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Association between severe neutropenia and progression-free survival in patients with advanced or recurrent breast cancer treated with palbociclib

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This study aimed to clarify the relationship between neutropenia and progression-free survival (PFS) under palbociclib treatment for advanced/recurrent breast cancer and the risk factors for severe neutropenia. We retrospectively identified 37 patients who received palbociclib for advanced breast cancer at Ogaki Municipal Hospital (Ogaki, Japan) between April 2018 and June 2020. Kaplan-Meier log-rank test was used to compare PFS (mild [neutrophil count 1,000-2,000/mm^3] versus severe [neutrophil count <500-1,000/mm^3]). Multivariate analysis was performed to evaluate the relationships between baseline patient characteristics and severe neutropenia development. There were three, four, 25, and five cases with grade 1, 2, 3, and 4 neutropenia, respectively. Median PFS in patients who developed severe neutropenia (n = 30) and those who did develop mild neutropenia (n = 7) was 176 days (range: 62-894 days) and 91 days (range: 19-384 days), respectively (log-rank test, p = 0.005). Severe neutropenia was independently associated with pre-treatment neutrophil count (odds ratio: 27.700; p=0.007). Severe neutropenia is more likely to occur with a pre-treatment neutrophil count of less than 3,680 mm^3. Neutropenia prolongs PFS under palbociclib treatment, suggesting management of AEs and patient education as highly important, especially to prevent drug interruption/dose reduction of palbociclib due to these AEs.

1. Introduction

Palbociclib inhibits the activity of the cyclin-dependent kinase (CDK) 4/6-cyclin D complex. This action arrests cell cycle progression and suppresses tumour growth (Fry et al. 2004). Studies published by Mukai et al. and Masuda et al. indicated the use of palbociclib in the following situations: First, it should be used in the initial endocrine therapy (combined with letrozole) for advanced or metastatic breast cancer with hormone receptor positivity and human epidermal growth factor receptor 2 negativity. Second, it should be used in the treatment of HR-positive/HER2-negative advanced or metastatic breast cancer (with or without menopause) that has progressed due to endocrine therapy (in combination with fulvestrant). According to the results of phase III trials (PALOMA-2 and PALOMA-3), palbociclib increased the progression-free survival (PFS) by approximately 10 months (approximately 5 months in patients who receive endocrine therapy) when combined with primary endocrine therapy in comparison to existing endocrine therapy (Mukai et al. 2019; Masuda et al. 2019).

A frequent adverse event (AE) of palbociclib is neutropenia, and severe neutropenia has a high frequency (Mukai et al. 2019; Masuda et al. 2019). Severe neutropenia may delay treatment or lead to reduction of the dose. Additionally, repeated postponement of treatment may lead to a decrease in the quality of life of the patient.

Chemotherapy-induced neutropenia has been reported in several cancer types as a factor that prolongs overall survival (OS) in patients with advanced cancer (Kishida et al. 2009; Kosaka et al. 2018; Kimura et al. 2017). Neutropenia is an index of chemotherapy-induced myelosuppression and may reflect whether the anticancer drugs are being administered in sufficient doses to show antitumor effects (Shitara et al. 2010). It has also been reported that absence of neutropenia reflects poor responsiveness to anticancer drugs used in chemotherapy and suggests an inadequate dose in individual patients (Shitara et al. 2010). Notably, these studies reported on drugs whose dosage is calculated based on the body weight and body surface area. However, palbociclib is administered in a fixed amount of 125 mg once daily.

With regard to palbociclib treatment, the relationship between neutropenia and PFS and the risk factors for severe neutropenia have not been clarified yet. If the PFS is long, the OS may be long too. Therefore, there is an urgent need to identify patients who are likely to benefit from palbociclib. Moreover, if the relationship between neutropenia and PFS and the risk of developing neutropenia are clarified, it will lead to strengthening of clinical decision making and patient outcome.

We aimed to examine the relationship between severe neutropenia and PFS in patients treated with palbociclib for advanced/recurrent breast cancer. Furthermore, we analysed the factors that may cause severe neutropenia in these patients.

2. Investigations and results

2.1. Patient characteristics

Patient characteristics are shown in Table 1. The median age was 65 years (range, 46–85 years), median body surface area was 1.15 m^2 (range, 1.20-1.78), and the median pre-treatment neutrophil count was 3,030/mm^3 (range, 1,360-11,294).

2.2. Development of neutropenia with palbociclib treatment

Overall, there were three cases with grade 1 neutropenia, four cases with grade 2, 25 cases with grade 3, and five cases with grade 4. Figure 1 shows the development of neutropenia after palbociclib treatment. The number of the treatment course during which neutropenia (worst grade) appeared at the earliest in each case was recorded. Neutropenia developed most frequently during the first course of palbociclib treatment (26/37, 70.3%), and neutropenia above grade 3 was observed in 20 out of 37 cases (54.1%) during the first course of treatment.

Table 1: Patient characteristics

n	37
Age, years	
Median (range)	65 (46-85)
Gender, n	
Male/Female	0/37
Height, cm	
Median (range)	156 (140-169)
Weight, kg	
Median (range)	52 (34-79)
Body surface area, m^2	
Median (range)	1.15 (1.20-1.78)
Treatment lines, n	
1st	7
2nd	10
3rd	8
4th	4
5th	4
6th	2
7th	2
Laboratory test values before chemotherapy	
Aspartate aminotransferase, IU/L	29 (8-161)
Alanine aminotransferase, IU/L	21 (7-103)
Total bilirubin, mg/dL	0.5 (0.3-1.8)
Creatinine clearance	67.9 (23.4-127.9)
Neutrophil count, / mm^3	3,030 (1,360-11,294)
Leukocyte count, /mm^3	5165 (2330-10020)
Platelet count, $\times 10^4/mm^3$	21.0 (10.0-69.2)
Metastatic site, n	
Lymph node	22
Bone	16
Lung	11
Liver	5
Peritoneal	1
Brain	1
Skin	1
Recurrence	1

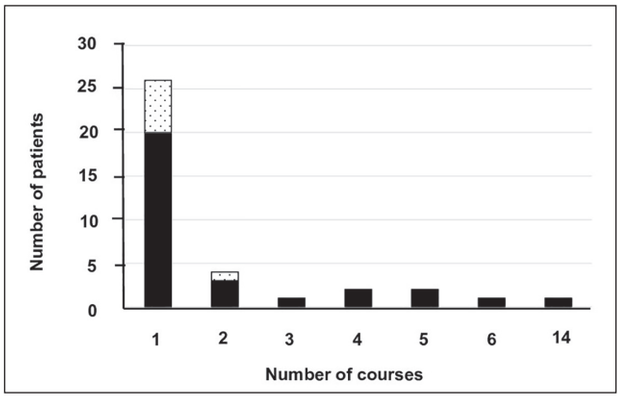

Fig. 1: Development of neutropenia with palbociclib treatment. The number of the palbociclib treatment courses during which neutropenia (worst grade) appeared at the earliest in each case was determined. Neutropenia Grade 3 or 4 Neutropenia Grade 1 or 2

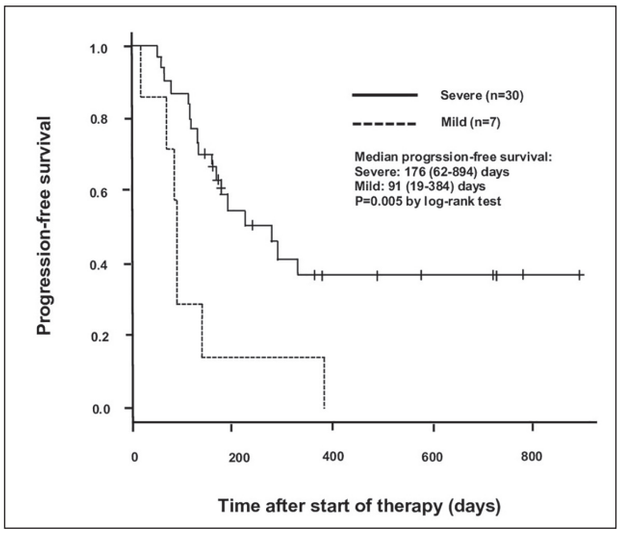

Fig. 2: Kaplan-Meier plots showing the difference in progression-free survival between patients who developed severe neutropenia and those who did not. Data were statistically compared using the log-rank test.

2.3. Progression-free survival

Figure 2 shows the Kaplan-Meier survival curves for patients after therapy with palbociclib and demonstrates PFS in the two patient groups (those who developed severe neutropenia or those who did not develop severe neutropenia). Median PFS in patients who developed neutropenia (n = 30) and those who did not develop neutropenia (n = 7) was 176 days (range: 62-894 days) and 91 days (range: 19-384 days), respectively (log-rank test, $p = 0.005$).

2.4. Risk factors for neutropenia after palbociclib treatment

Tables 2 and 3 show the results of the univariate and multivariate logistic regression analyses regarding risk factors for the development of neutropenia after palbociclib treatment. Patients with neutropenia were grouped according to whether they developed severe neutropenia (30 patients) or did not develop severe neutropenia (seven patients). Severe neutropenia was independently associated with the pre-treatment neutrophil count (odds ratio: 27.700, 95% confidence interval: 2.450–313.000; p=0.007). Using the ROC curve analysis, the area under the curve for the pre-treatment neutrophil count was 0.912, which was considered highly accurate for detecting severe neutropenia (0.8-1.0). The cut-off value calculated using the ROC curve was 3,680/mm^3.

3. Discussion

The results of this study revealed that severe neutropenia was associated with a longer PFS than the absence of severe neutropenia. Neutrophil count of less than 3,680/mm^3 before palbociclib administration was a risk factor for the development of severe neutropenia.

In the PALOMA-2 study, the incidence of neutropenia was 78.4% overall and 93.8% in the Japanese (Mukai et al. 2019). However, it was 100% in a Japanese study (Masuda et al. 2018). In this study, neutropenia was also observed in all 37 cases. It has been reported that Grade 3/4 neutropenia occurs frequently during the initial period of administration (cycles 1 and 2), and not many patients developed Grade 3/4 neutropenia for the first time after cycle 3 (Verma et al. 2016). In this study, grade 3/4 neutropenia occurred in 81.1% of the patients and during the first cycle in the majority of these patients. Therefore, the incidence is high in the Japanese population, and attention should be paid to AE management during the first course of palbociclib treatment.

Table 2: Univariate logistic regression analysis of risk factors for palbociclib treatment-related severe neutropenia

Factors	Odds ratio	95% confidence interval	*p* value
Age, years			
>62	0.167	0.0178–1.560	0.116
Body surface area, m^2			
<1.51	0.350	0.058–2.100	0.250
Body weight, kg			
<41	0.667	0.059–7.570	0.744
Treatment lines, n			
>6	0.667	10.059–7.570	0.744
Numbers of metastatic, n			
>2	2.860	0.477–17.100	0.250
Disease status (Unresectable/Recurrent)			
Unresectable	2.060	0.376–11.300	0.404
Neutrophil count, / mm^3			
<3680	30.000	2.930–307.000	0.004*

Table 3: Multivariate logistic regression analysis of risk factors for palbociclib treatment-related severe neutropenia (Grade3–4)

Factors	Odds ratio	95% confidence interval	*p* value
Age, years			
>62	0.202	0.0148–2.760	0.230
Body surface area, m^2			
<1.510	0.429	0.043–4.220	0.468
Neutrophil count, / mm^3			
<3680	27.700	2.450–313.000	0.007*

* <0.05

Severe neutropenia may lead to delayed treatment or a reduction in dose. Severe neutropenia may also manifest as febrile neutropenia (FN), which requires caution. In case of grade 4 neutropenia, treatment may be restarted with dose reduction after discontinuation, whereas for Grade 3 neutropenia, treatment may be restarted with the same dose unless it is FN. It has been reported that the neutrophil count at baseline tended to be higher in the patient group that could be continued on the 3-week treatment/1-week withdrawal regimen or managed only by a cycle delay (Masuda et al. 2019). This suggests that the baseline neutrophil count may be higher when accompanied by Grade 4 neutropenia or FN. Our study is the first one to reveal that severe neutropenia is more likely to occur when the neutrophil count is less than 3,680/mm^3.

There are several reports regarding the association between severe neutropenia and OS (Kishida et al. 2009; Kosaka et al. 2018; Kimura et al. 2017). For palbociclib, a global phase III study (PALOMA-3) showed that there was no significant difference in PFS between patients with Grade 2 and Grade 3 neutropenia (Verma et al. 2016). Masuda et al. (2019) reported that postponement of treatment due to neutropenia, discontinuation of treatment, or a reduction in the dose did not affect the treatment period in the three studies (PALOMA-2, the Japanese phase 2 study, and PALOMA-3. In contrast, a significant difference was found in PFS between patients with ≤Grade 2 and ≥Grade 3 neutropenia in our study. The reason for this difference may be ethnic differences along with the differences in the patient background and treatment lines. On comparing the analysis of the Japanese patients in the three studies, there was a significant difference in the baseline demographics and disease characteristics between the Japanese patients (Masuda et al. 2019). Japanese patients in the PALOMA-3 study were approximately 10 years younger (median age, 53 years) than those in the PALOMA-2 and Japanese phase 2 studies (median age, 67 and 63 years, respectively). A higher percentage of patients in the PALOMA-2 and PALOMA-3 had visceral metastases than patients in the Japanese phase 2 study (63%, 63%, and 48%, respectively) (Masuda et al. 2019). The PALOMA-2 and Japanese phase 2 studies investigated the use of palbociclib as first-line therapy, while PALOMA-3 examined the use of palbociclib after endocrine therapy. Our study predominantly examined palbociclib use after endocrine therapy, with a median patient age of 65 years and a 40.5% prevalence of visceral metastases.

Conventionally, chemotherapy dosage has often been set based on the body surface area. However, this method has been reported to potentially cause overdosing or underdosing of anticancer drugs in individual patients (Gurney 2002; Newell 2002). Lack of neutropenia suggests a dose deficiency in individual patients (Shitara et al. 2010). In this study, severe neutropenia was observed in 30/37 cases. Therefore, it can be said that the chemotherapy dose was necessary and sufficient in each patient. With regard to the onset of the effect of gemcitabine, it is more likely that the pharmacodynamics (PD) affect the survival time more than pharmacokinetics (PK), and the prognosis is better in patients who can continue gemcitabine administration regardless of relative dose intensity (Hatori et al. 2014). Palbociclib has a fixed-dose regimen. It can be expected that the effect of body weight on the amount of drug exposure will not be substantial enough to require dose adjustment. Therefore, similar to gemcitabine, PD may influence the prognosis of palbociclib-treated patients. Consequently, reducing the dose of these drugs should be avoided.

The results of this study can strengthen patient guidance in the future. Specifically, if the number of neutrophils before taking palbociclib is less than 3,680/mm^3, there is a high probability of severe neutropenia. Therefore, the patients can be instructed to thoroughly implement the FN measures. However, there was no significant difference in PFS between patients with or without a drug interruption/cycle delay (Masuda et al. 2019). If the neutrophil count is less than 3,680/mm^3, treatment may be postponed owing to severe neutropenia. Therefore, it may be possible to consider changing the palbociclib oral treatment regimen from 3 weeks of treatment, followed by 1 week off treatment to 2 weeks off treatment. By doing so, it is possible to reduce the number of hospital visits. Additionally, treatment may be postponed due to a low neutrophil count at the hospital visit itself.

The present study has several limitations. First, this study included only one institution and one ethnic group. Second, the findings may be limited by the fact that this study was a retrospective survey and did not include patients with the same treatment line. Finally, the OS was not examined. Thus, further well-designed studies are needed to address these factors and validate our results.

In conclusion, our findings showed that severe neutropenia prolongs PFS in patients under palbociclib treatment, and we believe this makes AE management and patient education even more important, especially to prevent drug interruption/dose reduction of palbociclib due to AEs such as FN.

4. Experimental

4.1. Subjects and methods

We retrospectively identified 38 patients who had received palbociclib for advanced breast cancer at Ogaki Municipal Hospital (Ogaki, Japan) between April 2018 and June 2020. However, we excluded one patient who had been transferred to another hospital. Thus, 37 patients were considered eligible for this study. Patient character-

istics were extracted from anonymised patient records. Patient characteristics, AEs (neutropenia), PFS, and timing of the manifestation of worst-grade neutrophilia were analysed retrospectively using data collected from the electronic charts and pharmacy service records. The occurrence of neutropenia (neutrophil count 1,000-2,000/mm^3) and severe neutropenia (neutrophil count <500-1,000 mm^3, grade 3-4) after starting palbociclib treatment were evaluated. The risk of severe neutropenia was evaluated according to age, body surface area, weight, treatment line, number of metastases, stage (progress/recurrence), and neutrophil count. The severe grades of AEs were evaluated according to the Common Terminology Criteria for Adverse Events, version 4.0 (US Department of Health and Human Services 2017). The study protocol was approved by the Institutional Review Board of Ogaki Municipal Hospital (Ogaki, Japan; approval number 20200716-1), and the requirement for informed consent was waived due to the retrospective nature of the study.

4.2. Treatment

The patients received 125 mg palbociclib orally (PO) once daily for 3 weeks, followed by 1 week off treatment. In addition, letrozole (2.5 mg/day, PO; continuous) was administered in 4-week cycles. Patients received oral palbociclib (125 mg daily for 3 weeks followed by a week off over a 28-day cycle) plus 500 mg fulvestrant (intramuscular injection on days 1 and 15 of cycle 1; then on day 1 of the subsequent 28-day cycles). Palbociclib dose modification was permitted in the event of treatment-related toxicity, and the lowest dose of palbociclib was 75 mg/day.

4.3. Statistical analysis

Differences between the patient groups were evaluated using the Mann-Whitney U-test or Fisher's exact probability test as appropriate. Univariate analyses were performed to analyse the relationships between the baseline characteristics of the patients and the development of severe neutropenia. Subsequently, the significant variables and previously reported risk factors were entered into a multivariate logistic regression model. Optimal cutoff values for the significant variables were determined using the receiver operating characteristic (ROC) curve analyses. The Kaplan-Meier log-rank test was used to compare the PFS. Differences were considered to indicate statistical significance when $p<0.05$. All analyses were performed using EZR software (version 1.30, Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R software (The R Foundation for Statistical Computing, Vienna, Austria) (Kanda 2013).

Conflicts of interest: None declared.

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