

Case Report

Durable and Drastic Response to the Trastuzumab, Letrozole, Abemaciclib, and Goserelin Combination as First-Line Therapy in HER2-Positive and Hormone Receptor-Positive Metastatic Breast Cancer: A Case Report

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Keywords

Case report · HER2+ HR+ breast cancer · CDK4/6 inhibitor · Trastuzumab · Letrozole · Targeted therapy for breast cancer

Abstract

Introduction: Chemotherapy combined with anti-human epidermal growth factor receptor 2 (HER2)-targeted therapy is currently a standard treatment for advanced HER2/HR-positive breast cancer (BC), although evidences showed that HR expression compromised effectiveness of the treatment. While cyclin-dependent kinase (CDK) 4/6 inhibitors combined with endocrine therapy is a key therapy for the BC with HR expression, data on the effectiveness and safety of CDK 4/6 inhibitors combined with trastuzumab and endocrine therapy as a first-line treatment for HER2-positive and HR-positive metastatic BC are limited. **Case Presentation:** Here, we report a case of a 46-year-old premenopausal woman diagnosed with stage 4 HER2/HR-positive invasive ductal carcinoma from both right and left breast with hypermetabolic activities in multiple lymph nodes, adrenal, bone, and skin. **Interventions:** Due to the patient's refusal to use chemotherapy, she was started on goserelin, abemaciclib, letrozole, and trastuzumab. **Outcomes:** The patient's symptoms were relieved with near resolution of the primary breast mass and nearly all of the metastatic sites. Metabolic resolution was observed in bone

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lesions. The disease was under control for 57 weeks. During the treatment, neutropenia (grade 1–2) and anemia (grade 1) occurred, which spontaneously recovered. Additionally, diarrhea improved after symptomatic treatment. **Conclusion:** We believe that the combination of trastuzumab, hormone suppression, and abemaciclib is a practicable and effective treatment for HER2-positive and HR-positive metastatic BC in premenopausal patients who cannot tolerate the first-line chemotherapy.

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Introduction

Human epidermal growth factor receptor 2 (HER2)-positive breast cancer (BC) is a special type of BC, representing an estimated 15–25% of all BC subtypes, of which 50% are co-expressing hormone receptors [1]. For patients with advanced or metastatic disease, the first-line therapy commonly recommended is chemotherapy + anti-HER2 therapy. However, some patients cannot tolerate the toxicity of chemotherapy because of their poor physical condition. Therefore, effective chemotherapy-free regimens are necessary. Here, we summarize a chemotherapy-free strategy; triple blocking of the HER2, CDK4/6, and HR pathways, for HER2-positive and HR-positive metastatic BC patients as a first-line treatment. The patient described in this case showed a dramatic response of an extensive metastatic disease.

Case Presentation

A 46-year-old, premenopausal lady presented with palpable mass at left axilla for 1 month. Mammography and ultrasonography revealed multiple masses at both breasts, with sizes varied up to 5 cm, occupied all quadrants of right breast and left upper outer quadrant of left axillary breast. Bilateral axillar and left supraclavicular lymphadenopathy were found. A positron emission tomography scan with computerized tomography (PET/CT) scan revealed; multiple hypermetabolic nodules in both breasts, multiple lymph nodes (clavicle, bilateral supraclavicular, internal mammary, axillary, prevascular, paratracheal, paraesophageal, parapancreatic, and left para-aortic nodal stations), bilateral adrenal nodules and multiple bone lesions (right humeral head, right iliac bone, T1 vertebral body and left lamina of T8 vertebra) (Fig. 1). Core needle biopsy from both breasts revealed invasive ductal carcinoma with lymphovascular invasion and positivity for HER2 (DISH+, equivocal score 2+)/ER (70–90%)/PR (10–20%) with Ki-67 of 30–35%. A diagnosis of bilateral invasive ductal carcinoma of breast with extensive metastasis was made. After a long discussion, the patient and her family declined any treatment with chemotherapy-based regimen. Next generation sequencing showed TP53 mutation and ERBB2 amplification without other targetable mutations. The care team decided to treat her with trastuzumab (8 mg/kg for an initial loading dose then 6 mg/kg every 3 weeks), letrozole (2.5 mg OD), and abemaciclib (150 mg BID). Goserelin (3.75 mg every 12 weeks) was also added because of her premenopausal status. The patient agreed and felt comfortable with the given option. A near-complete response was observed after 3 cycles of treatment, with complete or near resolution of the majority of lesions on PET/CT. There was clinical progression in the right breast after 8 cycles of treatment. She underwent a wide excision of the right breast mass and a total hysterectomy with bilateral oophorectomy to avoid further Goserelin injection, then resumed therapy. A metabolic progression in the left breast, confirmed by pathology,

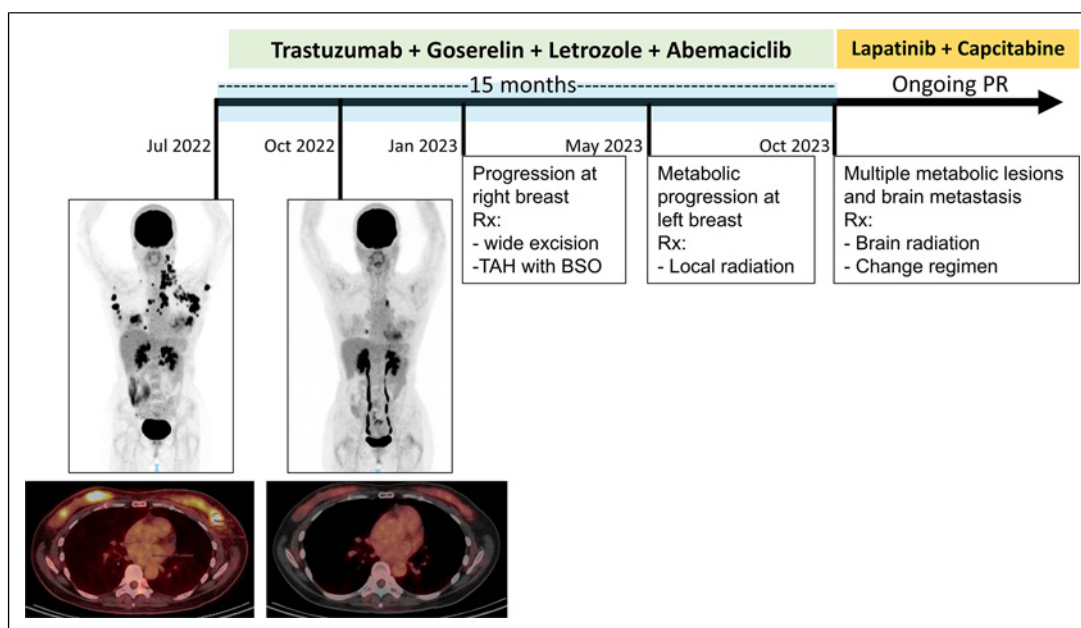


Fig. 1. Clinical and treatment time course of the patient.

was observed during a follow-up after the 11th treatment cycle. Volumetric modulated arc therapy was administered to the left breast in addition to the drug regimen. Pathology revealed that ER expression became low positive, PR became negative, and HER2 expression became stronger (score 3+) in both relapse tissues. After 57 weeks of treatment, new lesions were shown on a followed-up PET/CT in brain, right breast and left adrenal gland without any clinical symptoms (Fig. 1). At this point, lapatinib and capecitabine were given, along with local brain radiation to control the brain lesion. Currently, the patient is alive and responds well with an ongoing treatment. Throughout the treatment, she tolerated both regimens well and had a good quality of life. Only grade 1 anemia, and grade 1–2 neutropenia, and grade 2 diarrhea were found during the first regimen. The diarrhea was manageable using loperamide once a day prn. The patient had no other side effects while being on abemaciclib + letrozole + goserelin + trastuzumab.

Discussion

In recent decades, therapeutic advances in BC have significantly improved patient outcomes. These advances include the emerging role of neoadjuvant therapy [2] and immune checkpoint inhibitors [3], the discovery of novel molecular targets in BC, and the benefits of antibody-drug conjugates [4]. The transition to a post-genomic era has further enhanced our understanding of BC biology and helped identify molecular markers that predict treatment benefits. Additionally, the introduction of new drug combinations based on these molecular markers presents new challenges in treatment selection and drug toxicity monitoring [5–7].

To identify a novel chemotherapy-free regimen for metastatic HER2-positive BC, several approaches have been investigated. In this case, the pertuzumab + trastuzumab + chemotherapy regimen was initially considered by us as the treatment of choice. However, as the patient refused getting chemotherapy, double anti-HER2 blockage without chemotherapy has much shorter progression-free survival (PFS) [8].

Since, a large fraction of HER2-positive BC also expresses hormone receptors (ER/PR) at a high level, it presents a new opportunity to combine hormonal therapy with CDK4/6 inhibition, an effective standard therapy for hormone receptor-positive BC [9], into the HER2-targeting regimen. Evidence suggested that this notion may be scientifically justified. HER2 is a receptor tyrosine kinase that exerts its pro-proliferation activity partly via CDK4/6 [10, 11]. Accordingly, inhibition of CDK4/6 activity in mice bearing ErbB2 (Her2)-driven mammary carcinomas promoted BC cell senescence and blocked tumor growth [12]. A preclinical mouse model showed that over-expressions of Cdk4 and its partner cyclin D1 were essential for BC cells to proliferate under Her2 inhibition. This indicated that Cdk4 activity is required for BC cells to resist to anti-HER2 therapy. A treatment with CDK4/6 inhibitor re-sensitized HER2-therapy-resistant tumors to the inhibition of EGFR family kinases [13]. Both Cdk4 and Her2 are a negative regulator of TSC2 a pivotal tumor suppressor. Therefore, a treatment approach that block CDK4 and HER2, not only deprives cancer cell cycle and MAP kinase pathway, but also promotes TSC2-mediated cancer suppression [13, 14].

On the other hand, in HR-positive BC, acquired activation of HER2 has been linked to around 10% of the HR-positive BC that resistant to CDK4/6 inhibitor + hormonal therapy [15]. Recent findings from Brasó-Maristany et al. [16] indicated that HER2 blockage in the HER2-positive BC induced the luminal A phenotype, increasing the sensitivity to CDK4/6 inhibition. Interestingly, the phenotype switch can be reversed upon the withdrawal of anti-HER2 drugs, emphasizing that the combination regimen between anti-HER2 and anti-CDK4/6 needs to be maintained to achieve the synergistic effect. These data highlight that the HER2 and CDK4/6 pathways are dynamically interplaying in BC. The triple inhibition of HER2, CDK4/6, and hormone receptors is plausibly required to effectively suppress key growth signaling in BC. This triple inhibition also likely prevents resistance to anti-HER2 or anti-hormonal monotherapy, which can emerge when only one of the two key pathways is inhibited. This notion is consistent with recent preclinical findings in cell lines, suggesting that co-targeting the CDK4/6 pathway can void the escape mechanisms induced by ER/HER2 cross-talk and trigger the transition from cell quiescence to sustained senescence [17].

Ongoing clinical trials are testing analogous triple combinations with promising results. In a phase IB clinical trial, the LORDSHIPS study showed that patients with HER2-positive and HR-positive recurrent or metastatic BC, treated with letrozole, the pan-EGFR inhibitor pyrotinib, and the CDK4/6 inhibitor dalpiciclib, had a high overall response rate of 66.7% and a median PFS of 11.3 months. The toxicity of this treatment was tolerable [18]. In the MonarchHER phase II study, patients with HER2-positive and HR-positive advanced BC, who had received at least two prior HER2-targeted therapies, were treated with trastuzumab, fulvestrant, and abemaciclib. These patients showed a significantly increased overall response rate of 33% compared to 14% (odds ratio 3.2, 95% CI 1.4–7.1, $p = 0.0042$) and PFS of 8.3 months compared to 5.7 months (hazard ratio 0.67, 95% CI 0.45–1.00, $p = 0.05$) compared with patients treated with trastuzumab and investigator-selected chemotherapy [19]. In a multicenter phase II PATRICIA trial in patients who previously received 2–4 prior lines of anti-HER2-based regimens, combination of palbociclib, trastuzumab with and without letrozole were given. The palbociclib plus trastuzumab clearly increased PFS at 6 months from 33.3% (5/15) to 42.8% (12/28) in the HER2-positive/HR-positive group. An addition of letrozole slightly increased the benefit in the HER2-positive/HR-positive group to 46.4% (13/28) [20].

Based on these data and a patient's choice to decline a chemotherapy-based treatment, we were encouraged to give trastuzumab, letrozole, abemaciclib, and goserelin as the first-line regimen for this treatment-naïve case. As there is limited data in efficacy and side effects of double HER2 blockage + anti-CDK4/6 inhibitors + letrozole, we chose to give only trastuzumab to avoid any serious unexpected side effects. Along with surgery and radiotherapy, the

treatment gave a relatively long-termed response of more than 14 months, with tolerable toxicities. Recently, a comparable case report showed an effectiveness of the trastuzumab, palbociclib, letrozole, and leuprorelin combination, as the first-line therapy, in a patient with HER2-positive/HR-positive metastatic BC, yielding a 14-month PFS [21]. Unlike this case, in which HER2 expression was high (3+), our case showed only equivocal HER2 expression (IHC 2+). This result discouraged us from using the therapy that exclusively targets HER2, as poor response to trastuzumab is known to associate with overall low-level or equivocal HER2 amplification [22]. For this reason, the regimen with dual HER2 inhibition by pertuzumab and trastuzumab was also precluded since its potential lack of response in cases with HER2 heterogeneity [23]. Therefore, we selected the HER2/HR/CDK4/6 triple-blockage for this case, hoping that it would be most benefit for the patient according to her hormonal receptors and HER2 status.

After a long period of treatment, the recurring tumors were found to have lost ER and PR expression. Upregulation of HER2 from equivocal (2+) to positive (3+) was also observed. These results suggest that the initial significant response to triple blocking depended significantly on the expression of HR. The upregulation of HER2 expression may provide a bypassing resistance mechanism to CDK4/6 and hormonal suppression therapy, as it is a well-reported mechanism in drug-resistant HR-positive BC [24]. Therefore, at this point, the treatment was switched to the HER2-centric lapatinib plus capecitabine to match the new molecular profile and CNS penetration.

Fear of chemotherapy remains one of the factors causing treatment refusal or delay [25]. There is still a strong misconception about chemotherapy, especially intravenous (IV) chemotherapy, in Thailand. Many patients are very fearful and resolutely refuse IV chemotherapy. Interestingly, they have a better perception of surgery over IV chemotherapy, as evidenced in this instance.

To avoid unnecessary use of injections, the patient also chose the 12-week dose of goserelin instead of the monthly dose. As her disease progressed, the patient opted for a total hysterectomy and oophorectomy to avoid further goserelin injections. The patient agreed to use the oral chemotherapy capecitabine along with lapatinib only when a new brain lesion was detected.

Conclusion

This study showed that a combination of trastuzumab, letrozole, abemaciclib, and goserelin may be an effective alternative non-chemotherapy treatment strategy for HER2-positive and HR-positive metastatic BC in premenopausal patients as a first-line treatment. It can provide a drastic and long-term response, even in patients with a high burden of disease, without major toxicities.

Statement of Ethics

The case report complies with the guidelines for human studies and was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. This study protocol was reviewed, and the need for approval was waived by the Local IRB. Written informed consent was obtained from the patient for publication of this case report and any accompanying images. The CARE checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see <https://doi.org/10.1159/000542926>).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Conception, design, and drafting of the article: S.S., P.P., H.S., and S.J.; acquisition of data: S.S., P.P., and H.S.; analysis and interpretation of data: S.S., N.K., P.P., H.S., and S.J.; critically revising the article: N.K., P.P., H.S., and S.J.; review of the submitted version of the manuscript and approval of the final version of the manuscript: all authors.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding authors.

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