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EPIDEMIOLOGY

Real-world clinical outcomes and toxicity in metastatic breast cancer patients treated with palbociclib and endocrine therapy

Leticia Varella[1] · Akaolisa Samuel Eziokwu[1] · Xuefei Jia[1] · Megan Kruse[1] · Halle C. F. Moore[1] · George Thomas Budd[1] · Jame Abraham[1] · Alberto J. Montero[1]

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Abstract

Purpose Real-world data are critical to demonstrate the reproducibility of evidence and external generalizability of randomized clinical trials. Palbociclib is an oral small-molecule inhibitor of cyclin-dependent kinases 4 and 6 that has been shown to improve progression-free survival (PFS) when combined with letrozole or fulvestrant in phase 3 clinical trials. We evaluated real-world outcomes in metastatic breast cancer patients who received palbociclib in combination with endocrine therapy in routine clinical practice.

Methods Records of patients with advanced hormone receptor (HR)-positive breast cancer treated with palbociclib at the Cleveland Clinic health system from February, 2015 to December, 2017 were retrospectively reviewed. The primary end point was PFS.

Results In this cohort, 411 women were included. The median age and follow-up times were 53.5 years and 10.2 months, respectively. The median PFS for palbociclib plus letrozole was 15.1 months for patients treated in first line, 10.5 months in second line, and 4.2 months in third line and beyond. For patients who received fulvestrant plus palbociclib, the median PFS in first, second, and third line and beyond were 11.6, 12.3, and 6.4 months, respectively. The most common adverse events were hematologic, with grade 3–4 neutropenia occurring in 58% of patients. Thirty-one (8%) patients permanently discontinued palbociclib due to adverse events.

Conclusions Among patients with HR-positive advanced breast cancer, the estimated PFS in patients treated with fulvestrant and palbociclib was comparable to a previously reported phase 3 trial. However, the median PFS with letrozole and palbociclib was shorter than previously reported data from phase 2 and 3 trials. Palbociclib toxicity was very manageable, with a low drug discontinuation rate.

Keywords Breast cancer · Palbociclib · Cyclin-dependent kinase inhibitor · Real-world · Letrozole · Fulvestrant

Background

Worldwide, breast cancer is the most commonly diagnosed cancer in women [1]. In the United States alone, approximately 269,000 new cases of breast cancer are estimated in 2018. Despite a reduction in mortality in the past 3 decades, more than 40,000 women are expected to die in 2018 from breast cancer in the United States [2]. Approximately, 70% of breast cancers are hormone receptor (HR)-positive, expressing estrogen and/or progesterone receptors [3]. Endocrine therapy represents the cornerstone of treatment of metastatic HR-positive breast cancer [4]. However, treatment with endocrine therapy is not curative, due to intrinsic or acquired drug resistance.

Cyclin-dependent kinases (CDKs) are a subgroup of serine/threonine kinases that regulate cell cycle progression [5]. Palbociclib is an oral small-molecule inhibitor of cyclin-dependent kinases 4 (CDK4) and 6 (CDK6), which are enzymes that promote progression from the G1 phase to the S phase of the cell cycle. Inhibition of CDK4/6 leads to inhibition of retinoblastoma phosphorylation, thereby causing G1 arrest. In preclinical studies, palbociclib was shown to synergistically inhibit cell growth when combined with anti-estrogens [5]. This data led to clinical studies evaluating

✉ Leticia Varella
lev9027@med.cornell.edu

[1] Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH, USA

palbociclib in combination with endocrine therapy in metastatic HR-positive breast cancer patients.

The phase 2 study PALOMA-1 randomized post-menopausal women with metastatic HR-positive breast cancer to receive letrozole or letrozole plus palbociclib as first-line therapy. Progression-free-survival (PFS) was twice as long with the addition of palbociclib, leading the FDA in February 2015 to grant accelerated approval of palbociclib plus letrozole [6]. These results were later confirmed in the subsequent phase 3 PALOMA-2 trial [7].

The PALOMA-3 trial evaluated the impact of palbociclib on the effectiveness of fulvestrant in patients with metastatic HR-positive breast cancer who relapsed or progressed during prior adjuvant endocrine therapy. The results demonstrated that the addition of palbociclib led to a significant improvement in median PFS [8], leading to the FDA approval of palbociclib plus fulvestrant for women with HR-positive and Human Epidermal Growth Factor Receptor 2 (HER2)-negative advanced or metastatic breast cancer with disease progression following endocrine therapy. Since initial regulatory approval of palbociclib, two other oral CDK 4/6 inhibitors, ribociclib and abemaciclib, have been granted FDA approval with similar indications [9, 10].

Since its approval by the FDA, palbociclib has been widely prescribed, however, published studies examining real-world outcomes with palbociclib have been absent. Real-world data are critical to demonstrate the reproducibility of evidence and external generalizability of randomized trials. We herein report real-world clinical outcomes of palbociclib in combination with endocrine therapy in the treatment of metastatic breast cancer.

Methods

Study design and patients

In this retrospective study, patients with advanced or metastatic HR-positive breast cancer that received palbociclib at the Cleveland Clinic healthcare system, from February, 2015 to December, 2017 were included. Institutional Review Board approval was obtained, and data were collected through a review of electronic medical records. We identified patients with advanced breast cancer who received palbociclib through our Pharmacy database. Patients had histologically confirmed HR-positive and HER2-negative breast cancer and received palbociclib for at least 1 cycle. We defined a complete cycle of palbociclib when the drug was given once a day for 3 weeks followed by 1 week off in a 28-day cycle. Dose reductions and discontinuation of therapy were documented in the electronic charts. Both premenopausal and post-menopausal women were included. Male patients and patients receiving palbociclib in a clinical trial setting were excluded.

Endpoints

The primary endpoint was progression-free survival (PFS), defined as the time from initiation of palbociclib to radiologically or clinically confirmed disease progression or death.

Secondary endpoints included: overall survival (OS), defined as the time from initiation of palbociclib treatment to date of death or date of last follow-up; toxicity; and reason for treatment discontinuation.

Efficacy and toxicity assessment

In general, imaging (CT scans, bone scans, MRI, or PET-CT) was performed prior to initiating palbociclib, and at regular intervals during treatment. Biochemical and hematologic laboratory tests were performed on days 1 and 15 of the first two cycles and subsequently on day 1 of subsequent cycles in the vast majority of patients. Toxicity information was obtained from the clinicians' documentations during the clinical visits and telephone encounters.

Statistical analysis

Categorical clinical and pathologic factors were summarized as frequency counts and percentages, continuous factors as medians and ranges. Both PFS and OS were summarized using the Kaplan–Meier method, analyzed using the Cox proportional hazards model. All statistical analyses were performed using R version 3.5.0. $p < 0.05$ was considered statistically significant.

Results

Patient clinical and pathological features

We identified 444 patients who were prescribed palbociclib for advanced or metastatic HR-positive breast cancer over the study period. Ten male patients were excluded. A total of 23 patients were excluded because they either never received palbociclib despite being planned or received palbociclib in a clinical trial setting. Four-hundred and eleven women were included in our review. Their baseline clinical and pathological characteristics are summarized in Table 1. The median age was 53.5 years. Patients had Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 3. HER2 receptor was non-overexpressed in approximately 96% of women. Among all patients, 57.2% had received prior adjuvant or neoadjuvant chemotherapy for breast cancer, and 23.3% had stage 4 disease at the time of initial diagnosis. At

Table 1 Patient demographic and clinical characteristics

Characteristic	Number (%)
Median age (17–83)—years	53.5
Race, no. (%)	
White	352 (85.6)
African-American	49 (11.9)
Other	10 (2.4)
Hormone-receptor status—no. (%)	
Estrogen receptor-positive	387 (94.1)
Progesterone receptor-positive	339 (82.4)
Her 2 receptor-positive	15 (3.6)
Prior neoadjuvant or adjuvant chemotherapy, no. (%)	
Yes	235 (57.2)
No	167 (40.6)
Unknown	9 (2.2)
Disease stage at initial diagnosis, no. (%)	
0–II	210 (51.1)
III	83 (20.1)
IV	96 (23.3)
Unknown	22 (5.35)
Number of metastatic sites, no. (%)	
0	0 (0)
1	254 (61.8)
2	69 (16.8)
≥ 3	54 (13.1)
Unspecified	34 (8.3)
Metastatic sites, no. (%)	
Bone	
Any	217 (52.8)
Only	140 (34.1)
Visceral	151 (36.7)
Lymph nodes	58 (14.1)
Other	19 (4.6)
Unspecified	34 (8.3)

N = 411

the time when palbociclib was initiated, 62% of women had only one organ site of metastatic disease, 36.7% had visceral metastases, and 34% had bone-only disease.

Treatment characteristics

The majority of patients (55%) received palbociclib plus letrozole, 38.4% palbociclib plus fulvestrant, and 6.6% received palbociclib in combination with other antiestrogen therapies (anastrozole, exemestane, or tamoxifen) (Table 2). Palbociclib in combination with endocrine therapy was initiated in the first, second, third, or fourth or more line setting for treatment of metastatic breast cancer in 35.8%, 26%, 12.9% and 25.3% of patients, respectively.

Table 2 Treatment characteristics

Characteristic (%)	Number of patients
Endocrine therapy combined with palbociclib	
Letrozole	226 (54.9)
Fulvestrant	158 (38.4)
Other (exemestane, tamoxifen, anastrozole)	27 (6.6)
Line of therapy	
First	147 (35.8)
Second	107 (26.0)
Third	53 (12.9)
Fourth and beyond	104 (25.3)

Efficacy

At the time of analysis in January 2018, 95 deaths had occurred (23.1%), and 186 patients (45.2%) had had disease progression while receiving palbociclib. Of all patients, 48% were still receiving palbociclib as of December 31, 2017.

The median follow-up time was 10.2 months. The estimated median PFS for palbociclib plus letrozole was 8.9 months (95% CI 6.16 to 11.0) (Fig. 1). Among these patients, the median PFS was 15.1 months (95% CI 12.3

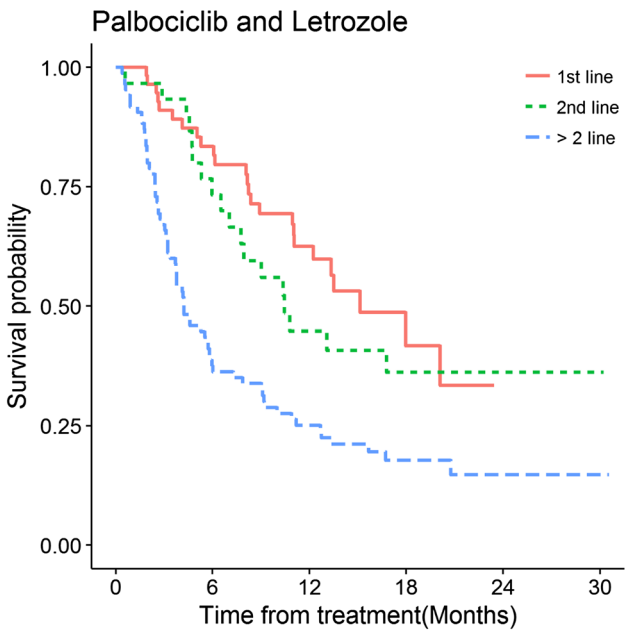

Fig. 1 Progression-free survival for palbociclib plus letrozole by line of therapy. The median estimated progression-free survival was 8.9 months (95% CI 6.16–11.0) among the 226 patients treated with palbociclib/letrozole. The median PFS was 15.1 months (95% CI 12.3–not reached) for those who received palbociclib/letrozole as first-line therapy; 10.5 months (95% CI 7.05–not reached) for those who received it in the second-line; and 4.2 months (95% CI 3.7–5.6) for those who received palbociclib/letrozole as third line and beyond treatment

Table 3 Progression-free survival by combination and line of therapy

Line of therapy (month)	Drug combination	*N*	No. event (progression)	Median PFS
First	Palbociclib/letrozole	57	25	15.1
First	Palbociclib/fulvestrant	34	21	11.6
Second	Palbociclib/letrozole	31	19	10.5
Second	Palbociclib/fulvestrant	39	19	12.3
Third and beyond	Palbociclib/letrozole	85	69	4.2
Third and beyond	Palbociclib/fulvestrant	32	25	6.4

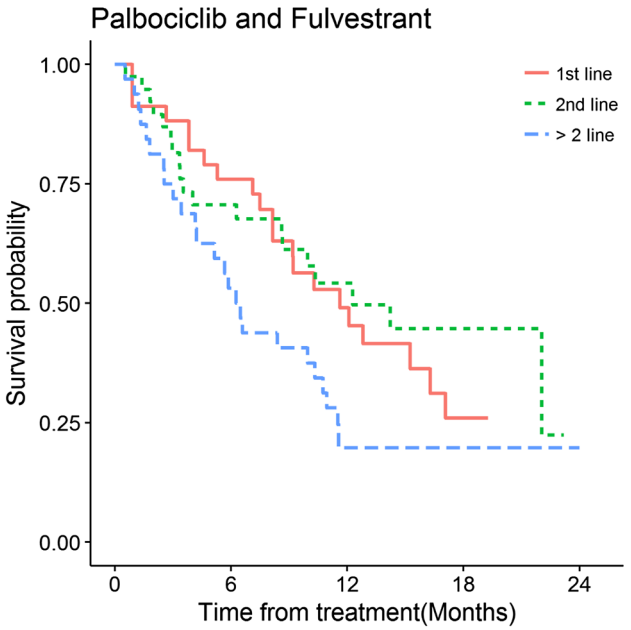

Fig. 2 Progression-free survival for palbociclib plus fulvestrant by line of therapy. The median estimated progression-free survival was 10.3 months (95% CI 8.16–12.3) among the 158 patients treated with palbociclib/fulvestrant. The median PFS was 11.6 months (95% CI 8.2–not reached) in patients treated in first line, 12.3 months (95% CI 8.66–not reached) in second line, and 6.4 months (95% CI 4.23–11) in third line and beyond therapy

to not reached) for those who received palbociclib/letrozole as first-line therapy; 10.5 months (95% CI 7.05 to not reached) as second-line therapy; and 4.2 months (95% CI 3.7 to 5.6) for third line and beyond (Table 3).

The estimated overall PFS for palbociclib/fulvestrant was 10.3 months (95% CI 8.16 to 12.3) (Fig. 2), with an estimated median PFS of 11.6 (95% CI 8.2 to not reached), 12.3 (95% CI 8.66 to not reached), and 6.4 months (95% CI, 4.23 to 11), respectively as first, second, or third line and beyond therapy.

The estimated median overall survival (OS) time for palbociclib/fulvestrant was 24.5 months, while median OS for palbociclib/letrozole has not been reached.

Table 4 Treatment discontinuation for toxicity

Adverse event	Number of patients
Fatigue	12
Neutropenia	7
Pancytopenia	4
Thrombocytopenia	3
Elevated liver enzymes	3
Anemia	3
Diarrhea	2
Acute respiratory illness	2
Rash	2
Mucositis	1
Headache	1
Anorexia	1
Arthralgia	1
Neuropathy	1
Dizziness	1
Fluid retention	1

N = 31

Toxicity

Among all patients, the most common adverse events were hematologic, with documented grade 3 or 4 neutropenia occurring in 57.7% of patients. Fatigue was the most commonly documented non-hematologic adverse event. Other less commonly reported toxicities included the following: anemia, thrombocytopenia, pancytopenia, diarrhea, anorexia, dyspnea, elevated liver enzymes, oral mucositis, headaches, skin rash, and nausea. Palbociclib was dose reduced on account of toxicity in 111 of 411 patients (27%). Permanent discontinuation of palbociclib due to adverse events occurred in 31 (7.6%) patients (Table 4).

Discussion

To our knowledge, our work is the first published report evaluating real-world outcomes of palbociclib and endocrine therapy in patients with HR-positive metastatic breast cancer. A study by Kish et al. evaluated prescribing patterns of palbociclib in a similar patient population; however, they did not report clinical outcomes [11].

There are some differences between our patient population and the two PALOMA randomized phase 3 trials, which are important to highlight. In our cohort, the median age was 53.5 years, reflecting a younger population than in the PALOMA-2 (median age 62 years) [7] and PALOMA-3 (median age 57 years) [8] trials. However, many of our patients had multiple comorbidities and many had an ECOG performance status of 2. Moreover, 57.2% of the patients in our study received prior neoadjuvant or adjuvant chemotherapy for breast cancer, as compared to 48% in PALOMA-2, possibly reflecting a high proportion of "high risk" patients. These factors may explain why the observed median PFS of 15.1 months with palbociclib plus letrozole as first-line therapy was shorter than the 24.8 months reported in PALOMA 2.

Our observed overall PFS of 10.3 months for palbociclib/fulvestrant was very similar to the 9.5 months reported in PALOMA 3 trial. It is important to note that 57 patients in our study received fulvestrant as first-line therapy and PALOMA-3 only included patients who had previously progressed after endocrine therapy.

Interestingly, the PFS for palbociclib-fulvestrant combination in our study was similar regardless of whether it was initiated as first or second-line therapy [HR 0.87 (95% CI 0.47–1.62)]. This finding is concordant with the report from MONALEESA 3 trial [12] in which the PFS hazard ratio with ribociclib/fulvestrant was similar in patients with treatment-naïve advanced breast cancer compared to those who had received one line of prior endocrine therapy. As expected, the median PFS times among patients in our cohort who had received palbociclib in combination with either letrozole or fulvestrant as third line or beyond treatment were shorter than patients who received it earlier as first or second-line therapy.

One of the strengths of this study is the large number of patients treated with palbociclib as fourth line or beyond therapy ($N = 104$). The only large trial that reported survival outcomes with palbociclib beyond second-line of therapy was the PALOMA-3 trial, which included 69 patients that had been treated with two or more prior lines of therapy.

In our cohort, the estimated median OS for palbociclib and fulvestrant was 24.5 months but the OS for palbociclib-letrozole could not be determined at the time of analysis due to insufficient number of deaths. There is currently no overall survival data available for PALOMA-2. In PALOMA-3, the addition of palbociclib to fulvestrant was associated with an overall survival absolute benefit of 6.9 months; however, that did not reach significance in the intent-to-treat population [13]. The median OS in the group treated with fulvestrant and palbociclib was 35 months, which was longer than the 24.5 months found in our study. It is challenging to compare differences in overall survival given that we lack information regarding treatment after patients received palbociclib.

The toxicity profile of palbociclib in our study is very consistent with the published clinical literature with CDK4/CDK6 inhibitors [7, 8, 10, 12]. Reversible hematologic toxicity, mostly mild to moderate neutropenia, was the most common adverse event, not associated with infections, and often only required dose reduction. The neutropenia rate was lower in our cohort than what has been reported in PALOMA-2 and 3, however, the frequency of blood draws was not mandated and varied by treating physician. We did not identify any episodes of febrile neutropenia within our cohort, and most patients were able to continue palbociclib despite mild-moderate toxicity.

Our study has several limitations. Some of the electronic records had missing information such as laboratory data, and incomplete documentation on treatment toxicities. Additionally, the median follow-up was relatively short, limiting the number of events including progression and death.

In conclusion, among hormone receptor-positive metastatic breast cancer patients in a non-clinical trial setting, the estimated PFS in patients receiving letrozole plus palbociclib in the first-line setting was shorter than that reported in PALOMA-2; however, our observed PFS with palbociclib and fulvestrant combination was comparable to PALOMA-3. Palbociclib was well tolerated, with a manageable toxicity profile and very low drug discontinuation rate.

Compliance with ethical standards

Conflict of interest Megan Kruse, MD is on Advisory Board for Novartis Oncology. Leticia Varella, MD; Akaolisa Samuel Eziokwu, MD; Xuefei Jia, MS; Halle C. F. Moore, MD; George Thomas Budd, MD; Jame Abraham, MD; and Alberto J. Montero, MD have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent The authors obtained a waiver of written consent from the Institutional Review Board (IRB) for retrospective medical record review for research.

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