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.

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).

Efficacy. The long stable disease rate was 20.5% (fulvestrant) compared to 22.6% (palbociclib-fulvestrant). The clinicopathological factors (Table I).

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. 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).

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.

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
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 I. Patients’ characteristics. |
|------------------------------------|
|                                    |
| Fulvestrant alone (n=39)            |
| Fulvestrant-fulvestrant (n=31)      |
| Age (years)                        | Fulvestrant | Palbociclib- | p-Value |
| Median (range)                     | 64 (44-89) | 64 (30-87)   | 0.522   |
| <70 years                          | 30         | 19           | 0.194   |
| ≥70 years                          | 9          | 12           |         |
| Menopausal status                  |            |              | 0.096   |
| Premenopausal                      | 3          | 7            |         |
| Postmenopausal                     | 36         | 24           |         |
| BMI                                |            |              | 0.436   |
| <25                                | 23         | 18           |         |
| ≥25                                | 10         | 13           |         |
| ECOG performance status            |            |              | 1.000   |
| 0                                  | 37         | 31           |         |
| 1                                  | 1          | 0            |         |
| Pathological subtype               |            |              | 0.118   |
| IDC                                | 31         | 30           |         |
| ILC                                | 4          | 0            |         |
| Unknown                            | 5          | 1            |         |
| Hormone-Receptor status            |            |              | 0.745   |
| ER-positive and PR positive        | 31         | 27           |         |
| ER-positive and PR negative        | 6          | 4            |         |
| Unknown                            | 2          | 0            |         |
| Ki-67                              |            |              | 0.062   |
| <40%                               | 15         | 6            |         |
| ≥40%                               | 8          | 12           |         |
| Unknown                            | 16         | 13           |         |
| Nuclear grade                      |            |              | 0.23    |
| 1 or 2                             | 22         | 18           |         |
| 3                                  | 1          | 1            |         |
| Unknown                            | 16         | 12           |         |
| Disease stage at initial diagnosis |            |              | 0.708   |
| I                                  | 3          | 3            |         |
| II                                 | 14         | 11           |         |
| 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   |
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.

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

| Response | Fulvestrant alone (n=39) | Palbociclib-fulvestrant (n=31) | p-Value |
|----------|--------------------------|-------------------------------|---------|
| 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.

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.
In a previous report, although the median PFS of the palbociclib-fulvestrant group was significantly longer for elderly patients with mild 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 than for the fulvestrant-alone group, we observed better CBR in the palbociclib-fulvestrant group in patients with extensive metastatic disease.

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

### 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 (2.248-3.266) | 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 ≥24                   | 26.1                  | 55.6                        | 1.813 (0.950-3.139) | 0.105   |
| BMI >24                   | 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-II                      | 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           |                       |                             |            |         |
| Viceral                   | 22.7                  | 73.3                        | 2.590 (1.217-5.516) | 0.006   |
| Non-viceral               | 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   |

|                            | 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    | 2 (1-5)   |           |
| Median (minimum-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 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, TO, TK; KN. Data extraction was done by HS, YM, NO, MA, RY, KH, KS. Manuscript editing was done by HS.

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