Prognostic Role of Tumor Subtype and Germline BRCA Mutation in Advanced Breast Cancer Patients Treated with Palbociclib Plus Endocrine Therapy

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Abstract

Background/Aims: Palbociclib is a cyclin dependent kinase 4 and 6 inhibitor which shows promising effect in hormone receptor positive breast cancer. The purpose of this study is to evaluate the real-world efficacy and toxicity of palbociclib plus endocrine therapy.

Methods: This is a retrospective study performed in two tertiary referral hospitals in Korea. Advanced breast cancer patients who were treated with 1st line palbociclib plus endocrine therapy were enrolled.

Results: A total of 216 patients were included between August 2016 and May 2019. Median age was 56 (29-89) years old and 75 patients (34.7%) were premenopausal. Median progression-free survival (PFS) was 33.0 months (95% confidence interval [CI] 24.7 to 41.3) and objective response rate was 59.3%. Luminal B patients had shorter PFS (Not reached vs. 33.0 months, $p = 0.019$) and tendency of lower ORR (58.3 vs. 62.0%, $p = 0.19$) compared to luminal A patients. Multivariate analysis revealed luminal B (adjusted hazard ratio 1.90, $p = 0.038$) and germline *BRCA* mutation (adjusted hazard ratio 5.57, $p = 0.002$) as an independent poor prognostic factor for PFS. The most common grade 3 or 4 adverse event was neutropenia (86.7%).

Conclusions: The efficacy and toxicity of palbociclib in the real-world was comparable to those of clinical trials. In addition, palbociclib with endocrine therapy was an effective treatment option for young patients. Luminal B and germline *BRCA* mutation was associated with inferior outcome.

Background

Breast cancer is the most commonly diagnosed cancer and is the leading cause of cancer death in women [1, 2]. The incidence rate of breast cancer is increasing annually in developing countries, which is probably due to nation-wide cancer screening and westernization of lifestyle [3, 4]. Up to 75% of breast cancers express hormone receptor (HR) and endocrine therapy is the main treatment option for these patients [5].

Recently, cyclin dependent kinase (CDK) 4 and 6 inhibitors have emerged as a new standard treatment option for patients with advanced HR-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer [6]. Three selective CDK 4/6 inhibitors (palbociclib, ribociclib, abemaciclib) have significantly improved progression-free survival (PFS) and overall survival (OS) in patients with HR-positive advanced breast cancer and have been approved by the United States Food and Drug Administration (FDA) [7–10]. In the phase III PALOMA-2 trial, palbociclib plus letrozole showed significant longer PFS compared to endocrine alone in HR-positive, HER2-negative advanced breast cancer [10]. In another phase III PALOMA-3 trial, patients who received palbociclib plus fulvestrant had longer median PFS and OS compared to those who received placebo plus fulvestrant [11, 12].

Asian have younger age of breast cancer onset (45 to 50 years old) compared to Western population (55 to 60 years) [13, 14]. In Korea, the median age at the time of breast cancer diagnosis is increasing, but

still the highest incidence is seen at the age of 40–49 [15]. While palbociclib has been approved by the US FDA since 2015, there are paucity of data on the real-world efficacy of palbociclib, especially in young Asian patients [16]. The purpose of this study is to evaluate the real-world efficacy and toxicity of palbociclib plus endocrine therapy in Korean patients with advanced breast cancer. This study included relatively younger patients compared to previous performed clinical trials.

Method

Study design and population

This study is a retrospective study performed in two tertiary referral hospitals in Korea [Seoul National University Hospital (SNUH, Seoul, Korea) and Seoul National University Bundang Hospital (SNUBH, Gyeonggi-do, Korea)]. Two hundred and sixteen breast cancer patients who received 1st line palbociclib plus endocrine therapy between August 2016 and May 2019 were included. Patients were excluded if they received previous systemic chemotherapy for advanced/metastatic disease. Neoadjuvant and adjuvant chemotherapy, and adjuvant endocrine therapy were allowed. Patients with histologically confirmed HR-positive and HER2-negative breast cancer were included.

All patients received 125mg of palbociclib per day administered orally in 4-week cycles (3 weeks of treatment followed by 1 week off) combined with endocrine therapy. Dose reductions of palbociclib were allowed (100mg or 75mg) on the discretion of treating physician. Palbociclib was combined with one of three endocrine therapies (letrozole, exemestane, or fulvestrant). Letrozole was administered orally at a dose of 2.5mg per day, exemestane was administered orally at a dose of 25mg per day, and fulvestrant was administered by intramuscular injection at a dose of 500mg at day 1 and 15, 29, then once monthly thereafter.

Eligible patients were identified from the electronic database and medical charts were identified from the electronic database medical record system of SNUH and SNUBH. The study protocol was reviewed and approved by the institutional review board of SNUH [H-1904-025-1024] and SNUBH [B-2006/616 – 405]. This study was carried out in accordance with the recommendations of the Declaration of Helsinki for biomedical research involving human subjects.

Analysis Of Tumor Subtype

Immunohistochemical (IHC) staining of estrogen receptor (ER), progesterone receptor (PR), and HER-2 was performed with tumor specimen. HER2 fluorescence in situ hybridization was performed in patients with HER-2 IHC grade 2. Nuclear expression of tumor cells was interpreted as positive for ER and PR, while membrane staining of tumor cells was considered positive for HER2. ER and PR expression was categorized as positive when $\geq 1\%$ of the tumor cells were stained [17]. HR was defined positive when either ER or PR was expressed. The intrinsic subtypes were defined by the 2013 St. Gallen Consensus Recommendations [18]. HR-positive, HER2-negative and Ki-67 $< 14\%$ were defined as luminal A. HR-

positive, HER2-negative and Ki-67 $\geq 14\%$ were considered luminal B [19]. Germline *BRCA* 1/2 mutation was tested based on the polymerase chain reaction and gene sequencing [20].

Primary endocrine resistance was defined as a relapse which occurred during the first 2 years of adjuvant endocrine therapy. Secondary or acquired endocrine resistance was defined when there was a relapse while on adjuvant endocrine therapy but after the first 2 years or within 12 months of completing adjuvant endocrine therapy [21].

Statistical analysis

The primary endpoint of this study was to investigate the real-world efficacy of palbociclib in terms of PFS. PFS was defined as the time from the start of palbociclib to radiologically or clinically disease progression, or death from any cause, whichever occurred first. Secondary outcomes were objective response rates (ORR), according to RECIST criteria version 1.1 and hematologic adverse events.

Categorical variables were compared using the chi-square test and continuous variables were compared using the independent-samples T test. Missing data were not imputed. Kaplan-Meier method was used to obtain estimates of median PFS, and comparisons were made using the log-rank tests. Two-sided *p*-values of less than 0.05 were considered statistically significant. Univariate and multivariate proportional hazards regression models were used to identify independent risk factors for survival by means of the Cox proportional hazards regression models. Factors associated with prognosis were included in the multivariate analysis and forward stepwise methods were used to eliminate non-significant variables. Statistical analyses were performed using IBM SPSS statistics version 25 (SPSS, Chicago, IL, USA).

Results

Patient characteristics

A total of 216 breast cancer patients who were treated with palbociclib plus endocrine therapy were included. Two hundred and five (94.9%) were treated palbociclib plus letrozole, 7 (3.2%) received palbociclib plus exemestane, and 4 (1.9%) received palbociclib plus fulvestrant. Baseline characteristics are summarized in Table 1. All patients were female with a median age of 56 (range: 29–89) years. Among 75 patients (34.7%) who were premenopausal at the time of diagnosis of advanced breast cancer, 71 received bilateral oophorectomy prior to palbociclib treatment and 4 received gonadotropin-releasing hormone agonist (GnRHa) with palbociclib treatment. All patients had histologically confirmed breast cancer with HR-positive and HER2-negative. According to St. Gallen molecular subtype, 132 (62.9%) had luminal A disease, and 78 (37.1%) had luminal B disease. Seventy-three (33.8%) patients were diagnosed with de novo stage IV disease and 143 (66.2%) had relapsed disease. Among 143 relapsed patients, 131 (91.6%) had received adjuvant endocrine therapy and 12 (8.4%) did not receive adjuvant endocrine therapy. Based on adjuvant endocrine therapy, 58 (44.3%) were endocrine sensitive, 21 (16.0%) were

primary resistance, and 50 (38.2%) had secondary resistance. Thirty-three (15.3%) patients were tested for germline *BRCA1* and *BRCA2* mutation status. Six (18.2%) had germline *BRCA1* or 2 mutation.

Table 1
Baseline characteristics

	Overall (<i>n</i> = 216)		Luminal A (<i>n</i> = 132, 61.1%)		Luminal B (<i>n</i> = 78, 36.1%)		<i>P</i> value
	N	%	N	%	N	%	
Age							
<50years	73	33.8	49	37.1	23	29.5	0.26
≥50years	143	66.2	83	62.9	55	39.9	
Estrogen receptor							
Positive	216	100.0	132	100.0	57	74.0	
Negative	0	0.0	0	0.0	20	26.0	
Progesteron receptor (<i>n</i> = 215)							
Positive	171	79.5	109	82.6	57	74.0	0.14
Negative	44	20.5	23	17.4	20	26.0	
Nucleic grade (<i>n</i> = 125)							
I-II	72	57.6	57	62.0	12	40.0	0.035
III	53	42.4	35	38.0	18	60.0	
Histologic grade (<i>n</i> = 120)							
I-II	77	61.2	59	67.8	14	48.3	0.059
III	43	35.8	28	32.2	15	51.7	
Disease presentation							
De novo stage IV	73	33.8	43	32.6	28	35.9	0.62
Relapsed disease	143	66.2	89	67.4	50	64.0	
Adjuvant endocrine therapy (<i>n</i> = 143)							
No	12	8.4	7	7.9	5	10.0	0.67
Yes	131	91.6	82	92.1	45	90.0	
Endocrine resistance (<i>n</i> = 131)							
Endocrine sensitive	58	44.3	37	41.6	17	35.4	0.53

Abbreviations: N, number; OFS, ovarian function suppression; BSO, bilateral salphingo-oophorectomy; GnRHa, Gonadotropin-releasing hormone agonist;

	Overall (n = 216)		Luminal A (n = 132, 61.1%)		Luminal B (n = 78, 36.1%)		P-value
	N	%	N	%	N	%	
Primary resistance	21	16.0	11	12.4	10	20.8	
Secondary resistance	50	38.2	34	38.2	16	33.3	
Partner endocrine therapy							
Letrozole	205	94.9	124	93.9	76	97.4	0.50
Exemestane	7	3.2	5	3.8	1	1.3	
Fulvestrant	4	1.9	3	2.3	1	1.3	
Menopausal status							
Natural postmenopausal	141	65.3	84	63.6	52	66.7	0.90
OFS using BSO	71	32.9	46	34.8	25	32.1	
OFS using GnRHa	4	1.9	2	1.5	1	1.3	
Germline BRCA 1/2 mutation							
Positive	6	2.8	3	2.3	3	3.8	0.34
Negative	27	12.5	19	14.4	8	10.3	
Test was not done	183	84.7	110	83.3	67	85.9	
Metastatic site							
Bone	132	61.1	76	57.6	52	66.7	0.19
Liver	32	14.8	19	14.4	13	16.7	0.66
Lung	85	39.4	55	41.7	27	34.6	0.31
Brain	5	2.3	3	2.3	2	2.6	0.89
Abbreviations: N, number; OFS, ovarian function suppression; BSO, bilateral salphingo-oophorectomy; GnRHa, Gonadotropin-releasing hormone agonist;							

Real-world Efficacy Of Palbociclib Plus Endocrine Therapy

After a median follow-up duration of 16.0 months, 75 progression events and 11 deaths have occurred. The median PFS of palbociclib plus endocrine therapy was 33.0 months (95% confidence interval [CI] 24.7 to 41.3). Among 123 (56.9%) patients who had measurable disease, there was no complete

response, 73 (59.3%) had partial response, 31 (25.2%) had stable disease, and 19 (15.4%) had progressive disease. The ORR was 59.3% (Table 2).

Table 2
Objective response rate

	Response rate, %	<i>P</i> -value
Objective response rate (n = 123)	59.3	
Intrinsic subtype		
Luminal A	62.0	0.19
Luminal B	58.3	
Age		
<50years	72.7	0.11
≥50years	67.1	
Menopausal state		
Natural postmenopausal	54.5	0.23
OFS using BSO or GnRH agonist	71.4	
Germline BRCA 1/2 mutation		
Positive	0.0	0.19
Negative	60.0	
Abbreviations: N, number;		

We next evaluated whether baseline characteristics may affect palbociclib efficacy. Patient age or menopausal status did not affect treatment response. There was no difference in PFS (not reached *vs.* 33.0 months, $p = 0.56$) and ORR (72.7% *vs.* 67.1%, $p = 0.11$) (Table 2) according patients age. Similarly, menopausal status did not affect PFS (33.0 months *vs.* not reached, $p = 0.82$) or ORR (54.5% *vs.* 71.4%, $p = 0.23$) (Table 2). However, molecular tumor subtype was associated with palbociclib response. Luminal A patients had longer PFS compared to luminal B patients (Not reached *vs.* 33.0 months, $p = 0.019$) (Fig. 1). In addition, there was a tendency of higher ORR in luminal A patients compared to luminal B patients (62.0% *vs.* 58.3%, $p = 0.19$) (Table 2). Among 33 patients who had germline *BRCA* 1/2 mutation test, 6 (18.2%) had germline *BRCA* 1/2 mutation. Patients with germline *BRCA* 1/2 mutation had shorter PFS compared to germline *BRCA* wild type patients (9.0 months *vs.* not reached, $p = 0.031$) and patients who were not tested for germline *BRCA* status (9.0 months *vs.* 33.0 months, $p = 0.001$) (Fig. 2). PFS was similar between germline *BRCA* wild type patients and those who did not have germline *BRCA* test (Not reached *vs.* 33.0 months, $p = 0.54$) (Fig. 2).

To adjust for baseline characteristics, we performed multivariable analysis with a Cox proportional hazard model. Due to limited number of patients who had germline *BRCA* status and low incidence of germline *BRCA* 1/2 mutation, patients who did not test germline *BRCA* status was combined with germline *BRCA* wild type in the multivariate analysis. Multivariate analysis revealed nuclear grade, intrinsic subtype, and germline *BRCA* 1/2 mutation as an independent prognostic factor for PFS (Table 3). Luminal B subtype (adjusted hazard ratio 1.90, 95% CI 1.04–3.47, $p = 0.038$) and germline *BRCA* 1/2 mutation (adjusted hazard ratio 5.57, 95% CI 1.91–16.24, $p = 0.002$) were independent poor prognostic factors for PFS.

Table 3 Multivariate analysis of progression free survival		
	Adjusted HR (95% CI)	P-value
Nucleic grade	2.09 (1.16, 3.77)	0.014
Intrinsic subtype		
Luminal A	1	0.038
Luminal B	1.90 (1.04, 3.47)	
Germline BRCA 1/2 mutation		
Negative or not tested	1	0.002
Positive	5.57 (1.91, 16.24)	
Abbreviations: HR, hazard ratio;		

The mean time to objective response was 3.8 months. There was no significant difference in mean time to objective response between luminal A and luminal B (3.9 vs. 3.6 months, $p = 0.32$). The mean duration of objective response was 15.1 months. Tumor subtype did not impact mean duration of response (16.5 months in luminal A vs. 13.1 months in luminal B, $p = 0.37$).

Adverse Events

The most common hematologic adverse events were neutropenia. Among 216 patients, 210 (97.2%) reported adverse events with any grade of neutropenia, and 182 (86.7%) reported events of grade 3 or higher grade neutropenia. And 7 patients (3.2%) reported events of neutropenic fever. Other hematologic adverse events included anemia and thrombocytopenia. Sixty (34.5%) showed grade 3 or 4 anemia and 7 (8.8%) showed grade 3 or 4 thrombocytopenia. There was no significant difference in neutropenia according to age at 50 (86.3 vs. 83.2%, $p = 0.47$).

Discussion

In recent years, CDK 4/6 inhibitors have changed the management of advanced HR-positive, HER2-negative breast cancer. There are ethnic differences in the prevalence of breast cancer that Asian countries have relatively younger age of onset compared to Western. There are yet paucity of data on the real-world efficacy of CDK 4/6 inhibitor in young Asian population. This study was conducted to investigate the real-world efficacy of palbociclib plus endocrine therapy in Asian women. We revealed that the efficacy of palbociclib plus endocrine therapy in young Asian women is comparable to that of previous conducted phase III clinical trials.

The phase III PALOMA-2 trial evaluated the efficacy of 1st line palbociclib plus letrozole in postmenopausal women with HR-positive, HER2-negative advanced breast cancer [10]. Palbociclib-letrozole group had higher ORR (55.3 vs. 44.4%, $p = 0.03$) and improved PFS (27.6 vs. 14.5 months, $p < 0.0001$) compared to placebo-letrozole group [10, 22]. In PALOMA-2 trial, PFS in patients over 65 was similar to that of patients under 65 (hazard ratio for disease progression or death, 0.57) [10]. In the phase III PALOMA-3 study, women with HR-positive, HER2-negative advanced breast cancer who had progressed on previous endocrine therapy were enrolled [11]. Patients were randomly assigned to palbociclib plus fulvestrant group or placebo plus fulvestrant group. Patients who received palbociclib plus fulvestrant had improved ORR (10.4 vs. 6.3%, $p = 0.16$), PFS (9.2 vs. 3.8 months, $p < 0.001$), and OS (34.9 vs. 28.0 months, $p = 0.09$) compared to those who receive placebo plus fulvestrant. Twenty percentage of patients enrolled in the PALOMA-3 trial was pre-/peri-menopausal and menopausal status did not affect PFS or OS [11, 12].

In this study, we have evaluated the real-world efficacy of 1st line palbociclib plus endocrine therapy in advanced or metastatic breast cancer patients. Palbociclib plus endocrine therapy showed a median PFS of 33.0 months (95% CI 24.7 to 41.3) with an ORR of 59.3%, which is similar to that of PALOMA-2 trial. All patients included in the present study were Asian who has younger age of breast cancer onset. The median age of our study was 53 years old which is younger than that of PALOMA-2 trial (62 years old). In line with previous conducted trials, patient age or menopausal status did not affect PFS or ORR of palbociclib plus endocrine therapy. However, St. Gallen intrinsic subtype was a significant prognostic factor. Multivariate analysis revealed Luminal B as an independent negative prognostic factor for PFS (adjusted hazard ratio 1.90, $p = 0.038$). It is known that while luminal A tumors have indolent feature and are sensitive to antiestrogen, luminal B tumors often show rapid progression and resistance to endocrine therapy [23]. Aggressive nature and endocrine resistant feature may have resulted in the poor PFS and ORR of luminal B tumors. Recent meta-analysis data show that CDK 4/6 inhibitor plus endocrine therapy is non-inferior to conventional chemotherapy in terms of PFS and time to progression [24]. In addition, CDK 4/6 inhibitor plus endocrine therapy showed similar ORR compared to conventional chemotherapy. As CDK 4/6 inhibitor plus endocrine therapy have superior toxicity profiles and drug administration route compared to conventional chemotherapy, it is the preferred treatment option in HR-positive, HER2-negative breast cancer patients. However, in the present study, luminal B patients had shorter PFS and tendency of low ORR compared to luminal A patients. As such, CDK 4/6 inhibitor plus endocrine therapy should be used in caution in Luminal B patients with visceral disease.

Another important result of our study is that we showed potential negative prognostic role of germline *BRCA* 1/2 mutation. Patients with germline *BRCA* 1/2 mutation had a worse PFS compared to patients with germline *BRCA* wild type and those who did not test germline *BRCA* status. Multivariate analysis revealed germline *BRCA* 1/2 mutation as an independent negative prognostic factor for PFS compared to patients with germline *BRCA* wild type or those who did not have germline *BRCA* test (adjusted hazard ratio 5.57, 95% CI 1.91–16.24, $p = 0.002$). Although there are limited number of patients with germline *BRCA* 1/2 mutation, this is in line with previous studies showing poor outcome of *BRCA* 1/2 mutation patients treated with endocrine therapy plus CDK 4/6 inhibitors [25]. We believe future study comparing frontline poly adenosine diphosphate ribose polymerase inhibitor with CDK 4/6 inhibitors in HR-positive breast cancer with germline *BRCA* 1/2 mutation will provide valuable information.

There are some limitations in the present study. The tumor specimens we used to identify tumor subtype was acquired in various time point. It would be ideal to obtain tissue prior to CDK 4/6 inhibitor treatment, but unfortunately, most samples were acquired at initial breast cancer diagnosis. Another limitation of the present study is that we did not have enough data on germline *BRCA* 1/2 mutation status or other genetic characteristics to draw answer on the prognostic role of molecular findings. However, the strength of our study is that our study was relatively homogeneous in terms of ethnic and that all patients received top-of-the-line medical care in a high-volume tertiary referral hospital.

Conclusions

In conclusion, the efficacy and toxicity of palbociclib in the real-world was comparable to those of previous conducted phase III clinical trials. In addition, palbociclib with endocrine therapy was an effective treatment option for young Asian breast cancer patients. However, as the ORR and PFS is inferior in luminal B subtype, CDK 4/6 inhibitor plus endocrine therapy should be used in caution in luminal B patients with visceral disease.

List Of Abbreviations

CDK

Cyclin dependent kinase

CI

Confidence interval

ER

Estrogen receptor

FDA

Food and Drug Administration

GnRHa

Gonadotropin-releasing hormone agonist

HER2

Human epidermal growth factor receptor 2

HR

Hormone receptor

IHC

Immunohistochemical

ORR

Overall response rate

OS

Overall survival

PFS

Progression-free survival

PR

Progesterone receptor

SNUH

Seoul National University Hospital

SNUBH

Seoul National University Bundang Hospital

Declarations

Ethics approval and consent to participate

The study protocol was reviewed and approved by the institutional review board of SNUH [H-1904-025-1024] and SNUBH [B-2006/616-405].

Consent for publication

All authors gave consent for the publication of the manuscript in *Breast Cancer Research*.

Availability of supporting data

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request

Completing interests

The authors declare that they have no competing interests.

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Contributions

DWL and SAI contributed to the study concept and design. SYP and KJS contributed to the acquisition of the data. All authors contributed to the analysis and interpretation of data, and drafting/revision of the article. All authors read and approved the final manuscript.

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Figures

Figure 1

Progression free survival according to St.Gallen molecular subtype Abbreviations: PFS, progression free survival.

Figure 2

Progression free survival according to germline BRCA 1/2 mutation status Abbreviations: PFS, progression free survival;