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Original Article

# Letrozole and Palbociclib in Advanced Breast Cancer: Outcome from Cancer Institute, Chennai

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## Abstract

**Background:** Cyclin-dependent kinase 4/6 inhibitor addition to hormonal therapy has shown to improve the survival of hormone receptor (HR)-positive, HER2-negative advanced breast cancer (ABC). **Methods:** We retrospectively analyzed untreated patients with HR-positive, HER2-negative ABC, who received letrozole and palbociclib at the Cancer Institute, Chennai, from October 2017 to January 2019. **Results:** A total of 24 patients were included in this study. The median progression-free survival (PFS) was 18 months, and the median overall survival (OS) had not reached. The 1-year PFS and OS were 73.7% and 89.2%, respectively. The common toxicities were neutropenia and fatigue but none of the patients had febrile neutropenia. **Conclusion:** Letrozole-Palbociclib is effective with manageable toxicity as the first-line treatment for HR-positive, HER2-negative ABC.

**Keywords:** *Advanced breast cancer, letrozole, palbociclib*

## Introduction

According to the GLOBOCAN 2018, breast cancer is the most common cancer in Indian women constituting 28% of all cancers.[1] In India, 21% of patients with breast cancer have metastasis at the time of presentation.[2] The first-line treatment for hormone receptor (HR)-positive and HER2-negative advanced breast cancer (ABC) without visceral crisis is hormonal therapy.[3] However, patients usually progress after a few months due to endocrine resistance.[4] The endocrine resistance can be overcome by the addition of mammalian target of rapamycin or cyclin-dependent kinase (CDK) inhibitors along with hormonal therapy.[5]

Flavopiridol (first-generation CDK inhibitor) is a synthetic flavone purified from *Dysoxylum binectariferum*, a plant indigenous to India and used in the Indian traditional medicine.[6] However, it was nonselective and had significant toxicity in early clinical trials.[7] The second-generation CDK inhibitors targeting CDK 4/6 pathway have shown activity and a manageable toxicity profile.[8] The addition of CDK 4/6 inhibitors such as palbociclib,[9] ribociclib,[10] and abemaciclib[11] has shown to improve the progression-free survival (PFS) by 1 year as compared to only hormonal therapy. Recently, it was shown that ribociclib with hormonal therapy improved the overall survival (OS) by 24% as compared to only hormonal therapy.[12] The advantages of CDK 4/6 inhibitors are oral therapy and manageable toxicity profile. Palbociclib was approved by the United States Food and Drug Administration in March 2017 as frontline therapy for HR-positive, HER2-negative ABC and was launched in India in October 2017. This initial report is our experience of the efficacy and toxicity of letrozole-palbociclib as the initial treatment in ABC.

## Methods

Data were obtained and analyzed from individual case records of patients with

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ABC who received letrozole and palbociclib from October 2017 to January 2019 at the Cancer Institute, Chennai. Patients included in this analysis were previously untreated, postmenopausal, HR-positive (estrogen receptor [ER] or progesterone receptor [PR] >1%), HER2-negative ABC who received the first-line therapy with tablet letrozole-palbociclib. Patients who had progression while on hormonal therapy and those who received palbociclib as the second-line therapy were excluded from the analysis.

The investigations performed at diagnosis were contrast-enhanced computed tomography chest and abdomen/pelvis with a bone scan or positron emission tomography–computed tomography scan. The schedule of treatment was tablet letrozole 2.5 mg once daily and capsule palbociclib 125 mg, 3 out of 4 weeks in a 28-day cycle. Patients had a complete hemogram before starting treatment, D14 of the first two cycles and before the start of each cycle. Adverse effects were captured according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (National Cancer Institute, Bethesda, Maryland, United States). Patients with Grade 3/4 toxicity due to palbociclib had a reduced dose of 100 mg or 75 mg daily in a step-wise fashion. Clinical breast examination was performed before each cycle and imaging once in 2–3 months and when clinically indicated.

### Statistical methods

Descriptive statistics were used for the baseline characteristics. PFS was calculated from the date of starting letrozole and palbociclib until the progression or death. OS was calculated from the date of starting letrozole and palbociclib until death. The Kaplan–Meier method was used to obtain estimates of median PFS, with corresponding two-sided 95% confidence intervals (CIs). The log-rank test was used for univariate analysis, and $P < 0.05$ was considered statistically significant. The analysis was done using SPSS version 23, IBM Corporation, New York, United States.

## Results

A total of 24 patients were included in this analysis, with a median duration of follow-up of 13 months (range: 5–28 months). The median age was 56 years (range: 25–71 years). Sixty-six percent of patients had a comorbid illness (diabetes mellitus in 33% and systemic hypertension in 33%). The histology was infiltrating ductal carcinoma in all the patients. The differentiation was Grade 1 (8%), Grade 2 (58%), and Grade 3 (33%). The median ER, PR, and Ki-67 were 90% (range: 40%–90%), 45% (range: 0%–90%), and 15% (range: 5%–80%), respectively. T-staging was T1 (4%), T2 (8%), T3 (16%), and T4 (54%) disease. The median tumor size was 6 cm (range: 2–12 cm). The nodal stage was N1 (29%), N2 (41%), and N3 (16%). The sites of metastasis were bone (70%), lung (54%), liver (25%), and lymph nodes (16%).

**Table 1: Baseline characteristics (*n*=24)**

| Variable | *n* (%) |
|---|---|
| Median age (range) | 56 (21-75) |
| Comorbid illness | 15 (66) |
| ECOG PS | |
| 0 | 14 (60) |
| 1 | 10 (40) |
| T1 | 13 (54) |
| T2 | 4 (16) |
| T3 | 2 (8) |
| T4 | 1 (4) |
| N1 | 7 (29) |
| N2 | 10 (41) |
| N3 | 4 (16) |
| Sites of metastasis | |
| Bone | 17 (70.8) |
| Lung | 13 (54.1) |
| Liver | 6 (25.0) |
| Lymph nodes | 4 (16.6) |
| Bone-only metastasis | 9 (37.5) |
| Grade 1 | 2 (8) |
| Grade 2 | 14 (58) |
| Grade 3 | 8 (33) |
| ER positive (range) | 90% (40-90) |
| PR positive (range) | 45% (0-90) |
| HER2neu | Negative |
| Ki67 (range) | 15% (5-80) |

ECOG – Eastern Cooperative Oncology Group; PS – Performance status; ER – Estrogen receptor; PR – Progesterone receptor

Metastatic disease confined only to bones was present in 9 patients (37.5%) [Table 1].

Among 24 patients, 21 patients had evaluable disease [Table 2]. At a median follow-up of 13 months, there were 19% complete response (CR, $n = 4$), 19% (PR, $n = 4$), 24% stable disease (SD, $n = 5$), and 38% progressive disease (PD, $n = 8$). Among the four patients who achieved CR, there was one patient with extensive disease involving the brain, liver, bone, and nodes who achieved a complete metabolic response.

Among the patients who had progressive disease ($n = 8$), 37.5% ($n = 3$) had systemic progression, 37.5% ($n = 3$) had locoregional progression, and 25% ($n = 2$) had both systemic and locoregional progression. The median PFS was 18 months (95% CI: 15–20 months), and the median OS was not reached. The 1-year PFS and OS were 73.7% and 89.2%, respectively [Figures 1 and 2]. Among the patients who had progressive disease ($n = 8$), three were switched to fulvestrant, two to tamoxifen, one to exemestane, and two were unwilling for further treatment and opted for the best supportive care.

Univariate analysis [Table 3] with age, Eastern Cooperative Oncology Group performance status (PS), type (*de novo* vs. recurrent disease), sites of metastasis, grade, Ki-67, and number of sites of metastasis and palbociclib dose

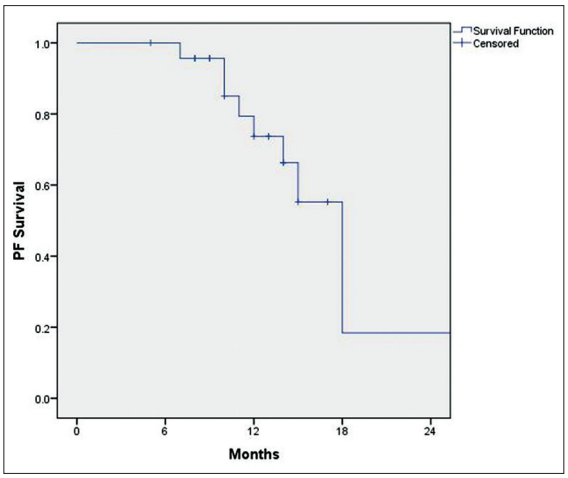


**Figure 1: Progression-free survival**

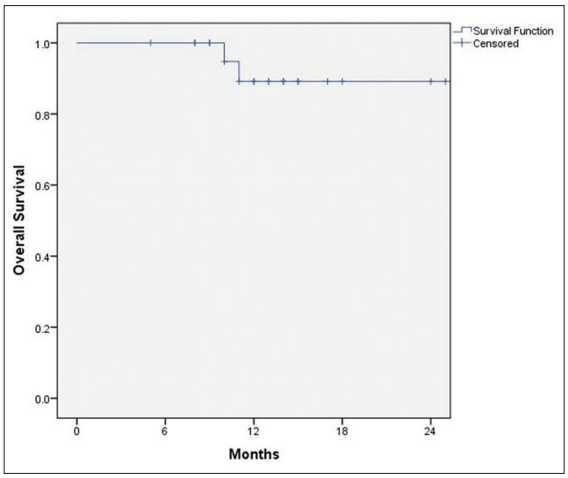


**Figure 2: Overall survival**

reduction were correlated with PFS. Patients with >3 sites of metastasis had a higher risk of progression (Hazard ratio: 8.7; 95% CI: 1.2–63.4; $P = 0.03$).

The nadir white blood cell count and platelet count were 2000 cells/mm$^3$ and 50,000/µl, respectively. However, it was not clinically significant, as none of them had febrile neutropenia or bleeding manifestations. None of the patients had Grade 4 toxicities. Grade 3 leukopenia was seen in two patients and thrombocytopenia in one patient. Grade 1 or 2 side effects were leukopenia 83%, thrombocytopenia in 25%, and fatigue in 33%. About 29% of patients required dose reduction due to fatigue or mucositis.

## Discussion

The striking difference between our patients and the Western population[13] is that majority of our patients have locally advanced disease (T4/T4 – 70%; N2/N3 – 57%) at presentation. There are no published studies form India on hormonal therapy with palbociclib except an abstract that showed a response rate of 41%.[14]

PALOMA-2 trial had 23% of patients with metastasis confined to the bones as compared to our study (37%). Patients with metastasis confined to bones have improved survival as compared to those with visceral disease.[15] The response rate was 55% in the PALOMA-2 trial as compared to 38% in this study. Complete response was seen in four patients (19%), and none of them had progressed at the time of follow-up. All the CDK 4/6 inhibitors trials excluded patients with brain metastasis. We had an unusual patient with brain metastasis who achieved a complete metabolic remission with letrozole and palbociclib. A recent study reported that CDK 4/6 inhibitors in combination with stereotactic radiation for brain prolonged survival.[16]

The median PFS in our study was 18 months as compared to the PALOMA-2 trial where it was 24.9 months. This reflects the fact that real-world outcome is usually inferior to that reported in clinical trials.[17] The reasons could be due to the inclusion of all comers, decreased compliance with drug intake, and shorter follow-up.

**Table 2: Response (*n*=18)**

| Response | *n* (%) |
|---|---|
| Complete remission | 4 (19) |
| Partial remission | 4 (19) |
| Stable disease | 5 (24) |
| Progressive disease | 8 (38) |

**Table 3: Univariate analysis of factors predicting progression-free survival**

| Characteristic | Frequency (*n*) | HR (95% CI) | *P* |
|---|---|---|---|
| Age (years) | | | |
| <50 | 9 | 1.00 | |
| >50 | 15 | 0.72 (0.19-2.72) | 0.63 |
| ECOG PS | | | |
| 1 | 19 | 1.00 | |
| 2 | 5 | 0.41 (0.79-2.17) | 0.29 |
| Disease | | | |
| *De novo* metastasis | 19 | 1.00 | |
| Recurrent disease | 5 | 1.70 (0.33-9.13) | 0.50 |
| Sites of metastasis | | | |
| Bone only | 9 | 1.00 | |
| Visceral | 15 | 1.50 (0.39-5.83) | 0.55 |
| Grade | | | |
| Low (Grade 1 and 2) | 16 | 1.00 | |
| High (Grade 3) | 8 | 1.86 (0.5-7.1) | 0.34 |
| Ki 67 (%) | | | |
| <15 | 7 | 1.00 | |
| >15 | 17 | 3.20 (0.39-25.69) | 0.27 |
| Sites of metastasis | | | |
| <3 | 20 | 1.00 | |
| ≥3 | 4 | 8.70 (1.2-63.4) | 0.03 |
| Dose reduction | | | |
| Yes | 6 | 1.00 | |
| No | 18 | 0.60 (0.12-2.9) | 0.53 |

ECOG – Eastern Cooperative Oncology Group; PS – Performance status; CI – Confidence interval; HR – Hazard ratio

Meta-analysis has shown that hormonal therapy with CDK 4/6 inhibitor significantly improves PFS as compared to those taking only hormonal therapy or chemotherapy in HR-positive, HER2-negative ABC.[18] There is an ongoing phase 3 randomized controlled trial comparing ribociclib and endocrine therapy versus chemotherapy as the first-line therapy in HR-positive, HER2-negative ABC in visceral crisis.

The febrile neutropenia was uncommon in the PALOMA trial (1.8%) and there was none in this study.[9] None of our patients had bleeding manifestations due to thrombocytopenia. Twenty-four percent of patients required dose reductions due to fatigue or mucositis. However, none of them required drug discontinuation. Currently, there is no standard therapy for patients who progress on letrozole and palbociclib. The options can be alpelisib and fulvestrant in PIK3CA-mutated tumors,[19] abemaciclib,[20] exemestane everolimus,[21] fulvestrant, or chemotherapy. Enrollment in clinical trials could be an option in view of lack of standard treatment.

The subset analysis from all the three CDK 4/6 inhibitors showed that all the subgroups (PS 0 vs. 1, visceral vs. bone metastasis, *de novo* vs. recurrent, chemotherapy naïve vs. treated, type of endocrine therapy) have uniformly derived benefit from the addition of CDK 4/6 inhibitors to hormonal therapy. The potential biomarkers are CCND1 amplification, loss of p16, CDK 4 and 6 levels, Rb expression, and Ki-67.[22] Overexpression of TK1 and CDK9 can lead to resistance to CDK 4/6 inhibitors.[23] Biomarkers analysis has shown that both luminal A and luminal B tumors respond to letrozole with palbociclib and lower PD1 levels associated with greater benefit.[24] The limitations of this study are single-institutional study, nonrandomized design, small sample size, and shorter follow-up.

## Conclusion

Letrozole-palbociclib is effective with manageable toxicity as the first-line treatment for HR-positive, HER2-negative ABC. Visceral metastasis or large primary tumor is not an indication to start the chemotherapy in HR-positive, HER2-negative ABC.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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