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Pathological Complete Response with CDK 4/6 Inhibitors in HR+/HER2- Locally Breast Cancer: Case of a Benign Bone Lesion Misidentified as Metastatic

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Abstract

Locally advanced breast cancer presents significant challenges to the multidisciplinary team, particularly in cases involving hormone receptor (HR)-positive, HER2-negative tumors, which typically show lower rates of pathological complete response to chemotherapy. Cyclin-Dependent Kinase (CDK) 4/6 inhibitors are the cornerstone of treatment in metastatic Hormone Receptor (HR)-positive, HER2-negative breast cancer and have more recently been considered in the adjuvant setting. However, their effectiveness in the neoadjuvant setting remains uncertain.

We report the case of a 55-year-old postmenopausal woman initially diagnosed with metastatic HR+/HER2- breast cancer due to a unique L5 bone lesion. Systemic treatment was initiated with an Aromatase Inhibitor (AI) and a CDK4/6 inhibitor. After six months of treatment, imaging reevaluation confirmed that the L5 lesion, which had remained unchanged, was benign, allowing for curative surgery. Final pathology revealed a complete histological response with no residual tumor, highlighting the potential of CDK4/6 inhibitors in managing locally advanced HR+/HER2- breast cancer.

Keywords: Breast cancer • Neoadjuvant treatment • Surgery • CDK 4/6 inhibitors • Complete pathological response

Introduction

Breast cancer is the second leading cause of global cancer incidence in 2022, with an estimated 2.3 million new cases, comprising 11.6% of all cancer cases. It remains the fourth leading cause of cancer-related deaths worldwide [1].

It's a heterogeneous disease that can be categorized into various molecular subtypes, each carrying distinct prognostic and therapeutic implications. Estrogen Receptor (ER)-positive, Human Epidermal Growth Factor Receptor 2 (HER2)-negative breast cancer, is the most prevalent subtype, comprising approximately 70% of all invasive breast cancers [2].

The cornerstone of systemic therapy for HR+/HER2- breast cancer is Endocrine Therapy (ET), recommended as adjuvant treatment in early stages of the disease and as the preferred approach in metastatic settings [3].

In recent years, the systemic approach to this disease has significantly evolved with the introduction and establishment of CDK 4/6 inhibitors. Initially used in metastatic settings, these inhibitors have improved survival outcomes and transformed the standard of care for metastatic breast cancer patients [4]. They have also gained traction in the setting of HR+/HER2– breast cancer [5].

In Estrogen Receptor (ER)-positive breast cancer, activation of the ER signaling pathway upregulates the ER-cyclin D-CDK4/6 pathway. The cyclin-CDK pathway plays a crucial role in regulating the cell cycle. Both CDK4 and 6 control the cell transition from G1 phase into S phase and their activity is mostly regulated by the association with D-family cyclins [6]. Thus, CDK4/6 ihibitors act to restrain proliferation of sensitive tumor cells; and preventing cell cycle progression by directly blocking the activity of the Cyclin D–CDK4/6 [7].

The efficacy of CDK4/6 inhibitors (Palbociclib, Abemaciclib and Ribociclib) was established in several key studies (PALOMA, MONARCH and MONALEESA) respectively in metastatic HER+/HER2- breast cancer [8-10]. The exciting results observed with CDK4/6 inhibitors in treating advanced ER-positive, HER2-negative breast cancer have triggered the evaluation of these agents in the early-stage setting.

We report a case of a postmenopausal female patient who was initially treated as having metastatic HR+/HER2- breast carcinoma due to a single bone lesion, which was later found to be benign. She was considered primarily unresectable and was proposed for systemic therapy with an Aromatase Inhibitor (AI) and a CDK4/6 inhibitor, achieving a pathological complete response. This case highlights the potential of this therapeutic approach in situations where high-level evidence is currently lacking.

Case Report

A 55-year-old woman with no significant medical history presented to the hospital after noticing a masse in her right breast, with no other associated clinical symptoms. Her menarche occurred at 14 years old and she reached menopause at 48. She has never been pregnant. The patient did not report any family history of breast, or ovarian cancer.

The physical examination revealed a 3 cm mass at the junction of the external quadrants of the right breast, with no palpable axillary lymphadenopathy. The rest of the physical examination revealed no obvious abnormalities.

The patient underwent mammography and a subsequent ultrasound examination, which revealed an irregular mass in the upper outer quadrant of the right breast measuring 18.6 x 17 mm, classified as BI-RADS 5, with microcalcifications extending approximately 3 cm at the junction of the external quadrants.

The core biopsy confirmed an invasive breast carcinoma, grade 3, with

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an immunohistochemical profile showing 100% expression of estrogen and progesterone receptors in tumor nuclei and HER2 score was 1+. The tumor exhibited a proliferative index of 20% as assessed by Ki67 expression.

To complete the locoregional assessment, a breast Magnetic Resonance Imaging (MRI) was performed, revealing a mass in the upper outer quadrant of the right breast measuring 18.5 × 16.7 × 17.5 mm, along with suspicious right axillary adenopathy, consistent with a malignant lesion classified as BI-RADS 5. Additionally, a broad lesion in the upper outer quadrant and at the junction of the external quadrants of the right breast measuring 29 × 10.5 × 34 mm was also classified as BI-RADS 5. No suspicious abnormalities were found in the left breast.

A thoracoabdominal-pelvic CT scan showed the right breast tumor mass and an osteolytic lesion in the vertebral body of L5. Bone scintigraphy confirmed the presence of a lesion at L5 (Figure 1).

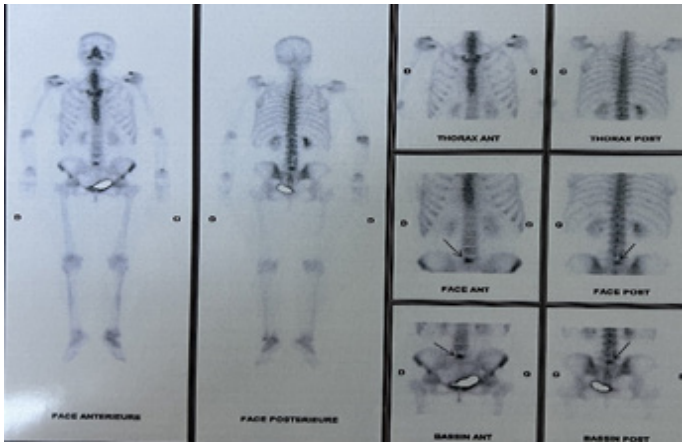

Figure 1. Initial bone scintigraphy showing a L5 bone lesion.

To further refine the staging, a Positron Emission Tomography (PET)/CT with 18ffluorodeoxyglucose (18F-FDG) was performed, revealing two hypermetabolic lesions (SUV=9.5 and 3.1)) in the lower inner quadrant of the right breast and an active lytic lesion at L5 (SUV 5.7), with no other images indicating distant metastases (Figure 2).

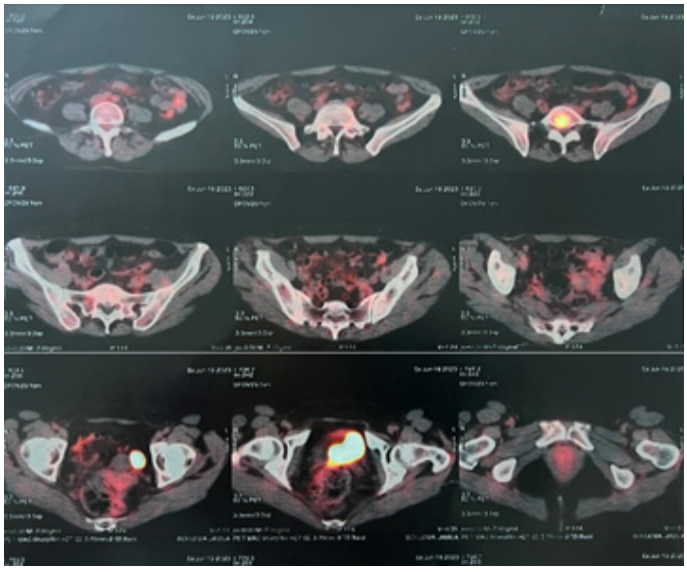

Figure 2. PET/CT with 18F-FDG at initial staging.

The case was reviewed in the breast multidisciplinary meeting, where the tumor was classified as metastatic with a single bone lesion. Consequently, systemic therapy with an Aromatase Inhibitor (AI) and a CDK4/6 inhibitor was recommended, with plans to reassess resectability in the future.

The patient initiated treatment with letrozole at a daily dose of 2.5 mg and palbociclib at 125 mg once daily for 21 days, followed by a 7-day break to complete a 28-day treatment cycle. She completed 6 full cycles of palbociclib with good tolerance, experiencing only grade 2 neutropenia.

An evaluation thoracoabdominal-pelvic CT scan showed a dense formation in the upper outer quadrant of the right breast related to the intramammary clip and a stable, benign-appearing L5 vertebral lesion. The radiology team's re-evaluation of the initial scan confirmed the benign nature of the vertebral lesion.

The patient subsequently underwent surgery with curative intent. A total mastectomy with right axillary lymphadenectomy was performed.

Final pathology showed no residual tumor post-neoadjuvant treatment, with 0 out of 20 lymph nodes positive for metastasis and a complete histological response classified Sataloff type TA NB, Chevallier grade 1.

The patient received adjuvant external beam radiotherapy to the right chest wall, supraclavicular and infraclavicular areas, delivering a dose of 42 Gy in 15 fractions of 2.8 Gy per fraction. Hormone therapy with letrozole 2.5 mg alone was continued for a planned duration of five years.

Discussion

The advent of selective CDK4/6 inhibitors marked an initial breakthrough in advanced breast cancer [11]. Subsequently, multiple clinical trials have demonstrated the efficacy of palbociclib, ribociclib and abemaciclib in this setting, leading to improved Progression-Free Survival (PFS) and Overall Survival (OS) [12-14].

Following these promising results in the treatment of advanced ER-positive, HER2-negative breast cancer, CDK4/6 inhibitors have been studied in the adjuvant setting for early breast cancer, combining with Endocrine Therapy (ET) *vs.* ET alone in three published trials with slightly different inclusion criteria: NATALEE [15], PALLAS [16] and MonarchE [17]. Among these, MonarchE and NATALEE reported positive outcomes.

However, in current practice, neoadjuvant hormonal therapy for luminal HER2-negative breast cancer is not commonly used. Chemotherapy has traditionally been the cornerstone of neoadjuvant treatment for HR+/HER2- breast cancer, with pCR rates in luminal-like tumors remaining significantly lower compared to triple-negative or HER2+ breast cancer [18].

In the neoadjuvant setting, several phase II trials have explored CDK 4/6 inhibitors combined with endocrine therapy (Table 1). The primary endpoint has been primarily Complete Cell Cycle Arrest (CCCA), defined as Ki67 $\leq$ 2.7%, leveraging the ability to perform serial biopsies of primary tumors.

The single-arm phase II NeoPalAna trial assessed the anti-proliferative effect of palbociclib in patients with stage II–III ER-positive, HER2-negative breast cancer. Patients first received anastrozole for 4 weeks, followed by the addition of palbociclib. Serial biopsies were taken and Ki67 levels were measured, with the primary endpoint CCCA, evaluated 2 weeks after starting palbociclib. Results showed that palbociclib improved cell cycle control compared to anastrozole alone [19].

The NeoPal study [20] investigated palbociclib and letrozole in patients with stage II-III node-positive breast cancer, luminal B. While the combination therapy was associated with a higher Residual Cancer Burden (RCB) 0-1, which increased with chemotherapy use, Ki67 suppression was comparable between both treatment groups. This similarity translated into similar Preoperative Endocrine Prognostic Index (PEPI) scores [21], which are associated with breast cancer-specific survival and relapse-free survival.

The combination of ribociclib plus letrozole in ER-positive, HER2-negative breast cancer has being assessed in several phase II neoadjuvant trials.

In the MONALEESA-1 trial [22], a three-arm study involving postmenopausal women with hormone receptor-positive, HER2-negative

Table 1. CDK4/6 inhibitors in early breast cancer: Neoadjuvant studies.

Trial	Phase	CDK 4/6 Inhibitor Arm	Control Arm	Study Population	Primary Endpoint	Outcomes
NeoMONARCH (25)	II	Abemaciclib + anastrozole	ET alone	Pre- and postmenopausal stage I-IIIB, HR+/ HER2- BC	CCCA	CCCA: 87% *vs.* 26%, favoring palbociclib
MONALEESA-1 (23)	II	Ribociclib + letrozole	ET alone	Postmenopausal, grade II/III with HR+ HER2- BC	CCCA	CCCA: 92% *vs.* 69% favoring ribociclib
NeoPalAna (20)	II	Palbociclib + anastrozole	ET alone	Pre- and postmenopausal, stage II/III HR+/ HER2-BC	CCCA	CCCA: 87% *vs.* 26%, favoring palbociclib
CORALLEEN (24)	II	Ribociclib + letrozole	Multiagent chemotherapy	Postmenopausal stage I/II/III with RH+/ HER2- BC, breast lesion diameter ≥ 2.0 cm	RCB rate	RCB 0/I was achieved in 11.8% in CT arm *vs.* 6.1% in anti CD 4/6 arm
NeoPAL(21)	II	Palbociclib + letrozole	Multiagent chemother	High-risk luminal breast cancer	(RCB 0-I)	RCB 0: 17.7 *vs.* 15.7 favoring chemotherapy

CCCA: Complete Cell Cycle Arrest Change, ROR: proportion of patients with low-Risk-Of-Relapse, RCB: Residual Cancer Burden

breast cancer, ribociclib was evaluated at two doses (400 mg/day and 600 mg/day) in combination with letrozole compared to letrozole alone. The primary objective was to assess Ki-67 levels across the three treatment arms. Results indicated that the combination therapies led to decreased Ki-67 levels compared to letrozole monotherapy.

In the CORALLEEN study [23], postmenopausal patients with stage I–III hormone receptor-positive, HER2-negative breast cancer were randomized to receive either letrozole and ribociclib or multi-agent chemotherapy. The primary endpoint was the proportion of patients achieving a low Risk Of Relapse (ROR) score in surgical samples. Approximately 46% of patients in both treatment arms achieved a low Risk Of Relapse (ROR) at surgery, suggesting effective tumor downstaging. The Pathologic Complete Response (pCR) rate was higher in the chemotherapy arm.

In this study both the chemotherapy and no-chemotherapy groups had a high proportion of low-risk disease at 24 weeks, suggesting potential for exploring neoadjuvant approaches to identify patients who might not need chemotherapy for good outcomes.

The NeoMONARCH study with abemaciclib and anastrozole addressed a similar question [24] and found that more patients achieved CCCA in abemaciclib-containing arms than in anastrozole alone arms. However, in an exploratory analysis examining patients based on their adherence to abemaciclib treatment, over one third of patients who stopped therapy for more than 4 weeks experienced an increase in Ki67 levels.

Adding CDK 4/6 inhibitors to neoadjuvant ET led to a higher rate of CCCA. However, there were no significant differences in pCR among the three treatments studied. Further studies are needed to determine if neoadjuvant CDK 4/6 inhibitors can improve long-term survival in luminal breast cancer patients and identify the most beneficial groups for this treatment.

Moreover, a case report highlighted the use of anti-CDK inhibitors in postmenopausal female patient diagnosed with locally advanced HR+/HER2- breast carcinoma that was initially deemed unresectable. The patient received 6 months of systemic therapy with an Aromatase Inhibitor (AI) and a CDK4/6 inhibitor, resulting in a positive clinical response with 30% size reduction compared to the tumor's original dimension, enabling curative-intent surgery [25].

In our case, the patient was initially considered metastatic based on a single bone lesion, which led to systemic treatment with CDK4/6 inhibitors and aromatase inhibitors for 6 months. Upon evaluation, the bone lesion was found to be benign and the patient underwent surgery. Histopathological analysis of the surgical specimen revealed a complete histological response.

This case, highlights the potential effectiveness of this therapeutic approach in a clinical scenario where robust evidence is still developing.

Conclusion

This case report highlights the potential role of CDK4/6 inhibitors in neoadjuvant therapy for HR+/HER2-. The complete pathological response observed in our patient underscores the effectiveness of this treatment in downstaging tumors. This case provides evidence for their possible use in patients with locally advanced disease. However, further research is needed to confirm the long-term benefits of this therapeutic approach and identify the patient populations that may benefit the most.

Disclosures

Human subjects

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Conflict of Interest

No disclosures or conflicts of interest will be reported.

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