의학석사 학위논문

폐경 후 한국인 여성에서 호르몬 수용체 양성, HER2 음성 전이성 유방암에 대한 1 차 내분비 요법으로 palbociclib 과 letrozole 병합 치료의 효과 및 안정성에 대한 후향적 분석

Real-world experience of palbociclib plus letrozole as first-line endocrine treatment in Korean postmenopausal women with hormone receptor-positive, HER2-negative metastatic breast cancer : a retrospective study

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이 논문을 의학석사 학위 논문으로 제출함

2021년 2월

울산대학교 대학원

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김혜영의 의학석사학위 논문을 인준함

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Abstract

Background: Palbociclib selectively inhibits cyclin-dependent kinase 4/6 to regulate cell cycle. Based on the results of the PALOMA-2 study which showed palbociclib plus letrozole combination therapy was effective for postmenopausal women with hormone receptor (HR)-positive and HER2-negative advanced breast cancer (ABC), palbociclib was approved in Korea in June 2017. We report the real-world outcomes of palbociclib plus letrozole combination therapy for Korean patients.

Material and Methods: This study is a retrospective cohort study of patients treated with palbociclib plus letrozole for postmenopausal women with HR-positve, HER2-negative ABC at the Asan Medical Center, Seoul, Korea between June 2017 and August 2019. Primary endpoint was progression-free survival (PFS) and secondary endpoints included overall survival (OS), objective response rate (ORR), clinical benefit rate (CBR), and safety.

Results: A total of 204 patients (pts) were enrolled with median age of 53 years (range, 29-82), 135 (66.2%) with visceral metastases and 80 (39.2%) received bilateral salpingo-

oophorectomy (BSO) . Median follow-up period was 19.2 months (mo) (range, 1.4 to 39.8). The median PFS was 26.0 mo (95% confidence interval [CI], 19.9 to 26.1) and the median OS was not reached. The median PFS of pts who underwent BSO was 26.0 mo (95% CI, 19.9 to 26.0) and was not reached in those with natural menopause. ORR was 38.2% (95% CI, 31.5 to 45.2), and CBR was 81.9% (95% CI, 75.8 to 86.8). The most common adverse events of any grade were neutropenia (95.0%), followed by anemia (51.4%), thrombocytopenia (33.3%), stomatitis (22.5%), fatigue (18.1%). The most frequently reported grade ≥3 adverse events were neutropenia (83.3%, 170/204), but febrile neutropenia occurred only in 4 (2.0%) pts. Dose reduction of palbociclib was required in 164 (80.4%) pts due to neutropenia and was stopped in 2 pts due to grade 4 neutropenia and thrombocytopenia.

Conclusions: Palbociclib plus letrozole in Korean pts with HR-positive, HER2-negative ABC demonstrated comparable efficacy to pivotal phase 3 trial. Although dose reductions of palbociclib due to hematologic toxicities were required more frequently in this population, dose adjustments seemed not affect the treatment outcome.

Key words: breast cancer, HR+HER2-, letrozole, palbociclib

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Introduction

Breast cancer is the most common cancer in women worldwide (1). Although the incidence of breast cancer has been declining in some countries(2), but the age-standardized incidence rates of breast cancer in Korea have risen since 1999 (3). In Korea, approximately 21,747 cases of every 100,000 women are newly diagnosed as breast cancer and although the long-term prognosis is good for patients whose disease has not spread, the five-year survival rates of advanced breast cancer patients are only 30 to 40% (4).

The majority of breast cancers are hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2-) and endocrine therapy has been a mainstay of therapy with better safety profile and quality of life compared with chemotherapy (5, 6). Recently, treatment with cyclin-dependent kinase 4/6 (CDK 4/6) inhibitor in combination with endocrine therapy has been a treatment option that improve outcomes and delay the acquired resistance to endocrine therapy (7).

Palbociclib is a first-in-class, highly selective, orally administered, reversible CDK 4/6 inhibitor (8). CDK 4/6, though phosphorylation of retinoblastoma-associated protein 1 (RB1)

are pivotal in the transition from G1 to S phase in many malignancies (8-10). The inhibition of CDK 4/6 by palbociclib induces the cell-cycle arrest and shows anti-tumor activities (11). In the side effects, the most common adverse event associated with palbociclib is neutropenia. However, neutropenia is distinct from that observed with cytotoxic agents in that it is rapidly reversible, reflecting a cytostatic effect on neutrophil precursors in the bone marrow (12-14).

On the preclinical data, the efficacy and safety of palbociclib as first-line therapy in combination with letrozole in patients with HR+/HER2- advanced breast cancer (ABC) were initially demonstrated in the phase 2 PALOMA-1 study(5) and subsequently confirmed in the phase 3 PALOMA-2 study (15). PFS was significantly longer in palbociclib plus letrozole arm compared with the placebo plus letrozole arm as first-line treatment in postmenopausal women with HR+/HER2- ABC (hazard ratio, 0.563; 95% CI 0.461-0.687; p<0.0001: median PFS 27.6 months vs 14.5 months, respectively) (16). Although palbociclib significantly improved outcomes in PALOMA-2, the incidence of myelotoxic adverse events was higher with palbociclib compared with placebo plus letrozole (15).

Because palbociclib was approved based on PALOMA studies including majority of non-

Asian patients (17), clinical efficacies and adverse events of the study were limited to adjust to Asian women. To better elucidate the efficacies and safety profile of palbociclib with letrozole, we planned this retrospective study for HR+/HER2- advanced breast cancer patients whose treatment with palbociclib plus letrozole therapy.

Patient and Methods

Patients and data collection

This study is a retrospective study of patients who received palbociclib with letrozole therapy for postmenopausal women with hormone-positive, HER2-negative metastatic breast cancer at the Asan Medical Center, Seoul, Korea between June 2017 and August 2019. The study protocol was approved by the Asan Medical Center Institutional Review Board (IRB 20200178)

End points and assessments

The primary endpoint was investigator-assessed progression-free survival (PFS). Secondary

endpoints included overall survival (OS), objective response (OR; partial or complete response according to Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1), clinical benefit rate (CBR; objective response or stable disease lasting 24 or more weeks according to RECIST version 1.1), and safety assessments.

Radiological tumor assessments by Computed tomography scan and/or magnetic resonance imaging were performed at baseline and about every 12 weeks. Laboratory testing were performed at baseline and monitored at every 4 weeks. Adverse events (AEs) were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.

Statistical analysis.

The Kaplan-Meier method was used to estimate median PFS and OS with corresponding 95% Confidence intervals [CIs]. Comparisons of PFS and OS were done using 1-sided *p*-value from log-rank tests. ORR and CBR were summarized and corresponding 95% CIs were calculated. All statistical analyses were performed with SPSS, version 26.0.

Results

Patient characteristics

Between June 2017 to August 2019, 204 patients who received palbociclib plus letrozole were included for this study. Demographics and baseline disease characteristics of patients are in Table 1. The median age of patients was 53 years (range, 29-82) and patients below 65 years were 86.8%. In Korea, as palbociclib and letrozole endocrine therapy was approved only for postmenopausal women, 80 (39.2%) of the patients prescribed in this hospital were patients who was induced with artificial menopause through BSO (salpingo-oophorectomy) or OFS (ovarian function suppression) treatment such as LHRH (Luteinizing Hormone Releasing Hormone). Three patients underwent both BSO surgery and LHRH therapy. Most patients have good Eastern Cooperative Oncology Group (ECOG) performance status, and 77.9% of patients had recurrent disease at study entry. Among recurred patients, fourteen (6.9%) patients with disease-free interval (DFI) of less than 24 months and 148 (72.5%) of ad DFI over 24 months were observed. And 154 (75.5%) of patients had previously experienced systemic endocrine therapy as adjuvant (including neo-adjuvant therapy) treatment for breast cancer.

Table 1. Patient demographics and baseline characteristics

Characteristic	Patients, n=204 (%)
Age, years	
Median (range)	53 (29-82)
< 65, n (%)	177 (86.8)
≥ 65, n (%)	27 (13.2)
Menopausal status	
Natural	124 (60.8)
Induced menopause (surgery or LHRH)	80 (39.2)
ECOG performance status, n (%)	
0	80 (39.2)
1	110 (53.9)
2	14 (6.9)
Occurrence at breast cancer	
Recurrence	159 (77.9)
De novo	45 (22.1)
Disease site	
Visceral [a]	135 (66.2)
Non-visceral	69 (33.8)
Bone only disease	26 (12.7)
Disease-free interval [b]	
Newly metastatic disease	42 (20.6)
≤ 24 months	14 (6.9)
> 24 months	148 (72.5)

Prior (neo)adjuvant therapy	
Hormone therapy	154 (75.5)
Tamoxifen	131 (64.2)
Letrozole	16 (7.8)
Anastrozole	7 (3.4)
Chemotherapy	128 (62.7)

Abbreviations: LHRH, Luteinizing Hormone Releasing Hormone;

ECOG, Eastern Cooperative Oncology Group

[a] Refers to lung (including pleura) or liver and other internal digestive organ or circulatory organs excluding skin, lymph node, bone involvements.

[b] Defined as the time between resection of the primary breast cancer and the diagnosis of recurrence

Efficacy

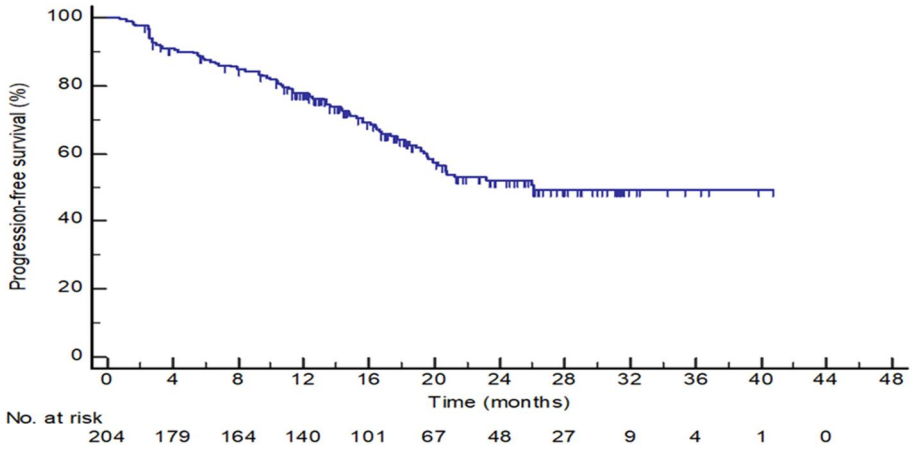
At the data cut-off date (August 19, 2020), median duration of follow-up was 19.2 months (1.4 to 39.8 months). The median PFS was 26.0 months (95% confidence interval [CI], 19.9 to 26.07) and the median OS was not reached (Fig. 1a). Median PFS of patients with BSO surgery was 26.0 months (95% CI, 19.9 to 26.0) and did not reach to median in those with natural menopause. (Fig. 1b). Figure 1c shows PFS according to the visceral disease status and median PFS of visceral disease was 19.9 months, (95% CI, 17.3 to 23.1 mo) vs not estimable of non-visceral disease status. And Figure 1d shows that PFS was influenced by DFI.

Data for OS are not yet mature (Fig. 2). At the time of data collection, 20 patients (9.8%) had died. 12-month and 24-month survival rate were 95.3% and 89.1%, respectively.

Figure 1. Investigator-assessed PFS in the patients

a

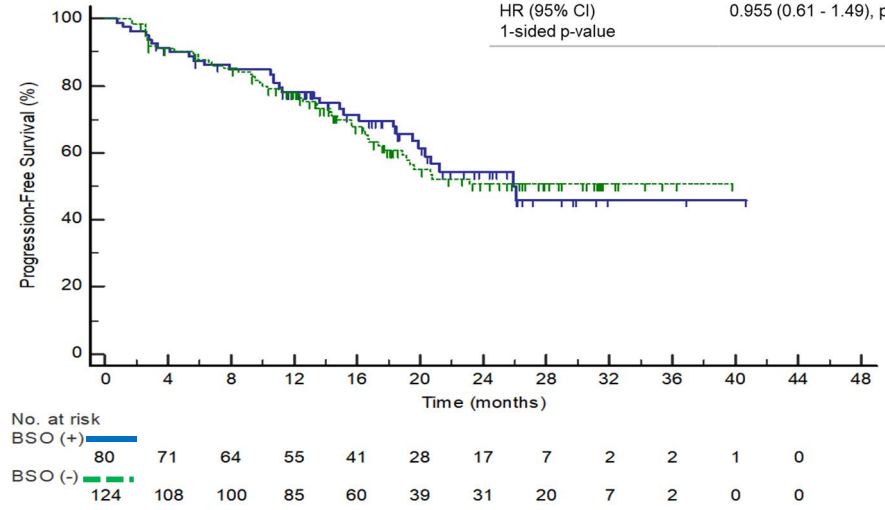
	PAL+LET (N=204)
Events, n (%)	80 (39.2)
Median PFS (95% CI), mo	26.0 (19.9 – 26.7)



a) PFS in patients with palbociclib plus letrozole

b

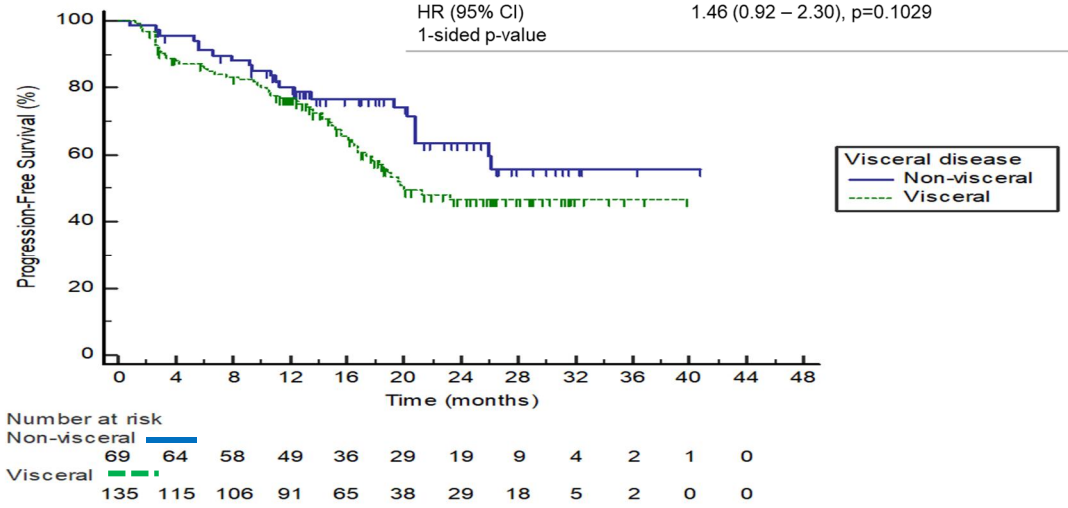
	BSO (+), N= 80	BSO (-), N= 124
Events, n (%)	31 (38.7)	49 (39.5)
Median PFS (95% CI), mo	26.0 (19.9 – 26.07)	NE
HR (95% CI) 1-sided p-value	0.955 (0.61 - 1.49), p=0.8415	



b) PFS with or without BSO surgery

c

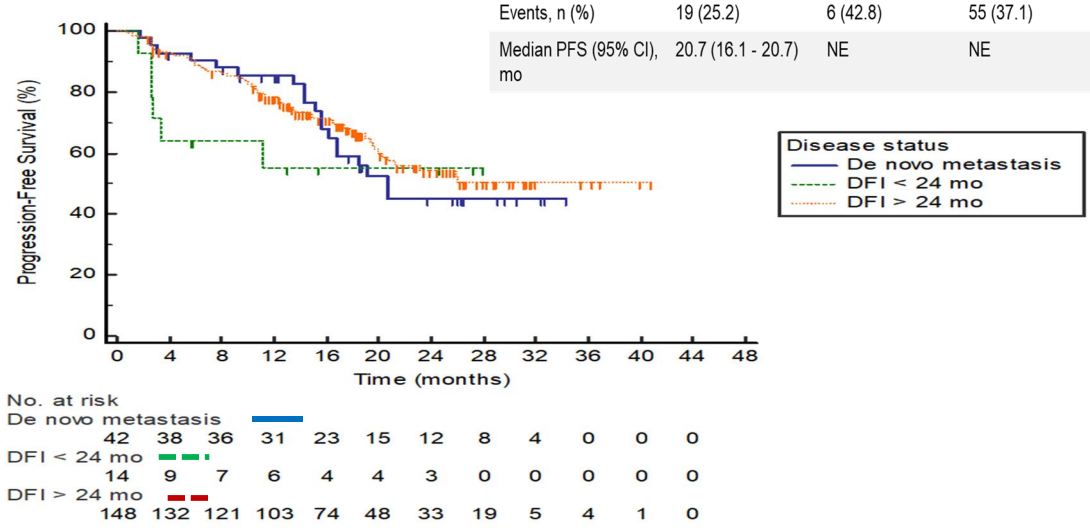
	Visceral, N= 135	Non-visceral, N= 69
Events, n (%)	58 (42.9)	22 (31.8)
Median PFS (95% CI), mo	19.9 (17.3 - 23.1)	NE
HR (95% CI) 1-sided p-value	1.46 (0.92 – 2.30), p=0.1029	



c) PFS according to visceral disease (visceral vs non-visceral disease)

d

	De novo meta N= 42	DFI ≤24 mo N= 14	DFI >24 mo N= 148
Events, n (%)	19 (25.2)	6 (42.8)	55 (37.1)
Median PFS (95% CI), mo	20.7 (16.1 - 20.7)	NE	NE



d) PFS according to disease-free interval (De novo metastasis, DFI ≤ 24 months, DFI >24 months)

Figure 2. Investigator-assessed OS in overall patients with palbociclib plus letrozole

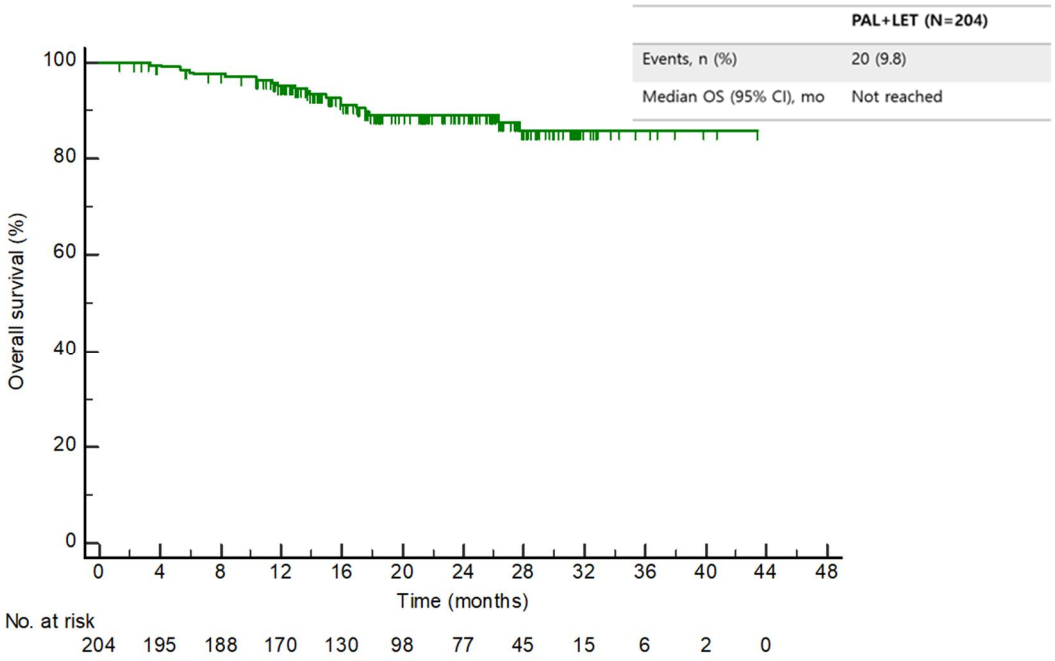


Figure 3. PFS according to dose of palbociclib

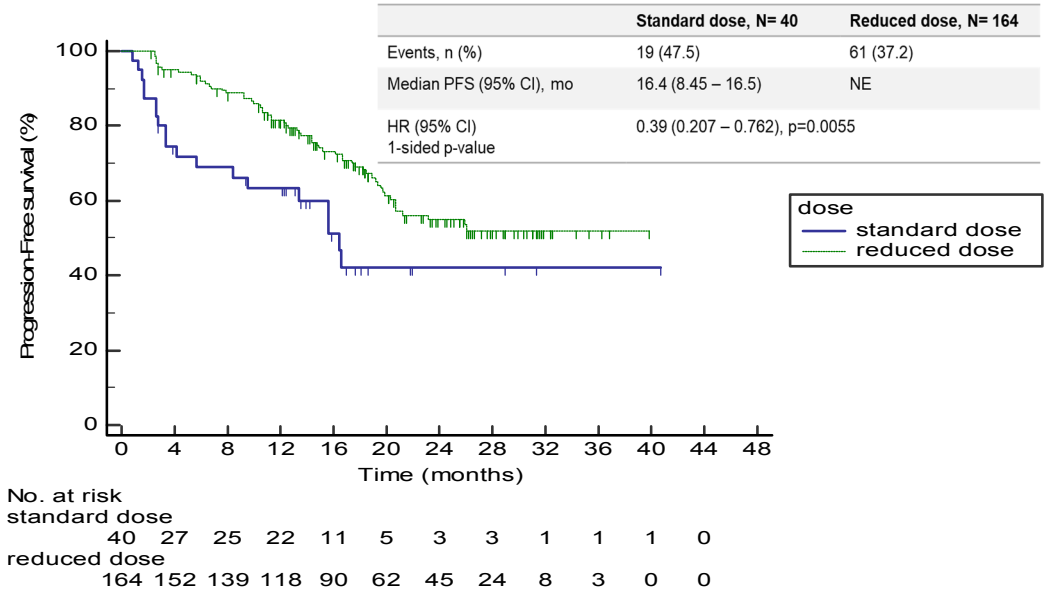


Table 2. Tumor response to palbociclib plus letrozole

Investigator assessed population	N=204
Best overall response, n (%)	
Complete response	8 (3.9)
Partial response	70 (34.1)
Stable disease	100 (49.0)
≥ 24 weeks	89 (43.6)
< 24 weeks	11 (5.4)
Disease progression	16 (7.8)
Indeterminate	10 (4.9)
ORR [a,c], % (95% CI)	38.2 (31.5 – 45.2)
CBR [b,c], % (95% CI)	81.9 (75.8 – 86.8)

[a] Objective response rate, proportion of patients achieving complete response (CR) and partial response (PR)

[b] Clinical benefit rate, proportion of patients with CR or PR or SD (stable disease) for 24 weeks or longer

[c] Exact method based on binominal distribution, calculated as 95% CI.

The objective response rate (ORR) was 38.2% (95% CI, 31.5 – 45.2) while clinical benefit rate (CBR) was 81.9% (95% CI, 75.8 – 86.8). Eight (3.9%) patients had complete response and only sixteen patients (7.8%) had experiences of disease progression and 14 patients of them had to change second line treatments such as chemotherapy or endocrine therapy including fulvestrant.

Table 3. Any grade of adverse events reported in patients

Overall patients, N=204 (%)				
Adverse events, (AEs)	All grade No (%)	Grade 1 or 2 No (%)	Grade 3 No (%)	Grade 4 No (%)
Any AEs	200 (98.0)	26 (12.7)	136 (66.7)	38 (18.6)
Hematologic AEs				
Neutropenia	194 (95.0)	24 (11.7)	132 (64.7)	38 (18.6)
Anemia	105 (51.4)	101 (49.5)	4 (2.0)	0
Thrombocytopenia	68 (33.3)	62 (30.3)	4 (2.0)	2 (1.0)
Non-hematologic AEs				
Stomatitis	46 (22.5)	46 (22.5)	0	0
Fatigue	37 (18.1)	37 (18.1)	0	0
Arthralgia	21 (10.2)	21 (10.2)	0	0
Nausea	19 (9.3)	18 (8.8)	1 (0.5)	0
Anorexia	18 (8.8)	17 (8.3)	1 (0.5)	0
Rash	12 (5.8)	12 (5.8)	0	
LFT elevation	11 (5.4)	10 (4.9)	1 (0.5)	0
Diarrhea	11 (5.4)	0	0	0
Alopecia	10 (4.9)	10 (4.9)	0	0
Constipation	8 (3.9)	8 (3.9)	0	0
Cough	7 (3.4)	7 (3.4)	0	0
Dyspnea	7 (3.4)	7 (3.4)	0	0
neuropathy	7 (3.4)	7 (3.4)	0	0
UTI	5 (2.4)	5 (2.4)	0	0

Febrile neutropenia	4 (2.0)	0	4 (2.0)	0
vomiting	4 (2.0)	3 (1.5)	1 (0.5)	0

Abbreviations: AEs, adverse events; LFT, liver function test; UTI, urinary tract infection

Adverse events and dose adjustments

The therapy related adverse events reported in patients is shown in Table 3. The most common AE was neutropenia and Grade 3 and 4 neutropenia were reported in 132 (64.7%) and 38 (18.6%) patients, respectively. Thus, Granulocyte colony stimulating factor (G-CSF) was administered to patients with Grade 3 or Grade 4 neutropenia, but only sixteen (7.8%) patients of total patients received G-CSF and no one admitted to hospitals. Also, other hematologic adverse events such as anemia and thrombocytopenia were frequently observed. However unlike neutropenia, adverse events of grade 3 and higher were rare (Grade 3 or Grade 4 anemia: 2%, thrombocytopenia: 3%, respectively). Stomatitis was the most common non-hematologic AEs in the patients and the events were of Grade 1-2 severity. The frequency of side effects was shown in order of fatigue, arthralgia, nausea and these events were predominantly of Grade 1-2 severity. At the time of analysis, only one patient needed hospitalization due to grade 4 thrombocytopenia, accompanied by diffuse alveolar hemorrhage in both lungs, which required inpatient treatment and dose reduction of palbociclib (125 mg to 75 mg).

Dose adjustments were made in 167 (81.8%) of patients with palbociclib plus letrozole

therapy. Except one patient, 203 (99.5%) patients were started on 125 mg/day dose used on other clinical trials (PALOMA-2). And 164 patients had to reduce the dosage of palbociclib due mostly to hematologic adverse events. Two patients experienced neutropenia and thrombocytopenia of grade 4, eventually stopped to treatment. And One to two weeks of drug taking delays were also reported in 118 (57.8%) of patients. The reasons reported for dose adjustments of drug are shown in Table 4.

Table 4. Dose adjustments in patients with palbociclib plus letrozole

Dose	No. of patients (%), n=204
Starting dose of palbociclib	
125 mg	203 (99.5%)
100 mg	1 (0.5%)
Dose adjustments	
Reduction	164 (80.4%)
Interruption d/t adverse events	2 (1%)
Delay	118 (57.8%)
Reason reported for dose adjustments	
Adverse events	162 (79.4%)
Neutropenia	154 (75.4%)
Thrombocytopenia	5 (2.4%)
General weakness	7 (3.4%)

Discussion

This study was a retrospective analysis of medical records of 204 postmenopausal patients with HR+/HER2- metastatic breast cancer receiving palbociclib plus letrozole therapy in Korea. The objectives of the study were to evaluate efficacy of first line endocrine therapy with palbociclib plus letrozole and analysis adverse events in real world practice.

Response and efficacy data from this study support the results in the PALOMA studies(18), despite a higher proportion of patients of patients in our population receiving a more reduced dose of palbociclib(15). The Patients in this study had more frequent dose reductions compared to those of patients of PALOMA-1 and PALOMA-2, but PFS and ORR showed considerable efficacies. Even in this study, the dose reduction group had a longer period of treatment than standard dose group (16.9 months vs 12.2 months, p - value = 0.003) and PFS showed longer in patients with reduced dose treatment than patients without dose reduction treatment (Figure 3).

Hematologic adverse events, particularly neutropenia, are among the most commonly observed toxicities. Although neutropenia is the most frequently reported AE, but relatively

few patients (2% of patients) experienced febrile neutropenia and the rate of permanent treatment interruption was very low (especially 1%). Common causes of frequent neutropenia were explained by followings. According to Asian subgroup analysis of PALOMA-2 study(19, 20), baseline neutrophil counts in Asian women was 20% lower than that of non-Asian. In addition, comparing the mean concentration of same dose of palbociclib in pharmacokinetic sampling, the mean steady concentration value was higher than that of the non-Asian, which could be the cause of frequent neutropenia in our study (19, 20).

However, several limitations should be noted. First, it was conducted retrospectively. In collected data, reviewers retrospectively analyzed the hematologic and non-hematologic adverse events by electronic medical recording systems. Some side effects of therapy might be underestimated due to missing records. Second, the patient follow-up duration was too short to evaluate the treatment efficacy such as PFS and OS. Because palbociclib plus letrozole therapy was approved since June 2017 in Korea, so this study showed relatively short follow-up periods than other studies. Third, evaluating hematologic events, baseline neutropenia and thrombocytopenia were not analyzed and the change in blood counts due to drugs did not be

assessed.

This study is a retrospective study analyzing the efficacy and adverse events after palbociclib and letrozole therapy was allowed in Korea. The dose adjustment due to hematologic AEs was common, but dose reduction or treatment delay did not affect the effectiveness of therapy. Therefore, it shows that palbociclib and letrozole administration is tolerated in Korean women even with lower dose than non-Asians, implying that additional studies on the appropriated dose for palbociclib are needed.

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국문요약

서론: Palbociclib 은 암세포 분화 촉진에 관여하는 사이클린 의존성 인산화효소 (CDK) 4 와 6 을 억제하는 새로운 약제이다. PALOMA-2 연구 결과는 palbociclib 과 letrozole 의 병용 요법이 호르몬 양성, HER2 음성인 진행성 유방암 환자에서 효과적임을 보여주었고, 국내에서는 2017 년 6 월 이후 허가되었다. 우리는 단일 기관에서 시행된 palbociclib 과 letrozole 의 병용 요법의 실제 임상 효과에 대해 보고하고자 한다.

방법: 2007 년 6 월부터 2019 년 8 월까지 서울아산병원에서 palbociclib 과 letrozole 의 병합 요법을 시행한 호르몬 양성, HER2 음성인 진행성 유방암 환자들을 대상으로 후향적으로 분석하였다. 일차 결과 지표로 무진행 생존기간이며 이차 결과 지표로 전체 생존기간, 객관적 반응률, 임상적 이득률과 안정성을 확인하였다.

결과: 총 204 명의 환자가 분석에 포함되었다. 연령의 중앙값은 53 세(범위, 29-82 세) 였으며, 135 명 (66.2%)이 내부 장기 전이를 동반하고 있었고, 80 명 (39.2%) 의 환자들이 양측 난관 난소 절제술을 받았다. 추적 기간의 중앙값은

19.2 개월이었고, 무진행 생존 기간의 중앙값은 26.0 개월 (95 % 신뢰구간, 19.9 - 16.1), 분석 시점에 중앙 생존 기간에 도달하지는 못했다. 양측 난관 난소 절제술 받은 환자들의 무진행 생존기간 중앙값은 26 개월 (95% 신뢰구간, 19.9-26.0) 이었고, 자연적 폐경의 환자들은 무진행 생존기간 중앙값에 도달하지 못했다. 객관적 반응률은 38.2% (95% 신뢰구간, 31.5 - 45.2), 임상적 이득률은 81.9% (95% 신뢰구간, 75.8-86.8) 이었다. 가장 흔한 부작용은 호중구 감소증 (95.0%) 이였으며, 빈혈 (51.4%), 혈소판 감소증(33.3%), 구내염 (22.5%), 피로감(18.15) 순으로 나타났다. 3 등급 이상의 이상 반응 중 가장 흔한 부작용은 호중구 감소증 (83.3%, 204 명 중 170 명)이었으나, 호중구 감소성 발열의 경우 오직 4 명(2%)의 환자들에서만 나타났다. 호중구 감소증 때문에 164 명 (80.4%)의 환자들은 palbociclib 용량을 감량하였고, 그중 2 명의 환자들이 4 등급의 호중구 감소증 및 혈소판 감소증으로 투약을 중단하였다.

결론: 호르몬 수용체 양성, HER2 음성인 진행성 유방암 환자에서 palbociclib 과 letrozole 의 병용 요법은 중추적인 3 상 시험과 비슷한 효능을 보여주었다. 이 연구에서는 혈액학적 부작용으로 인해 palbociclib 의 용량 감소가 더 빈번하

요구 되었지만, 이러한 용량 조정은 치료 결과에는 영향을 미치지 않은 것으로 나타났다.