sections were cultured with 5% BSA and blocked at room temperature for 30 min to inhibit endogenous peroxidase activity and then incubated with rabbit anti-ER (cat. no. 790-4325), anti-PR (cat. no. 790-4296) and anti-HER2 (cat. no. 790-4493) (all Roche Diagnostics) for 1 h at room temperature. The results demonstrated tumor staining positive for ER (10%), negative for PR, positive for HER2 (3+), and a Ki-67 proliferation index of 30% (Fig. 2A). Similarly, the left axillary lymph node biopsy revealed tumor staining positive for ER (30%), negative for PR, positive for HER2 (3+), and a Ki-67 proliferation index of 30% (Fig. 2B). These results, combined with those from the pathological examination and PET-CT scan, the patient was diagnosed with left-sided invasive BC (maximum breast mass diameter, 4.7 cm), accompanied by metastases to the left supraclavicular and parasternal regions, left anterior superior chest wall muscle space, multiple axillary lymph nodes, sternal body and bilateral iliac bones. According to American Joint Committee on Cancer staging, the clinical staging was cT2N3M1, stage IV and Luminal B HER2+ subtype (14).

According to the 2022 Chinese Society of Clinical Oncology guidelines for BC (15), the patient received six cycles of docetaxel + trastuzumab+ pertuzumab (THP) therapy as first-line treatment from February 2022 to July 2022. The regimen included docetaxel (75 mg/m^2; day 1), trastuzumab (8 mg/kg for the first cycle and 6 mg/kg for subsequent cycles; day 1) and pertuzumab (840 mg for the first cycle and 420 mg for subsequent cycles; day 1), administered every 21 days. Subcutaneous injection of denosumab (120 mg, every 3 weeks) was concurrently administered to prevent bone-related events.

PET-CT performed in June 2022 demonstrated a partial response to treatment (Fig. 1). Given this favorable treatment response, the patient transitioned to maintenance therapy, consisting of exemestane (25 mg oral daily) and palbociclib (125 mg oral daily for 21 days, followed by a 7-day break). RB protein expression was assessed by immunohistochemistry to predict the efficacy of the CDK4/6is (Fig. 3). Due to persistent grade IV leukopenia after one cycle of 125 mg palbociclib, the dose was reduced to 100 mg daily. The patient continued trastuzumab and pertuzumab during maintenance therapy with exemestane and palboxiclib.

In May 2024, the patient underwent PET-CT again, and the results indicated a sustained good response. Based on the previous PET-CT results, the last result was rated as a continuous partial response (Fig. 1). According to the RECIST 1.1 criteria (16), the patient achieved a progression-free survival (PFS) of ≥30 months as of the last follow-up in September 2024 (Fig. 4).

Discussion

HER2+ BC accounts for 15-20% of all BCs and is considered a more aggressive subtype (17). A total of >50% of HER2+ tumors also express hormonal receptors (4). Chemotherapy with a taxane + trastuzumab and pertuzumab is currently the frontline regimen for patients with advanced HER2+ BC based on the results of the CLEOPATRA trial. Trastuzumab emtansine (T-DM1) is the second-line option for current treatment (18,19). Furthermore, the results of the MARIANNE trial reported that the median overall survival rate was similar across the different treatment groups in the study: Trastuzumab + a taxane, 50.9 months; T-DM1, 53.7 months; and T-DM1 + pertuzumab, 51.8 months (19). None of the subgroups showed a significant benefit with one treatment regimen in comparison with the others. Therefore, T-DM1 is currently recommended as an appropriate choice for patients deemed unsuitable for taxane-based therapy. Moreover, data from the CLEOPATRA trial currently reports the longest PFS for patients with advanced breast cancer. Other clinical trials such as TANDEM, EGF30008 and ELECTRA have reported that combining HER2-targeted therapies with endocrine treatment notably prolongs PFS in metastatic TPBC (20,21). Based on these findings, it is recommended to incorporate hormone agents to HER2-targeted therapy following the completion of cytotoxic chemotherapy. Furthermore, preclinical evidence suggests that crosstalk between HER2 and ER signaling pathways contributes to resistance to hormonal therapy in BC (22). Meanwhile, multiple trials have reported that including

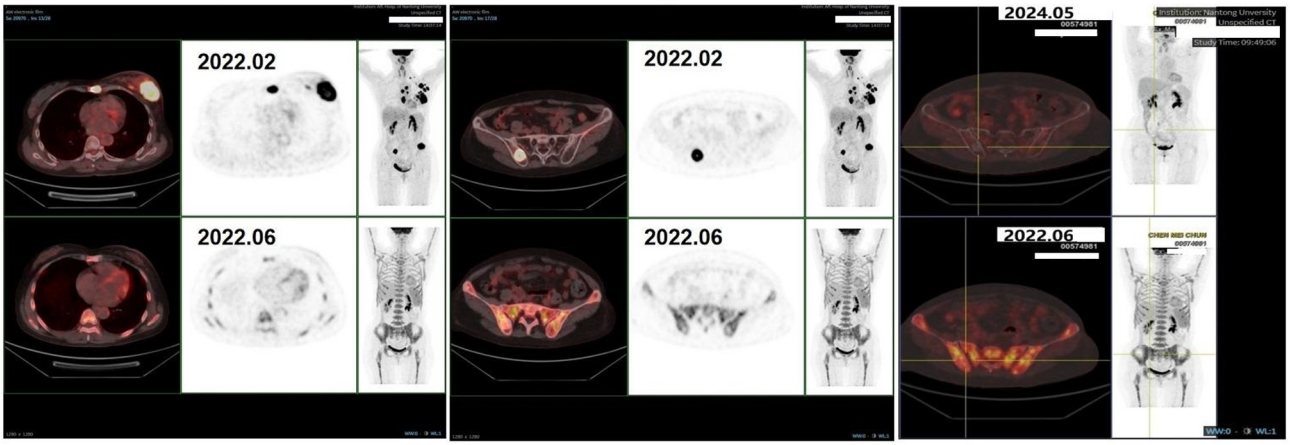

Figure 1. Positron emission tomography-computed tomography images before and after treatment.

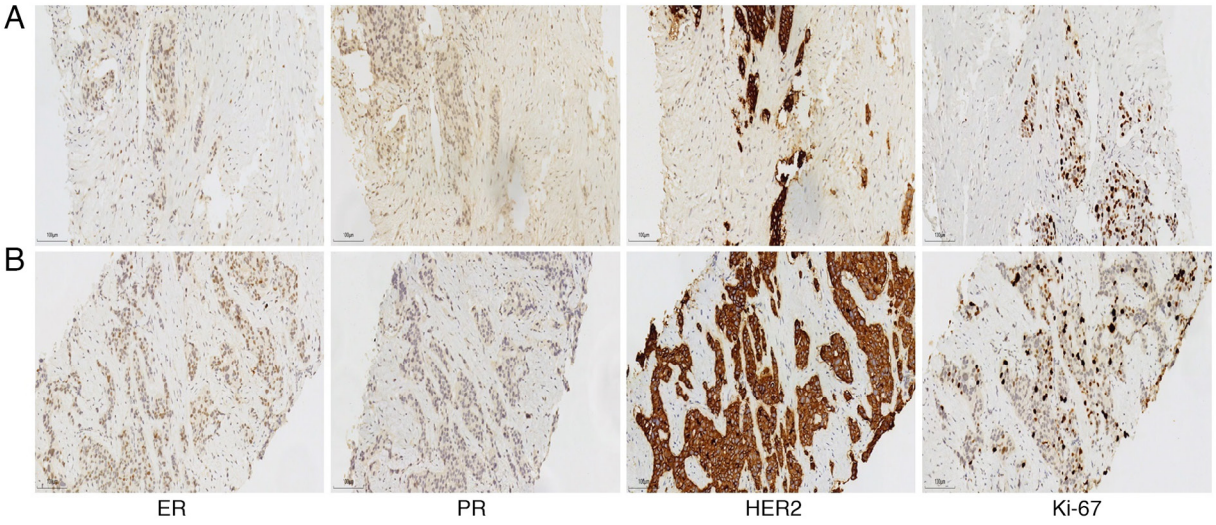

Figure 2. IHC images from the needle biopsy (magnification, x200). IHC images of (A) breast cancer and (B) left axillary lymph node tissue. IHC, immunohistochemistry; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2.

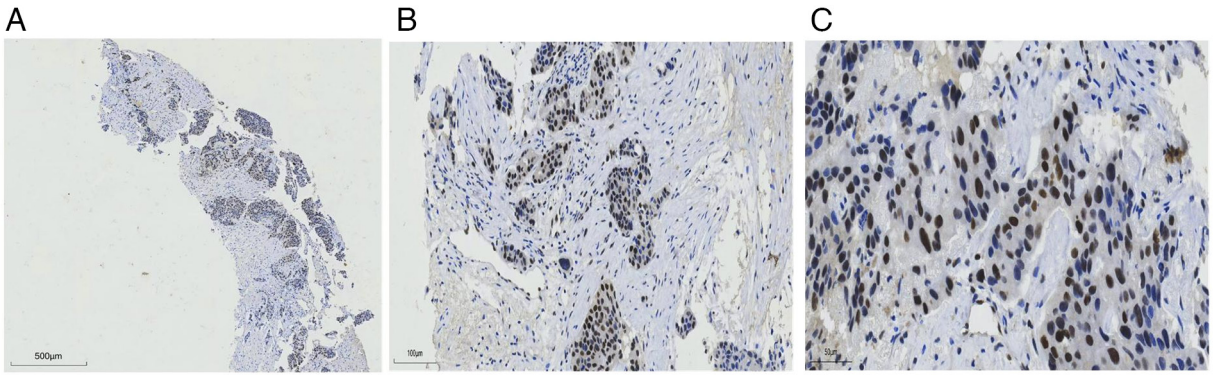

Figure 3. Expression of retinoblastoma protein in the biopsy, analyzed using immunohistochemical staining. (A) Low (x40), (B) medium (x100) and (C) high (x400) magnification.

CDK4/6is in endocrine treatment markedly improves PFS in metastatic cases (22,23).

CDK4/6 has emerged as a promising target in HER2$^+$ BC, as the cyclin D1/CDK4/6/pRB axis is also a key pathway influencing the efficacy of HER2-targeted therapies (6). ER and PR, which are classified as steroid hormone receptors (also known as nuclear receptors), directly bind to specific DNA sequences in the regulatory regions of target genes to

Figure 4. Timeline of treatment for the patient in the present report. PR, partial response; THP, docetaxel + trastuzumab + pertuzumab; q3w, every 3 weeks; qd, every day.

regulate transcription, promoting cell division, proliferation and invasion (24). Even estrogens, which engage in nongenomic ER activity outside the nucleus, have been reported to activate the HER2 signaling pathway (25). The elucidation of the CDK4/6-cyclin D-RB pathway, implicated in the pathogenesis of BC and other tumors, has led to the development of CDK4/6is to induce G1 cell cycle arrest and apoptosis. These inhibitors associate with cyclin D to form complexes that promote Rb protein phosphorylation and inactivation, driving cell division. Through the inhibition of CDK4/6, Rb is dephosphorylated, leading to cell cycle arrest (26). CDK4/6is (palbociclib, ribociclib and abemaciclib) have been extensively studied across several tumors, and CDK4/6 has also been implicated in resistance mechanisms to HER2-targeted therapies (27).

Furthermore, molecular studies indicate that the cyclin D-CDK4/6 pathway is often overactivated in HR+ BC (28). The amplification of the cyclin D1 oncogene (CCND1), CDK4 or deletions of the tumor suppressor genes CDK inhibitor 2A (encoding p16INK4a and p14ARF) have been observed in BC. Additionally, ER, which is the primary driver of tumor growth and survival in HR+ BC, directly targets CCND1 (22).

Evidence suggests that complex crosstalk between HER2 and ER signaling contributes to poor responses to standard therapies in patients with TPBC; therefore, it is reasonable to consider targeting both types of signaling pathways. Trastuzumab-treated resistant tumors exhibit CDK4/6-dependent proliferation (6). Marked progress has been made in the treatment of metastatic (M)BC, particularly in ER+ subtypes, where CDK4/6is are now recommended as standard additions to endocrine therapy (8). Considering the multifaceted signaling mechanisms in TPBC, combination therapies targeting both HER2 and ER signaling may be more effective in blocking the complex network. Moreover, HER2 and ER signaling converge on RB1, and inhibition of cyclin D1 and CDK4 has been reported to reverse resistance to HER2-targeted therapies in HER2+ BC. Although combined HER2 and CDK4/6 inhibition does not significantly increase tumor cell apoptosis, *in vitro* and *in vivo* studies have reported that this approach reduces cellular proliferation by inducing G1 cell cycle arrest (6).

Recently, a pilot trial investigating neoadjuvant pyrotinib combined with trastuzumab, dalpiciclib and letrozole in patients with TPBC reported a promising pathological response with an acceptable safety profile (29). Furthermore, the MONARCHER trial reported that abemaciclib, in combination with fulvestrant and trastuzumab, markedly improved PFS and overall survival in patients with HR+ and HER2+ advanced BC compared with standard-of-care chemotherapy + trastuzumab (7). Similarly, the SOLTI-1303 PATRICIA trial reported that palbociclib in combination with trastuzumab was safe and exhibited promising survival outcomes in patients with ER+/HER2+ advanced BC (30). These results suggest that combination therapy involving CDK4/6is, HER2-targeted therapies and endocrine therapy may be a promising approach for TPBC. However, the efficacy of CDK4/6is is often dependent on RB protein expression (31). Therefore, monitoring of RB protein loss or other RB mutations is recommended both before and after treatment progression with CDK4/6is. Low RB1 protein expression has been reported to reduce the effectiveness of CDK4/6-Cyclin D complex inhibition, leading to the tumor resistance to CDK4/6 inhibitors (32). A study using glioblastoma xenograft cells reported that an A193T missense mutation in RB exon 2, which reduced RB1 protein levels, was associated with resistance to CDK4/6is (32). Therefore, further exploration and analysis of the expression and regulatory mechanisms of RB1 may help to overcome the resistance and expand the application of CDK4/6is in TPBC. Although the patient in the present case achieved encouraging results, there are still certain limitations in the application of CDK4/6is for HER2+ and HR+ BC, such as the high cost of CDK4/6is and the lack of large-scale clinical trials specifically targeting HER2+ and HR+ subtypes (29). Furthermore, the underlying causes of heterogeneity within these subtypes require further investigation.

Treatment-related adverse events and comorbidities are critical to maintain effective and timely treatment, as they affect the quality of life of patients. The development of third-generation CDKis has led to marked improvements in selectivity, activity and toxicity profiles (33). For example, maintenance therapy with CDK4/6is is associated with fewer adverse events compared with chemotherapy, such as gastrointestinal reactions, liver function abnormalities and fatigue. However, attention must still be paid to potential adverse effects of CDK4/6is. In the present case, the patient experienced grade 3-4 reductions in white blood cell counts, increasing the risk of infection during treatment. Although the white blood cell levels recovered during the withdrawal of CDK4/6is, the risk of infection remained substantial during the period. Therefore, it is essential to manage the adverse reactions throughout the treatment course. Currently, CDK4/6is have been considered as one of the most promising therapies for HER2+ MBC and are likely to become standard clinical practice in the near future. Furthermore, the results of the present case support the feasibility and efficacy of combining CDK4/6is with HER2-targeted and endocrine therapies, providing a solid foundation for future clinical applications.

In conclusion, the present report details the case of a patient with HR+/HER2+ MBC who achieved a favorable outcome after six cycles of THP therapy, followed by treatment with exemestane (25 mg once daily) and palbociclib (initially 125 mg once daily for 21 days, followed by a 7-day break, then adjusted to 100 mg once daily). To date, the patient has achieved a PFS of ≥30 months. Therefore, the present clinical case helps to further recognize that the classic paradigm of dual target therapy, combining with endocrine therapy and CDK4/6is, demonstrates superior super efficacy in patients with HR+/HER2+ BC, especially in those with high RB expression, providing valuable insights for the clinical practice in the treatment of HR+/HER2+ BC.

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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

FL made recommendations for treatment and conceived the idea of the study. YHC designed and drafted the manuscript. JLZ obtained medical images and collected the data. HXD and YHC analyzed the data and revised the manuscript. FL and YHC confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by Ethics Committee of Affiliated Hospital of Nantong University (approval no. 2018-K020).

Patient consent for publication

The patient in the present report agreed to participate in the study and provided written informed consent for publication of the study.

Competing interests

The authors declare that they have no competing interests.

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