Efficacy and Safety of Palbociclib and Fulvestrant in Japanese Patients With ER+/HER2– Advanced/Metastatic Breast Cancer

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Abstract. *Background/Aim:* Published data have shown that palbociclib-fulvestrant can significantly improve the progression-free survival (PFS) of estrogen receptor-positive/human epidermal growth factor receptor 2-negative (ER+/HER2–) metastatic breast cancer patients, but not of Japanese patients. We conducted this retrospective study to verify the efficacy and safety of palbociclib-fulvestrant in Japanese patients. *Patients and Methods:* ER+/HER2– metastatic breast cancer patients treated with fulvestrant (n=39) or palbociclib-fulvestrant (n=31) at the Saitama Medical Center from July 2012 to November 2018 were evaluated. *Results:* Overall response rates (ORRs) were 2.6% (fulvestrant) and 41.9% (palbociclib-fulvestrant) ($p<0.001$), and clinical benefit rates (CBRs) were 23.1% and 61.3% ($p=0.002$), respectively. The palbociclib-fulvestrant group had significantly higher CBR and PFS (hazard ratio(HR):0.272, 95% confidence interval(95CI):0.128-0.574 for PFS). Grade 3/4 neutropenia occurred in 80.6% of the palbociclib-fulvestrant group, while febrile neutropenia was not detected. *Conclusion:* Japanese ER+/HER2– metastatic breast cancer patients tolerated palbociclib-fulvestrant, with significantly improved clinical outcomes.

Endocrine therapy for estrogen receptor/human epidermal growth factor receptor 2 (ER+/HER2–) tumours has greatly contributed to reduce early breast cancer recurrence (1). However, some patients relapse during, or following the completion of adjuvant therapy, and metastatic breast cancer (MBC) treatment remains a significant clinical issue.

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Tamoxifen or aromatase inhibitors are the standard of care for ER+ MBC (2-4). Fulvestrant is a selective ER down-regulator, with superior efficacy to aromatase inhibitors for ER+ MBC (5, 6), however, endocrine monotherapy has often offered limited clinical benefit (7, 8).

Targeting the molecular components of the cell cycle to interfere with cell-cycle progression is a logical strategy for cancer treatment. Cyclin-dependent kinases (CDK) 4 and 6 promote cell-cycle progression. Palbociclib selectively inhibits CDK4 and CDK6, which ultimately inhibits DNA synthesis (9, 10). Palbociclib is an approved novel molecular targeting drug for hormone receptor-positive/HER2– advanced or MBC combined with endocrine therapy (11). The phase 2 PALOMA-1 trial has demonstrated the efficacy and safety of palbociclib as first-line therapy combined with letrozole in patients with ER+/HER2– MBC (12). Patients treated with palbociclib-letrozole had significantly longer median progression-free survival (PFS) compared to those treated with letrozole (13). In the phase 3 PALOMA-3 trial, palbociclib-fulvestrant significantly improved PFS in patients with hormone receptor-positive/HER2– MBC who were resistant to endocrine therapy (14-17). Although neutropenia was the most frequent adverse event with palbociclib, the incidence of febrile neutropenia was very low.

A subgroup analysis of Japanese patients in the PALOMA-3 study (18) reported that palbociclib-fulvestrant had no significant effect on PFS compared to placebo-fulvestrant. In addition, the study showed that there was no significant difference in adverse events between the overall population and Japanese patients, except for a higher rate of neutropenia in Japanese patients receiving palbociclib.

Therefore, we conducted a retrospective study to verify the efficacy and safety of palbociclib-fulvestrant in Japanese patients.

Patients and Methods

ER+/HER2– advanced or MBC patients treated with fulvestrant (n=39) or palbociclib-fulvestrant (n=31) at the Saitama Medical Center from July 2012 to November 2018 were included. All patients

provided informed consent for treatment. This retrospective study was approved by the Institutional Review Board of the Saitama Medical Center (IRB no. 19-2), in accordance with the Declaration of Helsinki and its amendments (19). Fulvestrant, (500 mg, intramuscular) was administered on days 1 and 15 (cycle 1), then every 28 days starting from day 1 of cycle 1. Palbociclib, (125 mg/day, oral) was administered on days 1-21, followed by 7 days off treatment for every 28-day cycle. Premenopausal and perimenopausal women received subcutaneous injections of an LHRH agonist. The therapeutic effects were evaluated by RECIST guidelines (version 1.1) (20).

Dose interruption/reduction of palbociclib was defined as follows: i) for grade 3 neutropenia or thrombocytopenia, palbociclib was interrupted until recovery to grade ≤ 2 and then continued at the same dose, ii) for grade 3 neutropenia with fever, palbociclib was interrupted until recovery to grade ≤ 2 and then resumed with one dose-level reduction, iii) for grade 4 neutropenia or thrombocytopenia, palbociclib was interrupted until recovery to grade ≤ 2 and then resumed with one dose-level reduction, iv) for grade 3 non-hematologic abnormalities, palbociclib was interrupted until recovery to grade ≤ 2 and then resumed with one dose-level reduction. Two dose-level reductions in palbociclib were permitted. No dose reductions in fulvestrant were allowed. Laboratory tests were performed every 2 weeks during the first two cycles and on day 1 of subsequent cycles. The severity of adverse events was recorded and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE v4.0) (21).

Statistical analysis. Statistical analysis was performed using SPSS 23.0 (SPSS Inc., Chicago, IL, USA). Clinicopathological variables were compared using Fisher's exact and chi-squared tests. The Mann-Whitney test for categorical variables was used for age analysis. PFS was estimated by Kaplan-Meier with 95% confidence intervals (CIs). A log-rank test was used to compare PFS between groups. Hazard Ratios (HR) were estimated from the Cox proportional hazards regression models. Values of $p < 0.05$ were considered significant.

Results

Patients' characteristics. Patients from both groups had a median age of 64 years and all had HER2- disease. In the fulvestrant group, 92.3% were postmenopausal compared to 77.4% of the palbociclib-fulvestrant group. In the fulvestrant group, i) 79.5% were ER+ and progesterone receptor (PgR)+ compared to 87.1% in the palbociclib-fulvestrant group, ii) 56.4% had visceral disease compared to 48.4% in the palbociclib-fulvestrant group, and iii) 18.0% had bone disease only compared to 22.6% in the palbociclib-fulvestrant group. The median disease-free intervals (DFIs) were 25.4 months (fulvestrant) and 22.2 months (palbociclib-fulvestrant). There was no significant difference in the clinicopathological factors (Table I).

Efficacy. The fulvestrant group had a complete response rate of 0% compared to 3.2% for the palbociclib-fulvestrant group; the partial response rate was 2.6% (fulvestrant) and 38.7% (palbociclib-fulvestrant). The long stable disease rate was 20.5% (fulvestrant) compared to 22.6% (palbociclib-fulvestrant). The

overall response rates (ORRs) in the fulvestrant and palbociclib-fulvestrant groups were 2.6% and 41.9% ($p < 0.001$), respectively. The corresponding clinical benefit rates (CBRs) were 23.1% and 61.3% ($p = 0.002$), respectively (Table II).

The correlation between CBR and clinicopathological factors showed significant differences in CBR in patients with the following characteristics: age < 70 years (fulvestrant: 16.7% versus palbociclib-fulvestrant: 63.2%, $p = 0.002$), body mass index (BMI) ≥ 25 (fulvestrant: 10% versus palbociclib-fulvestrant: 69.2%, $p = 0.001$), ≤ 1 previous line of endocrine therapy (fulvestrant: 21.1% versus palbociclib-fulvestrant: 60%, $p = 0.001$), ≤ 1 previous line of chemotherapy (fulvestrant: 21.1% versus palbociclib-fulvestrant: 61.5%; $p = 0.002$), no sensitivity to prior endocrine therapy (fulvestrant: 22.5% versus palbociclib-fulvestrant: 60%, $p = 0.0049$), stage I-III at initial diagnosis (fulvestrant: 23.3% versus palbociclib-fulvestrant: 59.1%, $p = 0.011$), DFI ≥ 24 months (fulvestrant: 30% versus palbociclib-fulvestrant: 69.2%, $p = 0.038$), two or more metastatic sites (fulvestrant: 21.7% versus palbociclib-fulvestrant: 65%, $p = 0.006$), and visceral metastasis (fulvestrant: 22.7% versus palbociclib-fulvestrant: 73.3%, $p = 0.006$) (Table III). The palbociclib-fulvestrant group had significantly improved median PFS (13.3 months) compared to the fulvestrant group (3.9 months) [Hazard Ratio (HR): 0.272, 95%CI: 0.128-0.574, log-rank test $p < 0.001$] (Figure 1).

Adverse events. The most common adverse events in the palbociclib/fulvestrant group were leukopenia, neutropenia, anaemia, and fatigue (Table IV). More frequent hematological adverse events occurred in the palbociclib/fulvestrant group. No group experienced febrile neutropenia. The most common non-hematological adverse events were fatigue (41.9% in palbociclib-fulvestrant versus 5.2% in fulvestrant). Two patients experienced fever without neutropenia in the palbociclib-fulvestrant group. The only $>$ grade 3 non-hematological adverse event was liver dysfunction (5.1%), which occurred in the fulvestrant group. There were no serious adverse events in either group.

There was no dose discontinuation of palbociclib due to adverse events; however, 58.1% (18/31) required dose interruption and 71% (18/31) required dose reduction due to grade 3/4 neutropenia. Sixteen (51.6%) patients required one dose-level reduction and 6 (19.4%) required two dose-level reductions. The median number of courses for the first dose reduction was 2 (range: 1-5), and the median for the second dose reduction was 3 (range: 2-5).

Discussion

ER+/HER2- MBC treatment has remarkably changed over the past few decades. Aromatase inhibitors have shown effectiveness compared to tamoxifen in postmenopausal women with MBC (3,4). Subsequently, the selective ER

Table I. *Patients' characteristics.*

	Fulvestrant alone (n=39)	Palbociclib- fulvestrant (n=31)	p-Value		Fulvestrant alone (n=39)	Palbociclib- fulvestrant (n=31)	p-Value
Age (years)				No. of metastatic sites			0.154
Median (range)	64 (44-89)	64 (30-87)	0.522	1	16	11.0	
<70 years	30	19	0.194	2	9	11	
≥70 years	9	12		3	11	2	
Menopausal status			0.096	≥4	3	7	
Premenopausal	3	7		Disease-free interval (month)			
Postmenopausal	36	24		Median (range)	25.4 (0.5-138)	22.2 (0.5-22.2)	0.558
BMI			0.436	≤24 mo	13	8	1
<25	23	18		>24 mo	19	13	
≥25	10	13		Prior endocrine therapy			-
ECOG performance status			1.000	AI with or without GnRH agonist	35	23	
0	37	31		TAM with or without GnRH agonist	12	7	
1	1	0		Toremifen	9	9.0	
Pathological subtype			0.118	Fluvestrant	0	4.0	
IDC	31	30		mTOR inhibitor	2	4	
ILC	4	0		Prior chemotherapy			-
Unknown	5	1		Taxane	4	5	
Hormone-Receptor status			0.745	Anthracycline	1	2	
ER-positive and PR positive	31	27		Eriburin	3	5	
ER-positive and PR negative	6	4		Vinorelbine	0	1	
Unknown	2	0		Oral 5FU	2	1	
Ki-67			0.062	Most recent therapy			0.193
<40%	15	6		None	1	3	
≥40%	8	12		Endocrine	30	21	
Unknown	16	13		Chemo	6	3	
Nuclear grade			0.23	mTOR inhibitor	2	1	
1 or 2	22	18		CDK4/6 inhibitor	0	3	
3	1	1		Previous lines of therapy in the context of metastatic disease			0.539
Unknown	16	12		0	1	3	
Disease stage at initial diagnosis			0.708	1	12	11	
I	3	3		2	9	5	
II	14	11		≥3	17	12	
III	11	5					
IV	9	9					
Unknown	2	3					
Metastatic site							
Visceral	22	15	0.631				
Nonvisceral	20	19	0.472				
Bone only	7	7	0.766				

BMI: Body mass index; ECOG: Eastern Cooperative Oncology Group; IDC: invasive ductal carcinoma; ILC: invasive lobular carcinoma; ER: estrogen receptor; PgR: progesterone receptor; AI: aromatase inhibitor; GnRH: gonadotropin releasing hormone; TAM: tamoxifen; mTOR: mammalian target of rapamycin; 5FU: 5-fluorouracil; CDK: cyclin-dependent kinase.

down-regulator, fulvestrant, has been found to be significantly better PFS compared to aromatase inhibitors for postmenopausal women with ER+/HER2- MBC (6). Endocrine therapy has been a standard treatment strategy for ER+/HER2- MBC patients without a critical condition (22). Interestingly, endocrine therapy combined with a CDK4/6 inhibitor can significantly improve PFS compared to endocrine monotherapy, thus it has become a standard of treatment for ER+/HER2- MBC (13-15, 17, 23-25).

In a phase 3 trial, palbociclib-fulvestrant did not improve PFS in Japanese patients with ER+/HER2- MBC. The

frequency of grade 3/4 neutropenia was higher in Japanese patients than the overall population (18). Therefore, it was necessary to verify the efficacy and safety of palbociclib-fulvestrant for Japanese patients with ER+/HER2- MBC.

The palbociclib-fulvestrant group had significantly better ORR and CBR compared to the fulvestrant group. In the palbociclib-fulvestrant group of the PALOMA-3 trial, the ORRs were 21% in the overall population and 18.5% in the Japanese subgroup, and the CBRs were 66.3% in the overall population and 74.1% in the Japanese subgroup (18). The CBR in this study was like the trial, but the current study had

Table II. Comparison of overall response rate in the fulvestrant alone and palbociclib-fulvestrant groups.

	Fulvestrant alone (n=39)	Palbociclib- fulvestrant (n=31)	p-Value
Response			
CR	0	1	
PR	1	12	
LSD	8	7	
SD	4	2	
PD	26	9	
RR	2.6%	41.9%	<0.001
CBR	23.1%	61.3%	0.002

CR: Complete response; PR: partial response; LSD: long stable disease; SD: stable disease; PD: partial response; RR: response rate; CBR: clinical benefit rate.

a better ORR. However, there were fewer patients with visceral metastasis than in the PALOMA-3 trial (48% and 63%, respectively). Our result indicated better clinical response with palbociclib-fulvestrant than fulvestrant for Japanese patients with ER+HER2- MBC (18).

We observed higher CBRs: i) in patients aged <70 years, ii) with BMI ≥ 25 , iii) PgR positivity, iv) stage I-III at initial diagnosis, v) DFI 24 months or longer, vi) ≤ 1 previous line of endocrine therapy, vii) ≤ 1 previous line of chemotherapy, viii) no sensitivity to prior endocrine therapy, ix) two or more metastatic sites, and x) visceral metastasis in the palbociclib-fulvestrant group.

It has been previously shown that there was significantly improved median PFS with palbociclib-fulvestrant *versus* fulvestrant in the <65-year old subgroup and 65-74-year old subgroup, but no significant improvement in the ≥ 75 -year old subgroup (23). Our study also reports that there is no significant difference in CBR between fulvestrant and palbociclib-fulvestrant in the ≥ 70 -year old subgroup, suggesting that fulvestrant provides a sufficient benefit for elderly patients.

CBR in the palbociclib-fulvestrant group was significantly better compared to the fulvestrant group in patients with a BMI of ≥ 25 . A previous study has demonstrated that obesity is a risk factor for postmenopausal ER+ breast cancer (26). In fact, the efficacy of endocrine therapy for ER+ postmenopausal MBC is significantly worse for patients with a BMI of ≥ 25 than for those with a BMI <25 kg/m² (27). Although no direct evidence exists for the relationship between the efficacy of CDK4/6 inhibitor and obesity, endocrine therapy alone is less effective for obese patients, which may explain the improved CBR when combined endocrine therapy and palbociclib is administered.

Patients with stage I-III disease at initial diagnosis and DFI >24 months had significantly better CBR with

Figure 1. Kaplan-Meier curve for PFS in patients with ER+/HER2-MBC. Cox's proportional hazard ratio (95%CI):0.272 (range:0.128-0.574). PFS: Progression-free survival; ER: estrogen receptor; HER2: human epidermal growth factor receptor 2; MBC: metastatic breast cancer; CI: confidence interval.

palbociclib-fulvestrant compared to fulvestrant. This finding is supported in the PALOMA-2 trial, where patients receiving palbociclib-fulvestrant had longer PFS in the recurrent subgroup compared to the newly metastatic subgroup (13), and in the PALOMA-3 trial, where the palbociclib-fulvestrant group had significantly more OS in the DFI >24 months subgroup (24).

Increased PFS has been reported in patients receiving palbociclib-fulvestrant compared to fulvestrant, regardless of the number of previous endocrine therapy treatments. For example, patients who were administered palbociclib-fulvestrant having received 1 previous line of endocrine therapy had longer PFS compared to patients who received ≥ 2 previous lines (16). In this study, PFS was significantly longer in patients receiving ≤ 1 previous line of endocrine therapy compared to those who received ≥ 2 lines. This suggests a possible benefit for ER+/HER2-MBC patients to receive palbociclib-fulvestrant as an early treatment, prior to the application of multiple lines of endocrine therapy.

Palbociclib-fulvestrant has previously led to a significantly better prognosis compared to fulvestrant in patients with and without sensitivity to prior endocrine therapy (14). In this study, palbociclib-fulvestrant also resulted in a significantly better CBR in patients without sensitivity to prior endocrine therapy. Possibly, palbociclib-fulvestrant contributes to endocrine therapy resistance in MBC patients.

In the PALOMA-3 trial, the PFS in the palbociclib-fulvestrant group was significantly longer compared to the fulvestrant group in patients with two or more metastatic sites (16). PFS was also significantly better, regardless of

Table III. Correlation between CBR and clinicopathological factors in fulvestrant alone and palbociclib-fulvestrant treated patients.

	Fulvestrant alone (%)	Palbociclib-fulvestrant (%)	OR (95%CI)	p-Value
Age				
<70	16.7	63.2	2.656 (2.248-32.667)	0.002
≥70	44.4	58.3	1.375 (0.507-3.729)	0.67
Menopausal status				
Pre/Peri	0	85.7	-	0.033
Post	25	54.2	1.737 (1.010-2.985)	0.03
BMI				
<25	26.1	55.6	1.813 (0.950-13.198)	0.105
≥25	10	69.2	6.923 (1.041-46.027)	0.01
PgR				
Negative	16.7	0	-	1
Positive	22.6	70.4	2.786 (1.434-5.412)	<0.001
Disease stage at initial diagnosis				
I-III	23.3	59.1	2.054 (1.088-3.877)	0.011
IV	22.2	66.7	2.800 (0.789-9.940)	0.153
Disease-free interval (month)				
≤24	8.3	50	3.750 (0.635-22.142)	0.109
>24	30	69.2	1.912 (0.975-3.749)	0.038
Previous lines of endocrine therapy in the context of metastatic disease				
0 or 1	21.1	60	1.771 (1.048-2.993)	0.01
≥2	100	62.5	-	1
Previous lines of chemo therapy in the context of metastatic disease				
0 or 1	21.1	61.5	2.250 (1.243-4.073)	0.002
≥2	100	60	-	1
Prior Sensitivity to endocrine therapy				
No	22.6	60	1.592 (0.941-2.692)	0.049
Yes	33.3	58.3	2.000 (0.482-8.306)	0.62
No. of Metastatic sites				
1	25	54.5	1.765 (0.778-4.002)	0.224
≥2	21.7	65	2.592 (1.183-5.677)	0.006
Metastatic site				
Visceral	22.7	73.3	2.590 (1.217-5.516)	0.006
Non-visceral	23.5	50	1.857 (0.780-4.422)	0.157
Bone only	28.6	71.4	2.500 (0.708-8.827)	0.286

CBR: Clinical benefit rate; OR: odds ratio; CI: confidence interval; BMI: body mass index; PgR: progesterone receptor.

visceral metastasis (24). In this study, better CBR in the palbociclib-fulvestrant group was observed in patients with multiple metastatic sites and those with visceral metastasis, suggesting that palbociclib-fulvestrant therapy has more clinical benefit in patients with extensive metastatic disease.

Our results suggest that the most appropriate cases for treatment with palbociclib-fulvestrant are: i) aged <70, ii) obese, iii) PgR positive, iv) with DFI >24 months, v) early-line treatment with resistance to prior endocrine therapy, and vi) multiple metastases, including visceral metastasis. Endocrine monotherapy can have sufficient clinical benefit for elderly patients with mild metastatic disease.

In a previous report, although the median PFS of the palbociclib-fulvestrant group was significantly longer

Table IV. Dose discontinuation, interruption, and reduction of palbociclib treatment.

	N	%
Dose discontinuation	0	0
Dose interruption	18	58.1
Dose reduction (Total)	22	71
1 dose-level reduction	16	51.6
2 dose-level reduction	6	19.4
Course for dose reduction		
1 dose-level reduction		
Median (minimun-max)	2 (1-5)	
2 dose-level reduction		
Median (minimun-max)	3 (2-5)	

compared to the fulvestrant group in the entire population, Japanese patients in both groups had no significant difference in PFS (18). In our study, the median PFS was significantly improved in the palbociclib-fulvestrant group. Our result suggests a possibly significant improvement in the prognosis of Japanese patients receiving palbociclib-fulvestrant.

Japanese and other Asian patients have lower baseline neutrophil counts compared to non-Asian patients (18). This may explain the higher rate of neutropenia in Japanese patients treated with palbociclib. This higher incidence was not related to a higher palbociclib exposure, lower body weight, lower body surface area/BMI, or older age. The rate of grade 4 neutropenia in the palbociclib-fulvestrant group was 16.1%. This is similar to the PALOMA-3 trial, that reported 26% grade 4 neutropenia in Japanese patients receiving palbociclib, which was higher compared to the overall population (9%) (18). Neutropenia caused by palbociclib should not be viewed or managed the same way as neutropenia caused by chemotherapy. A previous study has reported that bone marrow suppression due to palbociclib is not associated with apoptosis, DNA damage response, or cell senescence *in vitro* (28). Patients treated with palbociclib recover human bone marrow mononuclear cell counts on day 9 following administration; however, this is not observed in patients treated with cytotoxic chemotherapeutic agents. Possibly, bone marrow suppression from palbociclib may less likely cause serious side effects, because patients recover sooner following treatment interruption compared to those treated by chemotherapy.

Although the rate of grade 3/4 neutropenia in this study was 80.6%, there was no febrile neutropenia or treatment discontinuation. A previous study has demonstrated that patients recover more quickly from neutropenia caused by palbociclib compared to neutropenia caused by chemotherapy (28). Approximately 50% of the palbociclib-fulvestrant group in this study had one dose-level reduction, and approximately 20% had two dose-level reductions. This supports the results of the PALOMA-3 trial, where 44% of the palbociclib-fulvestrant group and 15% of the Japanese subgroup had one dose-level reduction (18). The median number of courses of one dose-level reduction in palbociclib-fulvestrant in this study was two. In another study, PFS was similar between patients requiring a dose reduction and those who did not, indicating that palbociclib dose reduction does not affect prognosis (29). These results suggest that neutropenia due to palbociclib is an unlikely cause of febrile neutropenia if dose reduction is performed early, and the feasibility of palbociclib in Japanese breast cancer patients is equal to the entire population.

This study had certain limitations. This is a single-institution retrospective study with a limited sample size and a short observation period. However, this study indicated a

possibility that palbociclib-fulvestrant is effective and well tolerated in Japanese patients with ER+/HER2- MBC. Further studies are required to evaluate long-term prognosis with more cases of this particular patient population.

Conflicts of Interest

The Authors report no conflicts of interest related to this study.

Authors' Contribution

Drafting of the manuscript was done by HS and TS.. Literature search and analysis were done by HS, TT, TK, T.O, TK, KN;. Data extraction was done by HS, YM, NO, MA, RY, KH, KS. Manuscript editing was done by HS.

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