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Molecular Targeted Therapy for Hormone Receptor-Positive, Human Epidermal Growth Factor 2-Negative Metastatic Breast Cancer in Clinical Practice

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Background: The emergence of molecular targeted therapies (MTTs) has altered the treatment landscape for hormone receptor-positive (HR+), human epidermal growth factor 2-negative (HER2−) metastatic breast cancer (MBC). The objective of this study was to describe treatment patterns, clinical outcomes, and safety profiles for patients with HR+/HER2− MBC treated with palbociclib, abemaciclib, or everolimus in clinical practice.

Methods: Forty-five patients with HR+/HER2− MBC were enrolled; 40 received MTT as the third line or later and 5 received MTT as the first/second line. The results were compared with those of clinical trials.

Results: Median overall progression-free survival (PFS) was 5.3 months (95% confidence interval [CI] 2.8-8.4), and PFS was similar for patients receiving first/second line (5.5 months, 95% CI 1.8-) and third line or later (5.1 months, 95% CI 2.8-9.4) treatments. Eleven patients continued with the same regimen for >1 year; treatment is ongoing for 15 patients. In 23 patients (51%), everolimus was administered before cyclin-dependent kinase (CDK) 4/6 inhibitors. The most frequent grade 3 or worse adverse event (AE) with CDK4/6 inhibitors was neutropenia, whereas grade 3 or worse AEs with everolimus were *Pneumocystis* pneumonia, sepsis, and stomatitis.

Conclusions: MTT was mostly used in third or later lines, and PFS was similar for patients receiving first/second line and third or later line treatments. However, this study included heavily treated patients and a small number of cases. Treatment options should consider maximal patient benefit, as indicated by the results of clinical trials. (J Nippon Med Sch 2022; 89: 88−94)

Key words: hormone receptor-positive, molecular targeted therapy, palbociclib, abemaciclib, everolimus

Introduction

The treatment landscape of luminal type metastatic breast cancer (MBC) has changed owing to the emergence of molecular targeted therapies (MTTs)[1]. Hormonal or endocrine therapy (ET) is commonly prescribed for luminal type, non-life-threatening MBC because it is associated with fewer adverse events (AEs), lower costs, and less frequent hospital visits. However, many patients fail to respond to ET or eventually develop endocrine resistance[2]. According to the Advanced Breast Cancer 4 guidelines, the combination of molecular targeted agents (MTAs) and hormonal agents is effective in treating endocrine-resistant hormone receptor-positive (HR+), human epidermal growth factor 2-negative (HER2−) MBC[1].

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Cyclin-dependent kinase (CDK) 4/6 inhibitors, such as palbociclib, abemaciclib, and ribociclib, are a new class of MTAs that has shown promising results in clinical trials[3–10]. Palbociclib and abemaciclib were approved in Japan in December 2017 and November 2018, respectively. Another MTA with demonstrated efficacy in endocrine-resistant MBC is the mammalian target of rapamycin (mTOR) inhibitor everolimus, which was approved in Japan in March 2014. Compared with exemestane monotherapy, the combination of everolimus and exemestane significantly improved progression-free survival (PFS) in HR+, HER2− MBC patients progressing on nonsteroidal aromatase inhibitors[11]. The safety profile of these MTTs is highly variable.

Despite the promising results, MTAs are not commonly prescribed as a first or second line treatment in clinical practice;[12–15] ET remains the treatment of choice, especially for elderly patients, perhaps because the safety profile of ET is better than that of MTT. From a clinician's perspective, patients should receive the most beneficial treatment, after considering factors such as duration until treatment failure, comorbidities, and financial constraints. Here, we retrospectively analyzed data from patients who received MTAs for HR+, HER2− MBC in our hospital and compared these data with results from clinical trials. We aimed to identify treatment patterns, clinical outcomes, and safety profiles for patients with HR+/HER2− advanced breast cancer and/or MBC treated with palbociclib, abemaciclib, or everolimus in clinical practice.

Materials and Methods

In June 2020, data were collected (using the opt-out approach) from the electronic records of patients with HR+/HER2− MBC who received treatment with MTA (everolimus, palbociclib, or abemaciclib) at the Kawaguchi Municipal Medical Center from April 2014 to May 2020. Patients were treated with a combination of MTA and an endocrine agent, with no concurrent anti-cancer therapy. The MTT was selected at the physician's discretion.

Data collected from the patients included age, menopausal status, adjuvant therapy, recurrence pattern, lines of treatment, prior treatments, number of MTT, PFS, dose reduction parameters, outcomes, and AEs (per common terminology for adverse events v5.0 criteria)[16]. MTA dose was reduced as necessary, according to the dose modification criteria. Patients treated with CDK4/6 inhibitors visited the hospital once every 2 weeks for a complete blood count and to report any AEs, until the adequate dose was identified. After 2 months of treatment at the same CDK4/6 inhibitor dose, the frequency of hospital visits was reduced to once a month. Patients treated with everolimus visited the hospital once a month for monitoring of complete blood counts, blood sugar, and other AEs. This study was approved by the institutional review board of the Kawaguchi Municipal Medical Center (approval number 2020-2) and was performed in compliance with the Declaration of Helsinki. The requirement for informed consent was waived due to the retrospective nature of the study.

Data were reported in a manner similar to that described in the main PALOMA-3 report[4]. Standard descriptive statistics were used to report data related to patient characteristics and tolerability outcomes. The Kaplan-Meier method was used to estimate PFS. To compare our findings with real-world data, external reference data were used from a previous study[4]. Results were considered statistically significant if P was <0.05. Analyses were performed using SAS University Edition.

Results

From April 2014 to May 2020, 45 patients with HR+/HER2− MBC were treated with palbociclib, abemaciclib, or everolimus (60 treatment regimens). The combination partners for different MTAs that have been authorized for use in Japan include exemestane with everolimus, letrozole or fulvestrant with palbociclib, and nonsteroidal aromatase inhibitor or fulvestrant with abemaciclib. In premenopausal patients, CDK4/6 inhibitors are used only with fulvestrant, in conjunction with a luteinizing hormone-releasing hormone agonist.

The average age of patients who received any type of MTA was 61 years (range, 39-91 years). Forty-two patients were postmenopausal and 3 were premenopausal. Metastatic sites are shown in **Table 1**. In addition to adjuvant therapy, the number of chemotherapy regimens administered to patients ranged from 0 to 8. Seven (15.6%) patients received MTT just before best supportive care. MTAs were administered in lines ranging from first to 16th. Only 5 patients received MTT in the first or second line, whereas 40 patients received MTT in subsequent lines. Thirty-four patients received treatment with 1 MTA, 10 received 2 MTAs, and 1 received all 3 MTAs. Twenty-two patients had received a CDK4/6 inhibitor before an mTOR inhibitor, and 23 had received an mTOR inhibitor before CDK4/6 inhibitor therapy (**Table 1**). These data were compared with those of the PALOMA-3 population[5].

Palbociclib, abemaciclib, and everolimus were adminis-

Table 1 Patient characteristics (n = 45)

Characteristics	
Average age in years (median, range)	61 (59, 39–91)
Menopausal status	
Premenopausal	3 patients
Postmenopausal	42 patients
Metastatic site	
Bone	23
Lung/pleura	17
Liver	6
Lymph node	19
Local	4
Chest wall	1
Brain	1
Unknown	3
Average number of prior chemotherapy treatments (median, range)[a]	1.9 (1, 0–8)
Line when MTT was introduced (1st–16th line)	
1st and 2nd line	5 patients
3rd line or later	40 patients
Number of molecular targeted agents administered	
1	34 patients
2	10 patients
3	1 patient
Prior molecular targeted agent	
CDK 4/6 inhibitor	22 patients
mTOR inhibitor	23 patients

[a]Data were unavailable for 1 patient.

Table 2 Time-to-failure (TTF) for each targeted agent

	Palbociclib	Abemaciclib	Everolimus
Number of treatments	28	5	27
Average TTF in months (median, range)	8.2 (6.5, 0-22)	4.9 (3.2, 0.3-16)	6.2 (5.5, 0.3-18)
Treatment ongoing	10	3	2
Number of patients with TTF ≥1 year	6 (21.4%)	1 (20.0%)	4 (14.8%)
Combination partner	Letrozole, 16 Fulvestrant, 10 Fulvestrant + LH-RH agonist, 2	Letrozole, 3 Fulvestrant, 1 Fulvestrant + LH-RH agonist, 1	Exemestane, 24 Others, 3

LH-RH; luteinizing hormone-releasing hormone

tered to 28, 5, and 27 patients, respectively, among 45 patients. Average time-to-failure, the number of patients who received the same regimen for >1 year, and the combination partner for each MTA are shown in **Table 2**. Median PFS was 5.5 months among patients receiving first and second lines of treatment and 5.1 months among those receiving third or subsequent lines of treatment. Nine patients had a PFS of >1 year, and MTT was introduced in treatment line 5.9, on average (**Table 3**). The median PFS in this study was 5.3 months (95% confidence interval [CI] 4.9-15.1), as compared with 9.5 months in the PALOMA-3 study (95% CI 9.2-11.0) (**Fig. 1**). Eleven patients received more than 2 MTAs. The sequential data on PFS are shown in **Figure 2** and have been classified by the prior MTA received.

The most frequent AE (grade 3 or worse) associated with palbociclib treatment was neutropenia (**Table 4**). Of the 28 patients receiving palbociclib, 21 (75%) required

Table 3 Progression-free survival (PFS) in early and late lines of treatment

Line of therapy	Median PFS
1st and 2nd (5 cases)	5.5 months (ongoing; 2 cases)
3rd or later (40 cases)	5.1 months (ongoing; 8 cases)
All patients	5.3 months
Number of patients who received molecular targeted therapy for >1 year	9 (20%)
Average and median line of introduction of molecular targeted agents in patients with PFS>1 year (range)	5.7, 5.9 (3-10)

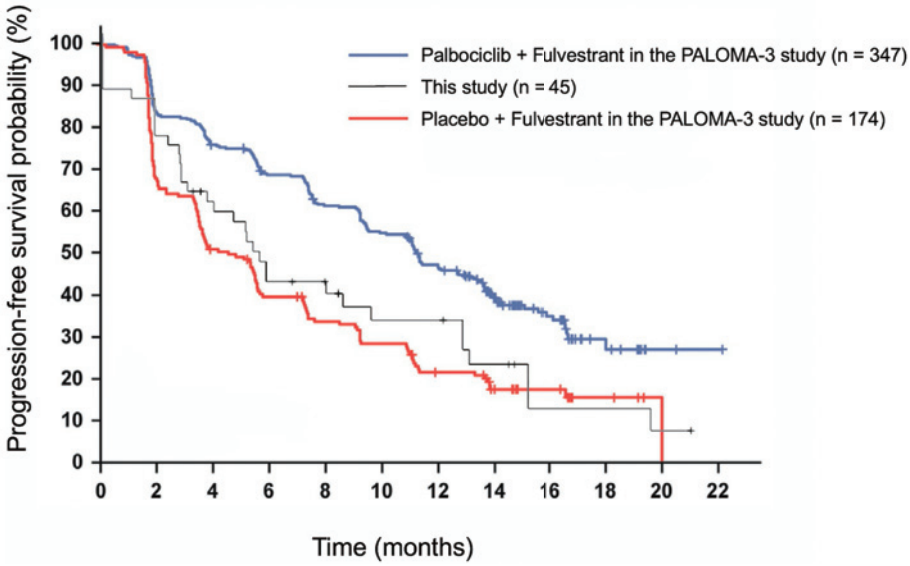

Fig. 1 Kaplan-Meier curves of progression-free survival of patients in this study and the PALOMA-3 study. The PALOMA-3 study data were adjusted according to the original data published by Turner et al. [5,6]

dose reduction or prolongation of interval. Although diarrhea was the most common AE reported in clinical trials of abemaciclib, no patient developed grade 3 or worse diarrhea in this study. A few serious AEs, such as *Pneumocystis* pneumonia, sepsis, and Fanconi syndrome, were observed for everolimus, although none was of grade 5 severity.

Discussion

In this study, MTTs were used mostly in the third line or later for HR+/HER2− MBC, mainly because MTTs were used initially in later lines. This could be attributable to a tendency to delay or avoid chemotherapy in elderly patients, or to the date of MTT availability in Japan and its subsequent introduction to the back-log of heavily treated patients. The PALOMA-3 study[4–6] compared fulvestrant with the combination of fulvestrant and palbociclib as a second line treatment, whereas the PALOMA-2 study[3] compared letrozole with the combination of letrozole and palbociclib as a first line treatment for HR+/HER2− advanced breast cancer and/or MBC patients. In our study, palbociclib was the most frequently used, and most patients were treated in the third line or later; thus, the PALOMA-3 study was chosen for comparison rather than PALOMA-2. Although the proportions of older and heavily treated patients were higher in our study than in the PALOMA-3 study, median PFS was similar for MTT use in late lines and early lines. PFS for first- and second-line patients was low; however, these patients had no visceral metastases. Although the number of patients was limited, follow-up data from ongoing treatment will help us further understand and evaluate these observations.

In our study, 9 (20%) patients received MTT for longer than 1 year and it was introduced in these patients at line 5.9, on average. Compared with the patients in the PALOMA-3 study[4]-who received second line combination therapy and had a PFS of 11.2 months-the patients in our study were more heavily treated and older. However, some of the present patients had a PFS comparable to

that of the PALOMA-3 study. Kaplan-Meier curves showed that PFS in the present patients was close to that of patients in the PALOMA-3 study[4], as determined by hormone monotherapy curves. It is noteworthy that PFS in our study declined immediately after introduction of MTT, suggesting that some patients underwent MTT just before offering best supportive care. MTTs should be used early, before hormone sensitivity is lost.

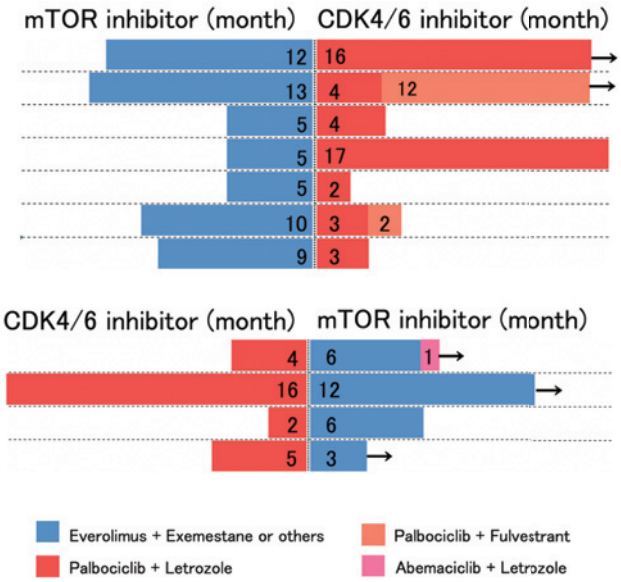

Fig. 2 Progression-free survival for each molecular targeted agent. Patients received (upper) mammalian target of rapamycin (mTOR) inhibitor treatment before initiation of cyclin-dependent kinase (CDK) 4/6 inhibitor treatment or (lower) CDK4/6 inhibitor treatment before initiation of mTOR inhibitor treatment. An " → " indicates treatment is ongoing.

There were only 11 cases of sequential treatment with MTTs in our study, including cases that are ongoing. Because the mTOR inhibitor was available earlier than CDK 4/6 inhibitors, slightly more patients received the mTOR inhibitor first (23 vs. 22 cases for mTOR vs. CDK4/6 inhibitor, respectively), and one CDK4/6 inhibitor was used later in patients with disease progression. However, with the increasing number of CDK4/6 inhibitors now available, these agents will likely be used first more often in the near future. Sequential treatment of progressive disease with prior MTT would likely be more significant. When resistance to CDK4/6 inhibitors is observed, mTOR or PI3K inhibitors may be effective[17–19]. Some reports state that use of prior MTT affects efficacy outcomes[12–15]; however, changing treatment from a CDK4/6 inhibitor to an mTOR inhibitor was shown to maintain the treatment effect[20].

When a different treatment option is called for, we need to refer to known basic mechanisms of drug action or resistance because there is little available evidence from clinical trials to guide the choice of subsequent treatments. Iida et.al. reported that cross-resistance can occur between 2 CDK4/6 inhibitors[21]; therefore, it would be better to choose an agent with a different mechanism of action in the next treatment step. In our study, there was no case in which one CDK 4/6 inhibitor was switched for another.

Studies of combinations of MTA and hormone therapy found that hormones have the same effect when used with or without MTA[12]. Furthermore, PFS was longer

Table 4 Summary of adverse events for 45 patients (60 treatment regimens)

Number of patients using the molecular targeted agent	Palbociclib 28	Abemaciclib 5	Everolimus 27
Adverse events (severity ≥ grade 3), n	Neutropenia, 12 Leukocytopenia, 1 Febrile neutropenia, 1 Anemia, 1 Vomiting, 1 Chronic renal failure, 1	Vomiting, 1 Abdominal pain, 1 Increase of hepatobiliary enzyme, 1 Leukocytopenia, 1 Malaise, 1	*Pneumocystis* pneumonia, 1 Sepsis, 1 Stomatitis, 1 Fanconi syndrome, 1 Gastrointestinal disorders, 1 Increased blood sugar, 1
Dose reduction, n (%)	21 (75%) 1-dose level reduction: 9 (32%) 2-dose level reductions: 8 (29%) 2-dose level reductions+ prolongation of interval: 4 (14%)	3 (60%) 1-dose level reduction: 3 (60%)	2 (7%) 50% reduction: 2 (7%)
Treatment discontinuation, n (%)	3 (11%)	2 (40%)	2 (7%)

when MTA was used in combination with hormones rather than alone[22]. Therefore, if possible, it is better to change both MTA and the hormonal agent, to avoid the possibility of cross-resistance. Results of ongoing clinical trials are expected.

Palbociclib prevents cell proliferation by arresting the cell cycle; hence, neutropenia resolves quickly after withdrawal of palbociclib[23]. Febrile neutropenia is also experienced in clinical practice. Grade 3 or higher AEs are usually managed in accordance with the dose modification criteria for the administered drug. Dose reduction was required for 75% of the patients who received palbociclib in this study. One- and two-step reduction was achieved for 32% and 29% of patients, respectively. For 14% of the patients, the duration of the withdrawal was prolonged even after a two-step dose reduction. The safety profile of palbociclib varies by race: the incidence of various AEs was higher in Asian and Japanese patients than in the overall population[24].

Compared with palbociclib, abemaciclib does not require treatment withdrawal, which in turn reduces the complexity of the treatment schedule. However, a post-marketing study of abemaciclib in Japan reported that 17 of 4,100 patients (0.4%) developed grade 5 interstitial lung disease, exhibiting both organizing pneumonia and diffuse alveolar damage patterns, including some rapidly progressive cases[25]. This is an important observation, as the clinical trials of abemaciclib did not report interstitial lung disease as an AE. There is no evidence indicating whether this observation is related to ethnicity. Special precautions are necessary in order to prevent severe AEs, especially in early lines of treatment. Assessment of blood samples is recommended, including KL-6 levels, as is a chest CT scan, before the use of MTT. Additionally, clinical symptoms such as dyspnea and cough should be carefully evaluated during treatment.

When using everolimus, serious safety-related complications, including *Pneumocystis* pneumonia, sepsis, and Fanconi syndrome, were observed in our study, and treatment had to be discontinued or changed. Interstitial lung disease is another AE reported for everolimus, with relatively slow progression[11]; however, there was no such case in our study.

The effectiveness of MTT for HR+ HER2− MBC is convincing, according to numerous clinical trials. Moreover, clinical trials of a triplet combination of 2 MTTs and an ET, and new targeted agents with different mechanisms of action, have been conducted with the expectation of better results. However, MTT is sometimes difficult to introduce to elderly patients and patients with complications, because of potential AEs, complex treatment schedules, frequent hospital visits, and costs in clinical practice. The present study mainly included patients with third or later line treatments with MTT because these cases had accumulated immediately after MTT was approved. As a result, median PFS was shorter than in the PALOMA-3 study.

This study has some limitations. First, it was conducted at a single center and used data collected from electronic medical records. Second, the sample size was small and included some patients still receiving treatment, as well as patients who received MTT just before best supportive care. Despite the limited number of older and heavily treated patients in a clinical practice setting, 20% of the patients had a PFS longer than 1 year in our study. Treatment should be chosen to maximize benefits for each patient with HR+ HER2− MBC.

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Conflict of Interest: None.

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