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Retrospective Analysis of Treatment Patterns and the Effectiveness of Palbociclib and Subsequent Regimens in Metastatic Breast Cancer

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Abstract

Background: Cyclin-dependent kinase (CDK) 4/6 inhibitors are now standard of care for hormone receptor-positive (HR+), HER2-negative metastatic breast cancer (MBC). However, guidelines are lacking regarding their optimal sequencing with other available agents. This study aims to examine physician practice patterns and treatment outcomes of palbociclib and subsequent therapies in a real-world setting.

Methods: A retrospective chart review was conducted for consecutive MBC patients who received palbociclib between February 2015 and August 2017 at the Siteman Cancer Center. Kaplan-Meier method was used to generate time-to-event curves and estimate median progression-free survival (mPFS). Log-rank test was used to compare differences.

Results: Two-hundred patients, with a median age of 59.4 years and a follow-up of 19.5 months, were included. Palbociclib was most frequently combined with letrozole (73.5%), followed by fulvestrant (25%), anastrozole (1%), and tamoxifen (0.5%). A majority of patients received palbociclib in the endocrine resistant setting (n=42, n=50, and n=108 in the first-, second-, and subsequent-line settings, respectively), the fraction of patients receiving palbociclib as the first- or second-line therapy increased in recent months (p=0.0428). The mPFS was 20.7, 12.8, and 4.0 months with palbociclib administered in the first-, second-, and subsequent-line settings, respectively (p<0.0001). Incidences of grade 3/4 neutropenia (41.5%) and dose reductions (29%)

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were comparable to literature report. Among patients who progressed on palbociclib (n=104), the most frequent next-line treatment was capecitabine (n=21), followed by eribulin (n=16), nab-paclitaxel (n=15), and exemestane plus everolimus (n=12). The mPFS with hormonal therapy or combinations (n=32) post first-, second-, and subsequent-line palbociclib was 17.0, 9.3, and 4.2 months, respectively (p=0.04). The mPFS with chemotherapy (n=70) was not-reached, 4.7, 4.1 months post first-line palbociclib, second-, and subsequent-line palbociclib, respectively (p=0.56).

Conclusion: Palbociclib is effective for HR+HER2– MBC in real-world practice. Hormonal therapy or a combination with targeted agents remains an effective option following palbociclib progression.

1. Background

It is estimated that over 150,000 patients are living with metastatic breast cancer (MBC) in the United States in 2017.¹ While progress in treatment strategies has led to significant improvement in overall survival in recent years,^{1–4} MBC remains largely incurable and claims the lives of over 40,000 patients each year.⁵ Cyclin-dependent kinase (CDK) 4/6 inhibitors are an exciting class of agents recently introduced in the clinic for the treatment of advanced hormone receptor positive (HR+) and HER2 negative (HER2–) breast cancer. Since the initial FDA approval of palbociclib in combination with letrozole in the first-line setting in February 2015 based on PALOMA 1 data,^{6,7} several phase III randomized trials have been reported and confirmed the efficacy of CDK4/6 inhibition in both first-line^{8–10} and endocrine resistant settings,^{11–13} leading to the approval of palbociclib in combination with fulvestrant, and 2 other CDK4/6 inhibitors, ribociclib and abemaciclib. As the treatment landscape for HR+HER2– MBC rapidly evolves, questions remain as to the optimal ordering of various treatment options and the efficacy of subsequent therapies post disease progression on a CDK4/6 inhibitor. An applied understanding of the practice pattern and outcomes of CDK4/6 inhibitors and subsequent treatments could generate a hypothesis for future prospective studies.

We, therefore, conducted this retrospective study, with the objective to examine a single institution's experience of physician practice patterns and the outcomes of palboiciclib and therapies post palbociclib progression in patients with MBC.

2.0 Methods

2.1 Patients

After obtaining approval from the Washington University Institutional Review Board (IRB), we conducted a retrospective chart review of all patients with MBC treated at Washington University in St. Louis Siteman Cancer Center who received palbociclib from February 9, 2015 to Aug 10, 2017. Charts were reviewed through the institution's electronic medical record (EMR). All clinical encounters, basic demographic information, surgery and pathology reports, and treatment history were reviewed. Patients were deemed eligible for inclusion in this analysis if they met each of the following criteria: age ≥ 18 years, male or female being post-menopausal or premenopausal receiving gonadotropin-releasing hormone (GnRH) agonist, diagnosis of stage IV breast cancer either de novo or recurrent and received

palbociclib. Two-hundred patients met the inclusion criteria and their clinical data was collected. The duration of therapy was used to calculate PFS for each treatment regimen. Palbociclib treatment was considered as first-line if it was administered in the setting of no prior systemic therapy in the metastatic setting or at least 1 year from the completion of adjuvant hormonal therapy. Palbociclib was considered second-line if received post progression on a first-line therapy for MBC or upon relapse on or within 1 year from the completion of adjuvant hormonal therapy. HR and HER2 status was defined using the ASCO/CAP guideline^{14,15}.

2.2 Statistical analysis

All statistical analyses were performed Using SAS (version 9.4, Cary, NC). The Kaplan-Meier product limit method was used to estimate mPFS and generate time-to-event curves. The log-rank test was used for all comparisons. All the reported P-values were two sided and statistical significance was claimed with p-values 0.05.

3.0 Results

Between February 2015 and August 2017, 230 patients were treated with palbociclib at our institution. Two hundred patients, with a median follow up of 19.5 (range 1.7 – 34.9) months, met the inclusion criteria and were included in the analysis (Fig 1). Patient demographics and clinical characteristics were detailed in Table 1. Of the patients, 98% were females while 78% were Caucasians and 19.5% were African Americans. The median age was 59.4 (range 50.7 – 67.7) years at the time palbociclib was started. The vast majority of patients (n=192) were diagnosed with HR+HER2– disease. Of the combination therapies with palbociclib, 73.5% of the patients received palbociclib and letrozole and 25% received palbociclib plus fulvestrant. Among the 42 patients who received palbociclib in the first-line setting, 39 (92.9%) received palbociclib and letrozole (n=39) and the remaining 3 (7.1%) patients received palbociclib and fulvestrant. Among the 50 patients who received palbociclib in the second-line setting, 34 (68%) received palbociclib and letrozole, and 14 (28%) palbociclib and fulvestrant (n=14). In the third-line and beyond setting, 68.5% were treated with palbociclib and letrozole (n=74) and 30.6% palbociclib plus fulvestrant (n=33).

Among the 192 patients with HR+HER2– disease, the mPFS on palbociclib was 20.7 months in the first-line setting (n=40), compared to 12.8 months and 4.0 months in the second-line (n=50) and subsequent-line settings (n=102), respectively ($p<0.001$) (Fig 2). The mPFS did not differ significantly in patients who received first-line palbociclib in the setting of either de novo metastatic disease (20.7 months, n=21) or at recurrence which occurred at least 1 year from the completion of adjuvant therapy (not reached, n=21) ($p=0.84$). Similarly, no difference in mPFS was observed among the 50 patients who received palbociclib as the second-line treatment, in the setting of relapse on adjuvant therapy (14.7 months, n=24) or progression on first-line therapy in the metastatic setting (11.4 months, n=26) ($p=0.31$). The percentage of patients on palbociclib as a first-line treatment was about 15% during the first year post palbociclib approval. This number increased to 25%-30% after one-and-half years of approval. Significantly more patients were initiated on

palbociclib as third- or later line therapy during an earlier time period (Feb 2015 to June 2016) compared to a later time period (July 2016 to Aug 2017) (61% vs 46.5%, $p=0.0428$).

Among the 133 patients who progressed on palbociclib, 104 moved on to the next line of treatment (Fig 1). Seventy patients received chemotherapy and 32 received hormonal therapy with letrozole ($n=10$), fulvestrant ($n=3$), tamoxifen ($n=2$), or anastrozole ($n=1$), or hormonal therapy in combination with targeted agents, including exemestane plus everolimus ($n=12$), exemestane plus entinostat ($n=2$), and fulvestrant plus palbociclib ($n=2$). The most common regimens following progression on palbociclib were single-agent capecitabine ($n=21$), eribulin ($n=16$), paclitaxel albumin-bound ($n=15$) and exemestane and everolimus ($n=12$) (Fig 1). The mPFS was 4.2 months for patients who received chemotherapy ($n=70$), versus 5.6 months for those who received hormonal therapy ($n=32$) ($p=0.34$). The mPFS was similar among patients on capecitabine, eribulin and paclitaxel. Exemestane-everolimus was the most commonly used hormonal therapy combination post palbociclib progression, and the mPFS was 4.9 months. Among patients who received chemotherapy, the mPFS was not reached, 4.7, and 4.1 months, following progression on first-line ($n=7$), second-line ($n=14$), and subsequent-line palbociclib ($n=49$), respectively ($P=0.56$) (Fig 3). For patients who received hormonal therapy or hormonal therapy plus targeted agents, the mPFS was 17.0, 9.3, and 4.2 months, following progression on first-line ($n=7$), second-line ($n=9$), and subsequent-line palbociclib ($n=16$), respectively ($p=0.04$) (Fig 4). Among the 7 patients who received hormonal therapy post progression on first-line palbociclib, 3 patients received letrozole, 1 fulvestrant, 1 fulvestrant plus palbociclib, and 2 received exemestane plus everolimus.

Seven patients received the combination of palbociclib and fulvestrant after disease progression on palbociclib plus letrozole. Among these 7 patients, 3 (Patient 6, 48, and 186) were switched to the combination of palbociclib and fulvestrant immediately following disease progression on the combination of palbociclib and letrozole for at least 6 months as their first-line therapy for MBC. All these 3 patients experienced prolonged disease control, with PFS of 7.9+ (treatment is ongoing at the time of analysis), 29.9 and 6.8 months. Four other patients had intervening therapy (3 received chemotherapy, 1 received exemestane and everolimus) before switching to palbociclib plus fulvestrant, none of whom experienced disease stabilization for over 6 months.

Data on neutropenia were collected and graded according to CTCAE version 4.1. Grade 1 neutropenia occurred in 15.5% of the patients ($n=31$), grade 2 in 31.5% of the patients ($n=63$). Grade 3 and 4 were observed in 77 (38.5%) and 6 (3%) patients, respectively. Dose reductions occurred in 58 patients (29%). Information on non-hematologic adverse events was collected based on physician progress notes and not graded, which included mucositis ($n=8$, 4%), fatigue ($n=7$, 3.5%), abscess ($n=4$, 2%), nausea/vomiting ($n=4$, 2%), diarrhea ($n=3$, 1.5%), rash ($n=3$, 1.5%), elevated AST/ALT ($n=3$, 1.5%), and neuropathy occurring in at least 1.5% of patients.

4.0 Discussion

Palbociclib in combination with hormonal therapy significantly improves PFS compared to hormonal therapy alone in patients with advanced HR+ HER2– breast cancer, leading to the FDA approval of palbociclib in combination with an aromatase inhibitor (as first line therapy) in Feb 2015 and with fulvestrant (for endocrine resistant disease) in March 2017. Since then, two other CDK4/6 inhibitors including ribociclib and abemaciclib, have gained FDA approval based on results from randomized phase III trials.^{12,13,16–18} As CDK4/6 inhibitors are becoming a standard of care in patients with advanced HR+ HER2– breast cancer, there is an unmet clinical need for assessing its impact on the clinical practice in the real-world setting.

In this retrospective single institutional study, palbociclib in combination with hormonal therapy led to mPFS of 20.7, 12.8, and 4 months, when administered in the first-line, second-line, and third-line or beyond settings, respectively. The data are comparable to the mPFS of 24.8 months in PALOMA 2 (first-line), 9.5 months in PALOMA 3 (endocrine resistant setting) trials, and 4.8 month in heavily pretreated HR+HER2– MBC¹⁹ treated with the combination of palbociclib and hormonal therapy. These data confirmed the efficacy of palbociclib in an applied setting. Interestingly, a significant proportion of the patients received palbociclib in the third-line or beyond, which is consistent with two other retrospective studies that examined the real-world palbociclib practice pattern.^{20,21} This likely reflects the prescription of palbociclib for existing patients already receiving therapy for advanced disease. More patients were started on palbociclib in the first-line setting with fewer patients in the third-line setting or beyond in more recent months. In this study, we did not observe any unexpected AEs. Clinically significant non-hematologic adverse events were uncommon. The maximum grade of neutropenia observed was Grade 3 and 4 in approximately 40% of our patients, and dose reductions occurred in 29% of patients, which were comparable to results from previous phase III studies.^{9,11}

CDK4/6 inhibitors have become an integral component in the treatment of advanced hormone receptor positive breast cancer. However, the optimal therapy post CDK4/6 inhibitor progression is unknown and there is no data in the literature in regards to the efficacy of various treatment strategies. In this study, among the 104 patients who received subsequent therapy, 70 (70%) received chemotherapy and 32 (30%) received hormonal therapy or hormonal therapy combinations. The higher proportion of patients who received chemotherapy is likely a reflection of treatment with palbociclib in the later settings. Nonetheless, hormonal therapy or combinations was effective, leading to a mPFS of 17.0, 9.3, and 4.2 months, post progression of palbociclib administered in the settings of first-line (n=7), second-line (n=9), and third-line/beyond (n=16), respectively. The efficacy of hormonal therapy and hormonal therapy combinations observed in this study provides reassurance of the practice and supports their use post CDK4/6 inhibitor progression. The comparison between the efficacy of hormonal therapy and chemotherapy cannot be made due to patient heterogeneity and selection bias.

Among the hormonal therapy or hormonal combinations administered post palbociclib progression, exemestane and everolimus was most commonly prescribed. The mPFS was 4.9

months, which is relatively short compared to the 7.8 months with the combination of exemestane and everolimus in the BOLERO 2 trial.²² However, majority of patients received this combination beyond the third-line setting in this retrospective study which differs from BOLERO 2 trial, its efficacy may be underestimated. Additionally, preclinical studies demonstrated an up-regulation of PI3K pathway signaling as a resistance mechanism to hormonal therapy^{23,24} and CDK4/6 inhibition^{25–27} and that PI3K/PDK1 pathway inhibition has anti-tumor activity upon CDK4/6 inhibitor resistance.^{25–27} A larger sample size and prospective studies are necessary for more precise estimation of the PFS and predictors of response for mTOR inhibitors in the setting of CDK4/6 inhibitor resistance.

Synergistic anti-tumor activity between hormonal therapy and CDK4/6 inhibition was initially observed in preclinical studies of HR+ breast cancer cell lines²⁸. Although CDK4/6 inhibitors, including palbociclib, have shown single agent activity in endocrine resistant patient populations^{29–31}, the mPFS increased for the combination of palbociclib with the hormonal therapy previously progressed on, when compared to palbociclib alone (10.8 vs 6.5 months, (hazard ratio 0.69; 95% CI 0.4 –1.1) in a randomized phase II trial in postmenopausal women with HR+ HER2– advanced breast cancer who progressed on the same hormonal therapy³⁰. One practical question is whether continued CDK4/6 inhibition remains important at disease progression on an aromatase inhibitor (AI) plus CDK4/6 inhibitor. In a small study of 16 patients with metastatic breast cancer treated with palbociclib and letrozole, mutations in ESR1 in the (ctDNA) detected early in therapy was associated with a significantly shorter PFS (3.3 versus 9.0 months, $p=0.038$)³². Since ESR1 mutations are an established acquired resistance mechanism to AIs^{33–36}, perhaps a more effective endocrine therapy partner for the CDK4/6 inhibitor would be most effective in this setting. Notably, prolonged disease control was observed among the three patients who remained on palbociclib but switched from letrozole to fulvestrant at disease progression. All three patients had an initial clinical benefit (6 months of PFS) from letrozole and palbociclib combination therapy. It is unknown however whether these three patients harbored ESR1 mutation and whether fulvestrant alone would have led to the same clinical benefit in these three patients and continued CDK4/6 inhibition post progression is not a standard practice. The utility of continued CDK4/6 inhibition after progression is being addressed in prospective clinical trials. The ongoing PACE trial (Palbociclib After CDK and Endocrine Therapy) () is a randomized phase II study that compares the PFS of fulvestrant alone (Arm A) with fulvestrant plus palbociclib (Arm B) and fulvestrant plus palbociclib and avelumab (Arm C) in the setting of acquired resistance to previous CDK4/6 inhibition for advanced HR+ HER2– breast cancer. The Trinita trial () is a single arm phase II trial that assesses the anti-tumor activity of adding the CDK4/6 inhibitor ribociclib to the combination of exemestane and everolimus in patients who developed acquired resistance to CDK4/6 inhibitors. However, HR+ HER2– breast cancer is a clinically and molecularly heterogeneous group of diseases and resistance mechanisms to CDK4/6 inhibitors may differ among individual patients. Loss of Rb as an acquired mechanism to CDK4/6 inhibitor has been observed in both preclinical²⁵ and clinical settings³⁷, for which subsequent CDK4/6 inhibition may not be effective. In addition, amplification of CDK6³⁸, G1/S phase cyclins²⁵ or FGFR pathway components³⁹ have been implicated in resistance to CDK4/6

inhibitors. An individualized treatment approach based on the specific resistance mechanisms may therefore be necessary.

Our study has several limitations including the relatively small sample size, the retrospective analysis in nature, selection bias of treating physicians in choosing different treatment regimens and relatively short follow up of 19 months. Nonetheless, this study confirmed the activity of palbociclib in combination with hormonal therapy in an applied setting and the activity of hormonal therapy or combination therapy in at least a subset of patients. The significant variances of the practice pattern upon disease progression on palbociclib argues for the need of future studies in addressing optimal treatment approaches in this setting.

5.0 Conclusion

To our knowledge, this is the first retrospective study that examined both the applied practice pattern of prescribing the CDK4/6 inhibitor palbociclib and subsequent treatment regimens and their survival outcomes after a patient progresses on palbociclib. The mPFS and safety profiles were comparable to that observed in previous studies. We also observed that more patients were started in the first-line setting in a more recent time period. Among the wide range of treatment regimens prescribed post palbociclib progression, capecitabine and the combination of exemestane and everolimus were among the most common. Although the practice pattern in our institution may not be generalizable to other institutions and a few patients received non-standard approaches such as continuation of CDK4/6 inhibition post progression, the study confirmed the efficacy of CDK4/6 inhibitor and activity of subsequent hormonal therapy or in combination with mTOR inhibition. Future clinical trials that inform the ideal sequencing of various therapy regimens in the context of the clinical and molecular heterogeneity of advanced HR+ breast cancer are warranted.

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Figure 1. Common therapies post palbociclib progression.

This flowchart shows the next-line treatments after progression on palbociclib.

Figure 2. Kaplan-Meier PFS curves with palbociclib administered in the first-, second-, and third-line/beyond settings in HR+, HER2– metastatic breast cancer.

The Kaplan-meier survival curves depict the progression free survival (PFS) in patients who were treated with palbociclib in the first-, second-, or third-line/beyond setting.

Abbreviations: mPFS, median progression free survival; HR, hormone receptor; HER, human epidermal growth factor receptor; ≥3rd-line, third-line and beyond.

Figure 3. PFS with chemotherapy post progression on first-, second-, and third-line palbociclib. Kaplan-meier survival curve of the PFS of patients treated with chemotherapy after progression on palbociclib administered in the first-, second-, or third-line/beyond setting. Abbreviations: mPFS, median progression free survival; ≥3rd-line, third-line and beyond.

Figure 4. PFS with hormonal therapy post progression on first-, second-, and third-line palbociclib.

Kaplan-meier survival curves of the PFS of patients treated with hormonal therapy after progression on palbociclib administered in the first-, second-, or third-line/beyond setting. Abbreviations: mPFS, median progression free survival; ≥3rd-line, third-line and beyond.

Table 1.

Patient demographics and clinical characteristics

Age: Median (range) -- year	59.4 (50.7 – 67.7)
Gender – no. (%)	
Female	196 (98)
Male	4 (2)
Race – no. (%)	
White	156 (78)
Black	39 (19.5)
Asian	4 (2)
Other	1 (0.5)
Biomarker prior to palbociclib use – no. (%)	
HR+HER2–	List Total (n=192)
ER+PR+HER2–	127 (63.5)
ER+PR-HER2–	63 (31.5)
ER-PR+HER2–	1 (0.5)
ER+PR unknown HER2–	1 (0.5)
HER2+	List total (n=6)
ER+PR+HER2+	4 (2)
ER+PR-HER2+	1 (0.5)
ER-PR-HER2+	1 (0.5)
Unknown	2 (1)
Concurrent hormonal therapy (HT) – no. (%)	
Letrozole	147 (73.5)
Fulvestrant	50 (25)
Anastrozole	2 (1)
Tamoxifen	1 (0.5)
HT combined with different lines of palbociclib use – no. (%)	
1 st -line palbociclib	List Total (n=42)
With letrozole	39 (92.9)
With fulvestrant	3 (7.1)
2 nd -line palbociclib	List Total (n=50)
With letrozole	34 (68)
With fulvestrant	14 (28)
With anastrozole	1 (2)
With tamoxifen	1 (2)
3 rd -line palbociclib	List total (n=108)
With letrozole	74 (68.5)
With fulvestrant	33 (30.6)

With anastrozole	1 (0.9)
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Abbreviations: HR, hormone receptor; ER, estrogen receptor; PR, progesterone receptor; HT, hormone therapy.

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