Case Report

Pathological complete response after neoadjuvant cyclin-dependent kinase 4/6 inhibitor and neoadjuvant endocrine therapy in locally advanced hormone receptor-positive breast cancer

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ABSTRACT

Breast cancer (BC) comprises different molecular subtypes, each having its own individual prognostic factors and thus having a distinct treatment algorithm. With the advent of cyclin-dependent kinase 4/6 (CDK 4/6) inhibitors, hormone receptor-positive (HR+) BC now has an additional targeted therapeutic option apart from endocrine therapy. As of now, CDK 4/6 inhibitors are Food and Drug Administration (FDA) approved in the metastatic and adjuvant settings. However, for the neoadjuvant setting, systemic chemotherapy is the standard of care. Systemic chemotherapy may not be a suitable option for elderly and frail patients in terms of associated side effects. Thus, due to tailored oncological management, many phase II and III trials of neoadjuvant CDK 4/6 inhibitors are ongoing. CDK 4/6 inhibitors are better tolerated than systemic chemotherapy and have less reported adverse events. Here, we report a case of locally advanced BC (HR+) achieving pathological complete response from neoadjuvant CDK 4/6 inhibitor with minimal toxicity. Thus, CDK 4/6 inhibitors appear to have a promising and upcoming role in the neoadjuvant setting for hormone-positive BC.

Key words: Breast cancer, Hormone-positive breast cancer, pCR, Locally advanced breast cancer, Neoadjuvant cyclin-dependent kinases 4/6 inhibitor

Breast cancer (BC) comprises various phenotypic and genotypic factors that contribute to its complexity in the treatment. With the recent advances in molecular pathology, different molecular subtypes have been identified as receptors such as estrogen receptor, progesterone receptor, and human epidermal growth factor 2 (HER2). According to St. Galen's consensus, four major molecular subtypes are identified for BC, namely, luminal A, luminal B, HER2 enriched, and basal type [1]. These molecular subtypes help in prognosticating and selection of adjuvant therapy. For hormone receptor-positive (HR+) BC, endocrine therapy was the only adjuvant systemic therapy available until the introduction of cyclin-dependent kinases 4/6 (CDK 4/6) inhibitors in the armamentarium. CDK 4/6 inhibitors work at the checkpoint of G1-S phase of the cell cycle and prevent the progression of cell cycle, thus leading to cell death [2]. At present, CDK 4/6 inhibitors are approved for advanced HR+ BC [3,4]. For locally advanced BC, systemic chemotherapy is the treatment of choice as neoadjuvant therapy. However, for patients who decline or are ineligible for systemic chemotherapy, CDK 4/6 inhibitors show a promising alternative.

Here, we present a case report of neoadjuvant CDK 4/6 inhibitors for focally advanced BC.

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CASE REPORT

A postmenopausal female in her early 70 s presented with a complaint of a lump in the right breast for 1 year which was gradually progressive in nature and associated with intermittent dull aching pain. She is a known hypertensive and diabetic on regular oral medications for the past 10 years. She has no significant past history and no family history of cancer.

On clinical examination, she is average built with fair general condition having eastern cooperative oncology group performance status 2 (ECOG PS 2). There is a 3 × 3 cm fixed, firm mass in the right upper outer quadrant of the breast with

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nipple retraction and overlying skin involvement. A single 1 × 1 cm free, mobile right axillary node was also palpable. A rest of the systemic examinations were within normal limits.

The patient was evaluated for breast malignancy. Whole-body fluorodeoxyglucose (FDG) positron emission tomography (PET) computed tomography (CT) showed multiple FDG avid enhancing soft-tissue lesions in the right upper outer quadrant, largest 1.2 × 1.3 cm, standardized uptake value (SUV) max 4.8 with FDG avid right axillary lymph node level I and II, 14 × 7 mm, SUV 1.4. Histopathological evaluation from the breast mass showed invasive duct carcinoma, Grade 3. Immunohistochemistry showed lesions to be Estrogen Receptor/Progesterone Receptor (ER+/PR-) and HER2 negative with Ki67 (MIB1- 30%) (Fig. 1). Baseline hematological workup showed no significant abnormalities. The patient was diagnosed as locally advanced BC (cT4B N1 M0) (HR+) stage IIIB.

The patient was counseled regarding systemic chemotherapy as a neoadjuvant treatment. However, the patient refused systemic chemotherapy in view of advanced age, low ECOG status, and multiple comorbidities. After discussing with the family members, she was started on tablet letrozole 2.5 mg and tablet palbociclib 125 mg. CDK 4/6 inhibitor was tolerated well by the patient without any need for dose modifications. Post 6 months of therapy assessment, FDG PET CT was done which showed an interval decrease in size, number, and metabolic activity of the primary breast lesion which was suggestive of a favorable partial response.

The patient was then advised for surgical evaluation for which she underwent a modified radical mastectomy with the right axillary lymph node dissection. The post-operative period was uneventful. The post-operative histopathological report showed a complete pathological response (ypT0N0) (Fig. 2). She received post-mastectomy radiotherapy: Hypofractionated regime 40Gy/15# which she tolerated well.

The patient is now on endocrine therapy (Tab letrozole 2.5 mg) and adjuvant CDK 4/6 inhibitor (Tab palbociclib 125 mg) for the past 8 months and doing well till now with no significant adverse events (disease-free interval of 8 months).

DISCUSSION

BC is a heterogenous group encompassing a varied array of different subtypes. With the recent advances in systemic chemotherapy and immunotherapy, we are now increasing the overall survival of the BC warriors. Multiple targeted receptors have been identified for their therapeutic uses such as ER/PR and HER2 receptors. Systemic chemotherapy as a neoadjuvant therapy plays a key role in HER2-enriched and triple-negative BC [5,6]. This neoadjuvant chemotherapy increases the pathological complete response (pCR) and rates of breast conservation surgeries in HER2-enriched and triple-negative BC [7]. This increase in pCR translates to improved survival of these subtypes of BC. Studies have shown that the HR+ subtype of BC is less responsive to neoadjuvant systemic chemotherapy. For these subsets of populations, other modalities like endocrine therapy can be additionally considered as a treatment option. Systemic chemotherapy is associated with its own set of adverse events such as myelosuppression, alopecia, gastrointestinal toxicities, and neurological abnormalities. A systematic review of neoadjuvant endocrine therapy versus systemic chemotherapy showed no statistical difference in response rate between the two giving the need for patient-tailored neoadjuvant therapy [8]. Many of the retrospective data utilizing neoadjuvant endocrine therapy comprised more geriatric population with multiple comorbidities versus patients receiving systemic chemotherapy. Long-term data show no significant survival difference in the two arms [9].

With the advent of CDK 4/6 inhibitors such as palbociclib, ribociclib, and abemaciclib, the combination treatment of endocrine therapy and CDK 4/6 inhibitors has again shown a promising result. Initially up till now, these combinations are approved in metastatic settings but many phase 2/3 trials are going on in the early breast and locally advanced HR+ BC [10]. The NeoPalAna study utilizing neoadjuvant palbociclib and anastrozole in stage II/III HR+ BC showed an increase in complete cell cycle arrest, thus showing its anti-proliferative action. In the PALLET study, neoadjuvant palbociclib with letrozole was given showing a significant reduction in Ki 67 in them [11]. In the CORALLEN study, neoadjuvant ribociclib with letrozole were given for postmenopausal HR+ BC, here also there is evidence of molecular downstaging of the tumor [12]. In the NeoMONARCH trial, neoadjuvant abemaciclib showed a greater reduction in Ki67 with an acceptable adverse events profile [13]. Neoadjuvant letrozole and palbociclib showed encouraging clinical response in high-risk luminal BC [14]. Safety-wise, CDK 4/6 inhibitors are well tolerated with most common side effects include diarrhea,

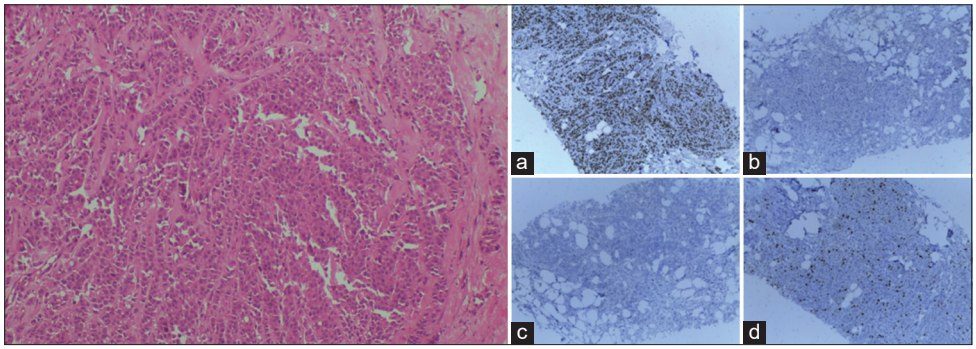

Figure 1: Left side shows H/E stained invasive duct carcinoma, Grade 3. Right-sided images show immunohistochemistry; (a) estrogen receptor (positive); (b) progesterone receptor (negative); (c) human epidermal growth factor receptor 2 (negative); and (d) MIB1: 30%

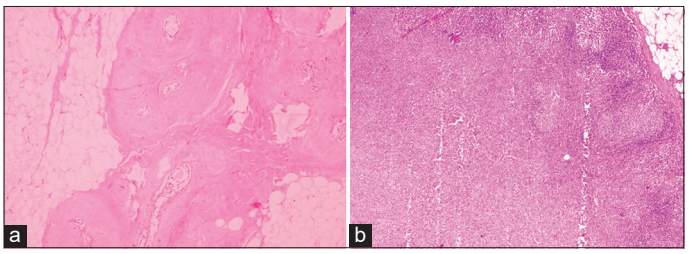

Figure 2: (a) Breast tissue showing hyalinization without any evidence of tumor (post-operative) and (b) lymph node showing histiocytes without tumor component (post-operative)

neutropenia, fatigue, anemia, and thrombocytopenia [15]. Meta-analysis shows that neoadjuvant CDK 4/6 inhibitors have a similar efficacy and lesser toxicity than neoadjuvant systemic chemotherapy [16].

Thus, considering the different variants of BC, a patient-tailored treatment which includes its staging and molecular profiling along with the patient's performance status and comorbidities has to be taken into account for the management.

CONCLUSION

With the advent of endocrine therapy and CDK 4/6 inhibitors, HR+ BC now has more targeted treatment options. These new therapies are less toxic than the currently approved systemic chemotherapy. Although currently matured overall survival data are still lacking for a direct head-to-head comparison between neoadjuvant CDK 4/6 inhibitors and neoadjuvant systemic chemotherapy, CDK 4/6 inhibitors can be utilized on an individual basis for patient directed tailored treatment.

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AUTHORS' CONTRIBUTIONS

Dr. Ankur Mahajan, Dr. Saroj Kumar Das Majumdar: Data Collection, Manuscript preparation and editing; Dr. Sandip Kumar Barik, Dr. Deepak Kumar Das, Dr. Dillip Kumar Parida: Manuscript editing; Dr. Rashmi Patnayak, Dr. Manas Baisakh: Pathological assessments. All the authors read and approved the final version of the manuscript.

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