Efficacy and toxicity of palbociclib in heavily treated patients with metastatic breast cancer

Naoko Iwamoto¹, Tomoyuki Aruga¹, Katsumasa Kuroi², Chiaki Saita¹, Mai Onishi¹, Risa Goto¹, Toshiyuki Ishiba¹, Yayoi Honda¹, Hiromi Miyamoto¹

¹ Department of Breast Surgery, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital
² Department of Breast Surgery, Ebara Hospital

Abstract

Background: Palbociclib is reported to improve progression-free survival (PFS) in patients with estrogen-receptor (ER)-positive, human epidermal growth factor 2 (HER2)-negative metastatic breast cancer (MBC). However, evidence of the effects of palbociclib in heavily treated patients is limited. The present study aimed to determine the effects and toxicity of palbociclib in heavily pretreated patients and to find the differences between the patients treated with palbociclib in upfront line and those with in later-line.

Methods: This retrospective, single-center, observational study enrolled 26 patients with ER-positive, HER2-negative MBC who started palbociclib (125 mg) plus endocrine therapy between December 2017 and July 2018. These patients were divided into 2 groups, upfront (<3) and later-line groups (≥4 lines prior therapy). Progression-free survival (PFS) estimated using the Kaplan-Meier method was compared between 14 patients who received upfront-line therapy and 12 who received later-line therapy.

Results: Among the 26 patients, 22 (85%) had visceral metastasis. The median number of prior treatment lines for MBC was 3.5 and the median follow-up was 5.1 months. Median PFS was 3.6 months in later-line group, and PFS was significantly shorter than in the upfront-line group (p = 0.046, median PFS: not reached in upfront line group). The incidences of grade 3/4 neutropenia were 86% and 83% in the upfront- and later-line groups, respectively. One patient developed febrile neutropenia. The treatment schedule was interrupted in 13 (93%) and 11 (92%) patients in the upfront- and later-line groups, respectively. The number of the patients who required dose reduction was higher in later-line group than upfront-line group (67% vs. 57%).

Conclusion: Although the toxicity of palbociclib is tolerable with a low incidence of febrile neutropenia, palbociclib is less-effective for heavily pretreated patients in comparison with lightly-pretreated patients. Our findings indicated that palbociclib could be used as a front-line treatment for MBC.

Keywords: palbociclib, metastatic breast cancer, neutropenia

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Introduction

It was reported that adding the CDK (cyclin-dependent kinase) 4/6 inhibitor palbociclib to endocrine therapy improves the progression-free survival (PFS) of patients with estrogen receptor (ER)-positive, human epidermal growth factor 2 (HER2)-negative metastatic breast cancer (MBC). Evidence of an effect of palbociclib in heavily treated patients is limited, because patients in the PALOMA-2 trial had received palbociclib as first-line treatment and most (86%) of the patients in the PALOMA-3 trial had received less than two prior lines of therapy before starting palbociclib.

However in PALOMA-2 and PALOMA-3 trials, the most common adverse event (AE) was neutropenia, and the incidence of grade 3/4 neutropenia in PALOMA-3 trial was higher in Asians than in non-Asians and, the incidences of interruption and dose reduction were both higher in Asian than in non-Asian patients. Palbociclib was approved during December 2017 in Japan, but its effects and toxicity in clinical practice remain not to be wellknown.

The present study aimed to determine the effects and toxicity of palbociclib in patients with MBC after prior treatment and to find the differences between upfront-line group and later-line group.

Methods

Patients

We enrolled 26 patients with ER-positive, HER2-negative MBC who started at least one cycle of palbo-
ciclib plus either an aromatase inhibitor or fulvestrant between December 15, 2017 and July 31, 2018. These patients were divided into 2 groups with a number of prior treatment, upfront (<3 lines) and later-line groups (≥4 lines prior therapy). We retrospectively examined medical records to estimate PFS and analyze toxicity.

**Practice protocol**

Patients received palbociclib (125 mg) on days 1 - 21 of a 28-day cycle. Complete blood tests and absolute neutrophil counts were obtained every two weeks at least during the first two cycles. Adverse events were classified based on the Common Terminology Criteria for Adverse Events (CTCAE) ver. 4.0.

Palbociclib therapy was interrupted when patients developed grade 3 neutropenia and/or thrombocytopenia. When these adverse effects recovered to grade 2 or better, palbociclib 125 mg was resumed one week later. If more than one week was required for recovery, palbociclib was resumed at the reduced dose of 100 mg. The palbociclib regimen was also interrupted when patients had grade 4 neutropenia and/or thrombocytopenia, then resumed at the reduced dose of 100 mg when patients recovered to grade 2 or better. If grade 4 neutropenia and/or thrombocytopenia developed again, the regimen was interrupted until the patients recovered to grade 2 or better. Palbociclib was resumed for the second time at a dose of 75 mg.

All patients received palbociclib plus endocrine therapy with daily 2.5 mg of letrozole or 1 mg of oral anastrozole, and intramuscular injections of fulvestrant on days 1, 15 and 29 of the first month, followed by a single monthly dose. Tumors were assessed by computed tomography (CT) within 8 - 12 weeks of starting palbociclib. Measurable disease was assessed according to RECIST (Response Evaluation Criteria in Solid Tumors) version 1.1. Bone metastases were evaluated by CT or magnetic resonance imaging (MRI). Treatment continued until disease progressed or toxicity became intolerable.

**Statistical analyses**

Progression-free survival was estimated from Kaplan-Meier curves and compared using log-rank tests between groups of upfront-line and later-line. Data were statistically analyzed using Bell Curve for Excel (Social Survey Research Information Co. Ltd., Tokyo, Japan). The threshold for significance was P < 0.05.

**Results**

Table 1 summarizes the baseline characteristics of the 26 patients who met the inclusion criteria. The median age was 64 (range 42 - 86) years, all were female, and 92% of them were postmenopausal. Twenty-two (85%) of them had visceral metastasis and most (n = 24, 92%) patients had undergone therapy before palbociclib administration and two (8%) had not received any prior therapy for MBC. The median number of prior lines of therapy for MBC was 3.5 (range 0 - 9). Fourteen patients had received palbociclib in ≤3 (upfront-line), and 12 had undergone in ≥4 (later-line) prior lines of therapy. Palbociclib was combined with fulvestrant (n = 16), letrozole (n = 9) and anastrozole (n = 1). Premenopausal patients received palbociclib plus fulvestrant with a luteinizing hormone-releasing hormone (LHRH) agonist.

**Effects of regimens containing palbociclib**

The database was closed on 31 July 2018, and all patients remained alive on that date.

Fifteen (58%) patients continued palbociclib and 11 (42%) discontinued due to progressive disease (PD) and AE (n = 9 and n = 2, respectively). The median follow-up period was 5.1 months. The median PFS was 3.6 months in later-line group and not reached in the upfront-line group, and PFS was significantly longer in upfront-line group (p = 0.046; Figure 1).

**Toxicity and dose reduction**

Table 2 describes the AE, the most common AE was
neutropenia (any grade, 100% (n = 26); grade 3, 77% (n = 20) and grade 4, 8% (n = 2)). One patient developed febrile neutropenia. The incidences of grade 3/4 neutropenia were 86% and 83% in the upfront- and later-line groups, respectively (Table 2). Other hematological AE comprised anemia (n = 16, 62%) and thrombocytopenia (n = 12, 46%), and most of hematological AE beside neutropenia were of grades 1 or 2. The most common non-hematological AE were stomatitis (n = 6, 23%), fatigue (n = 6, 23%) and nausea (n = 3, 12%).

Figure 2 shows the treatment duration, palbociclib doses and reasons for discontinuation of the treatment. The treatment schedule was interrupted in 24 (92%) patients due to grade 3/4 neutropenia in 22 (92%), and grade 1 renal failure in 1 (4%) and grade 2 weight loss in 1 (4%) patient. The incidences of interruption were not different between the groups (upfront vs. later-line: 93% vs. 92%). The median duration of the first interruption was 24 days. The dose was reduced for a median duration of 35 days in 16 (62%) patients, among them, 12 (75%) received 100 mg of and four (25%) patients received 75 mg of palbociclib at the time of a second dose reduction (Figure 2). Incidences of dose reduction was higher in patients in later-, than in the upfront-line group (67% vs. 57%). The median relative dose intensity (RDI) was 67.2% (range 40% - 100%).

**Table 2. Adverse events**

|                  | Upfront-line (n = 14) | Later-line (n = 12) |
|------------------|-----------------------|---------------------|
|                  | Any grade | Grade 3 | Grade 4 | Any grade | Grade 3 | Grade 4 |
| Neutropenia      | 14 (100%) | 11 (79%) | 1 (7%)  | 12 (100%) | 9 (75%) | 1 (8%)  |
| Thrombocytopenia | 7 (50%)   | 1 (7%)  | 0       | 4 (33%)   | 0       | 0       |
| Anemia           | 10 (71%)  | 0       | 0       | 6 (50%)   | 0       | 0       |
| Stomatitis       | 4 (29%)   | 0       | 0       | 2 (17%)   | 0       | 0       |
| Fatigue          | 4 (29%)   | 0       | 0       | 2 (17%)   | 0       | 0       |
| Nausea           | 3 (21%)   | 0       | 0       | 0         | 0       | 0       |
| Febrile neutropenia | 1 (4%) | 1 (4%)  | 0       | 0         | 0       | 0       |
| Renal failure    | 0         | 0       | 0       | 1 (8%)    | 0       | 0       |
| Weight loss      | 1 (7%)    | 0       | 0       | 0         | 0       | 0       |
| Diarrhea         | 1 (7%)    | 0       | 0       | 0         | 0       | 0       |
| Rash             | 1 (7%)    | 0       | 0       | 0         | 0       | 0       |
| Hepatic dysfunction | 1 (7%) | 0       | 0       | 0         | 0       | 0       |
Discussion

Large randomized trials of palbociclib have found a longer median PFS in patients who received first-, compared with second- or third-line therapy (PALOMA-2 and PALOMA-3 trials: 24.8 and 9.5 months, respectively). Subgroup analysis suggested palbociclib did not improve PFS in patients with ≥3 prior lines. Previous studies have found that median PFS of palbociclib-including treatment as later-line group was 3.1 to 5.8 months. The present study found that the effects of palbociclib was limited in the patients who underwent later line therapy. Thus a benefit for highly pretreated patients would be unpromising.

The incidence of neutropenia differs among ethnicities and the those of grade 3/4 neutropenia induced by palbociclib was higher in Asian than in non-Asian patients in the PALOMA-3 trial (92% vs. 78%). The incident of dose reduction was also higher in Asians than in non-Asians (52% vs. 29%), but only one (4%) patient in the present study developed rare febrile neutropenia. Sixteen (62%) of our patients required a dose reduction mainly because of neutropenia. The incidences of grade 3/4 neutropenia were high regardless of the number of prior therapy lines, being 86% and 83% in the upfront- and later-line groups, respectively. None of our patients could complete the full palbociclib regimen without interruption and/or reduction for three months. The frequent dose reductions and regimen interruptions led to the rather low median palbociclib RDI of 67.2%. Moreover, only 50% (n = 13; data not shown) of our patients had RDI >80% during the first eight weeks. Masuda et al. reported that the PFS of patients who required a dose reduction and those who received the full dose were similar. The PFS was not different between the Asian and non-Asians patients in the PALOMA-3 trial of palbociclib, even though the incident of interruption and dose reduction was significantly higher in the Asian cohort. Considering these findings, some room exists for debate regarding the initial dose of palbociclib that is tolerable for Japanese patients who require a higher RDI, especially during several initial courses. Clinicobiological factors associated with sustainability of palbociclib dose for Asian patients need to be developed.

The present study has several limitations. Various doctors evaluated the therapeutic effects on the patients and AE, which might have led to interobserver bias. The sample size was small, and the median follow-up period was 5.1 months, which was quite short. Further observations and data integration are required.

In conclusion, median PFS was significantly longer in the upfront-, than in the later-line group (p = 0.046). Neutropenia was the most common AE among many other AE.
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