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ABCG2 genetic variant as a predictor of severe neutropenia in Japanese patients with hormone receptor–positive, HER2-negative advanced breast cancer treated with palbociclib: an exploratory real-world study

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Abstract

Purpose: Palbociclib in combination with endocrine therapy (ET) is widely used for treating hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer. However, severe neutropenia is a common adverse effect, particularly in Asian populations. This study aimed to validate the clinical and genetic risk factors for palbociclib-induced severe neutropeniain a real-world setting and provide insights that may contribute to safer and more individualized breast cancer treatment in clinical practice.

Methods: We conducted a retrospective pharmacogenetic analysis using DNA samples from the National Cancer Center Biobank in Japan and analyzed 84 Japanese patients treated with palbociclib plus endocrine therapy (ET). Seven single-nucleotide polymorphisms (SNPs) in drug metabolism and transporter genes (*ABCB1*, *ABCG2*, *CYP3A4,* and *CYP3A5*) were genotyped, and their associations with severe neutropenia were evaluated using multivariate logistic regression.

Results: Severe neutropenia occurred in 60 patients (71.4% of total). Multivariate analysis identified low baseline absolute neutrophil count (ANC ≤ 4510/μL; odds ratio [OR] = 16.249, $p < 0.001$) and the *ABCG2* rs2231142 AA genotype (OR = 19.198, $p = 0.019$) as independent risk factors, whereas no significant associations were observed for *ABCB1*, *CYP3A4*, and *CYP3A5*variants.

Conclusions: *ABCG2* rs2231142 and low baseline ANC may be associated with severe neutropenia in Japanese patients with HR-positive/HER2-negative advanced breast cancer receiving palbociclib plus ET, suggesting their possible utility in risk stratification and treatment individualization.

Introduction

Palbociclib is a first-in-class cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) [1, 2], and its combination with endocrine therapy (ET) is the standard first- or second-line treatment for patients with metastatic or advanced hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer [3]. HR-positive, HER2-negative breast cancer is the most common subtype of breast cancer, accounting for approximately 70% of cases [4]. In the PALOMA-2 trial, palbociclib combined with the nonsteroidal aromatase inhibitor letrozole prolonged progression-free survival (PFS) from 14.5 to 24.8 months compared to letrozole plus placebo [5]. Similarly, in the PALOMA-3 trial, the combination of palbociclib and fulvestrant extended PFS from 3.8 to 9.2 months compared to fulvestrant and placebo [6]. Real-world clinical data from Japanese patients have shown comparable results [7]. Neutropenia is the most frequent hematologic toxicity associated with palbociclib therapy, necessitating treatment interruption or dose reduction in 37% to 73% of patients [8, 9]. In the two pivotal phase III clinical trials, the PALOMA-2 and PALOMA-3 trials, the incidence of grade ≥3 neutropenia was reported to be 66.4% and 62.0%, respectively [5, 6]. Subgroup analyses conducted in Japanese populations demonstrated an even higher incidence of grade ≥3 neutropenia (87.5 %), suggesting that Japanese patients may be more susceptible to this hematologic toxicity than the overall study population [10, 11]. Neutropenia was also identified as the most common cause of dose reduction in these trials, with 29.8% of patients requiring a

dose reduction of palbociclib due to neutropenia [12]. Furthermore, a pharmacokinetic analysis within the PALOMA-2 trial reported that the trough concentrations of palbociclib were higher in Asian patients than in non-Asian patients, which could partially explain the higher incidence of dose reduction observed in the Asian subgroup [13].

Pharmacogenomic analyses conducted in the PALOMA-2 and PALOMA-3 trials focused on two genes: adenosine triphosphate–binding cassette subfamily B member 1 (*ABCB1*; P-glycoprotein) and excision repair cross-complementing 1 (*ERCC1*). In the overall study population, the *ABCB1* rs1128503 variant was associated with the development of grade 3/4 neutropenia [14]. However, these trials were conducted as international multicenter studies, and the number of Asian participants was limited in these studies. No significant association between *ABCB1* rs1128503 and severe neutropenia was observed in the Asian subgroup. Meanwhile, Asian patients have been reported to experience a higher incidence of grade 3/4 neutropenia [15], suggesting the potential involvement of race-related genetic or clinical factors. However, the underlying mechanisms of this phenomenon remain unclear. Previous studies have identified several clinical predictors of palbociclib-induced severe neutropenia, including a lower baseline absolute neutrophil count (ANC) and a higher age-adjusted Charlson comorbidity index [16-18]. To the best of our knowledge, only a limited number of genes have been investigated in pharmacogenetic studies of palbociclib. Given the pharmacokinetic characteristics of palbociclib, metabolism via cytochrome P450 isozyme (CYP) 3A enzymes and elimination via ABC transporter proteins, a comprehensive analysis, including genes related to pharmacokinetics, is warranted. In particular, pharmacogenomic studies based on real-world data from Japanese patients are extremely scarce, highlighting the need for comprehensive investigations in the Japanese population. A previous study included an analysis of Asian populations; however, these findings were based on patients enrolled in a clinical trial[14]. Given that neutropenia significantly affects patients' performance status and overall health, further investigation of the relationship between genetic polymorphisms and neutropenia in a real-world setting is warranted.

In the present study, we investigated the association between various pharmacokinetics- and pharmacodynamics-related single-nucleotide polymorphisms (SNPs) and the development of grade ≥3 neutropenia in Japanese patients with HR–positive, HER2-negative advanced breast cancer who received palbociclib in combination with ET. Additionally, we evaluated the influence of baseline clinical parameters, including ANC at treatment initiation, body mass index (BMI), and liver enzyme levels, on the occurrence of neutropenia.

This study aimed to explore the risk factors for severe neutropenia associated with palbociclib in a real-world setting and provide insights that may contribute to safer and more individualized breast cancer treatment in clinical practice.

Patients and Methods

Patients

Medical data were retrospectively collected from the electronic medical records of patients diagnosed with breast cancer who received palbociclib in combination with ET at the National Cancer Center (NCC) Hospital East, Japan, between December 2017 and September 2023. All patients received palbociclib at the standard starting dose without dose reductions during the first treatment cycle. The analysis was not limited to a specific line of treatment. Patients who received concomitant treatment with strong CYP3A inhibitors or inducers were excluded from the study. Deoxyribonucleic acid (DNA) samples were obtained from the NCC Biobank Registry, and a retrospective analysis was conducted to identify the clinical and genetic predictors of severe neutropenia. The study protocol was approved by the Institutional Review Boards (IRBs) of both the NCC and the University of Shizuoka in September 2023 (approval numbers: 2023-159 and 5-41). This study was conducted using clinical data and DNA samples from participants registered in the NCC Biobank. All participants had provided written informed consent at the time of biobank enrollment for the use of their biological samples and clinical information in research. The IRBs approved the use of these materials for this study without requiring additional individual consent. This study was conducted in accordance with Ethical Guidelines for Life Sciences and Medical Research Involving Human Subjects published by Japan's Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labour and Welfare, Japan, and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Assessment

The ANC was recorded as the primary outcome measure. Hematological toxicities were assessed using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Severe neutropenia was defined as grade 3 (neutrophil counts < 1,000 cells/μL) and grade 4 (neutrophil counts < 500 cells/μL). The observation period was limited to the first two treatment cycles, during which the lowest neutrophil count and corresponding day of occurrence were recorded. Several baseline variables, including sex, age, body mass index, metastatic site, performance status, and baseline laboratory data that could potentially affect the onset of severe neutropenia, were collected for all patients in this study.

Pharmacogenetic analysis

In this study, we investigated the effects of variants in pharmacokinetic and pharmacodynamic genes on palbociclib in combination therapy with ET. The purpose of the current exploratory study was to comprehensively investigate the pharmacogenomics of variant drug transporter genes (*ABCB1* and *ABCG2*) and drug metabolism enzyme genes (*CYP3A4* and *CYP3A5*). We selected the following representative 7 variants with the following criteria of minor allele frequency > 0.05, as reported in the Hap-Map data of the Japanese population[19]: *ABCB1* rs1128503 (C>T), rs2032582 (G>T/A), and rs1045642 (C>T); *ABCG2* rs2231137 (G>A) and rs2231142 (C>A); *CYP3A4* rs2242480 (C>T); and *CYP3A5* rs776746 (A>G). All variants, excluding *ABCG2* rs2231142, were determined using polymerase chain reaction-restriction fragment length polymorphism (PCR–RFLP) analysis. The polymorphism *ABCG2* rs2231142 was determined using allele-specific polymerase chain reaction. For further

confirmation, direct sequencing was performed on representative samples at FASMAC Co., Ltd. (Atsugi, Kanagawa, Japan) using an Applied Biosystems 3730xl Genetic Analyzer.

Statistical analysis

The association between each SNPs and the occurrence of severe adverse events, defined as grade ≥3 neutropenia, was evaluated using three genetic inheritance models. Specifically, the Cochran–Armitage trend test was applied under the additive model, whereas Fisher's exact test was used under the dominant and recessive models. Owing to the limited sample size, correction for multiple comparisons was not applied; therefore, the findings should be interpreted with caution and considered as exploratory. Genetic variants that demonstrated statistically significant associations in univariate analyses under either the dominant or recessive model were considered candidate predictors for subsequent multivariate analysis. In addition to genetic factors, univariate analyses were performed for baseline clinical and demographic characteristics of the patients. Variables demonstrating clear trends ($p < 0.10$) were included as covariates in the multivariate logistic regression model. In this model, adjusted odds ratios (ORs), 95% confidence intervals (CIs), and corresponding *p*-values were calculated. Subgroup analyses were conducted using the same approach. Based on the multivariate model derived from the overall study population, a risk prediction equation was constructed using the estimated partial regression coefficients to calculate the probability of severe toxicity in individual patients. All adverse events occurring after the administration of CDK4/6i were graded according to the CTCAE version 5.0, which classifies severity from grade 1 to grade 4.

Results

Patient Characteristics

A total of 84 patients were included in the final analysis. Of these, 60 patients (71.4%) developed grade 3/4 neutropenia during the first two cycles of palbociclib treatment, including 10 patients (11.9%) who experienced grade 4 neutropenia. Febrile neutropenia occurred in two patients (2.4%). The median time to onset was 26 days for grade 3/4 neutropenia and 24 days for grade 4 neutropenia. The patient characteristics stratified by neutropenia severity are summarized in Table 1. The median baseline ANC was significantly lower in patients who developed grade 3/4 neutropenia than in those who experienced grade 1/2 (3180/μL vs. 4675/μL, $p < 0.001$). Other variables, including sex, age, BMI, liver function, and type of combination ET, showed no significant differences between the two groups.

Univariate Analysis of Genetic Factors

The association between genetic variants and the incidence of severe neutropenia was evaluated using dominant and recessive models (Table 2). In the recessive model, patients with the *ABCG2* rs2231142 AA genotype had a significantly higher incidence of severe neutropenia than those with the CC or CA genotypes (100% vs. 67.1%, $p = 0.029$). Other variants related to palbociclib metabolism, such as *CYP3A5* rs776746 and *CYP3A4* rs2242480, showed trends toward increased or decreased risks. No

significant associations were found for *ABCG2* rs2231137, *ABCB1* rs1128503, rs2032582, and rs1045642. The observed genotype distributions were consistent with the Hardy–Weinberg equilibrium ($p > 0.05$).

Multivariate Analysis

Multivariate logistic regression analysis identified low baseline ANC (≤4510/μL) (OR = 16.249, 95% CI: 4.450–77.025, $p < 0.001$) and *ABCG2* rs2231142AA genotype (OR = 19.198, 95% CI: 1.464–3017.494, $p = 0.019$) as independent predictors of severe neutropenia (Table 3). Other variables, such as platelet count, performance status, and genotypes of *CYP3A4* rs2242480 and *CYP3A5* rs776746, were not significantly associated with neutropenia in the multivariate analysis.

Discussion

In this study, we conducted an exploratory pharmacogenomic study to identify the predictive factors for severe neutropenia in patients with HR–positive, HER2-negative advanced breast cancer receiving palbociclib in combination with ET. Our results suggest that *ABCG2* genetic variants and baseline neutrophil counts may serve as potential predictors of severe neutropenia. Given the high incidence of severe neutropenia among Japanese patients receiving palbociclib—reportedly exceeding 85% in real-world studies [10, 11]—and previous observations that Asians tend to have higher trough concentrations of palbociclib [13], it is plausible that genetic variants affecting drug metabolism and transport contribute to inter-individual variability in toxicity. Palbociclib is primarily metabolized by *CYP3A* enzymes and eliminated via efflux transporters, such as the breast cancer resistance protein (BCRP) encoded by the *ABCG2* gene. Therefore, we hypothesized that functional genetic variants of these genes may alter systemic drug exposure and increase the risk of hematologic toxicity, particularly neutropenia.

A low ANC at treatment initiation was identified as a significant risk factor for severe neutropenia in this study. This finding suggests that a reduced bone marrow reserve prior to treatment may predispose patients to hematologic toxicity resulting from the myelosuppressive effects of palbociclib. Moreover, patients with lower baseline neutrophil counts may be more vulnerable to interindividual variability in drug exposure, potentially leading to relative overexposure and an increased likelihood of toxicity. These observations indicate that the baseline neutrophil count may serve as a clinically relevant predictor of severe hematologic adverse events from both pharmacokinetic and pharmacodynamic perspectives. Our findings are consistent with previous reports indicating that a lower baseline ANC is a clinical risk factor for early dose-limiting toxicity in patients treated with CDK4/6i [16, 17].

While previous international studies, such as PALOMA-2 and PALOMA-3, identified *ABCB1* variants as potential predictors of neutropenia [14], these associations were not observed in Asian subpopulations. Consistent with this, our study found no significant association between *ABCB1* variants and severe neutropenia, highlighting the potential ethnic differences in pharmacogenetic profiles. In this study, in

addition to a low baseline neutrophil count at the initiation of treatment, the *ABCG2* rs2231142AA genotype was identified as an independent risk factor for severe neutropenia. In contrast, variants in *ABCB1*, *CYP3A4*, and *CYP3A5* were not significantly associated with severe neutropenia in the multivariate analysis. *ABCG2* encodes BCRP, an efflux transporter expressed in the liver, intestine, and kidney that plays a critical role in the elimination of xenobiotics, including anticancer agents. The 421 A allele reduces transporter activity, impairing palbociclib efflux and leading to elevated systemic drug exposure. As palbociclib-induced neutropenia occurs in a concentration-dependent manner, reduced *ABCG2* function may increase the risk of hematologic toxicity. These findings suggest that functional variants of *ABCG2* may influence the pharmacokinetics of palbociclib and contribute to interindividual variability in treatment-related toxicity, supporting its potential utility as a biomarker for personalized dosing strategies in clinical practice.

In contrast, a recent pharmacogenomic study conducted in Italy reported that *ABCB1* rs1128503, rs2032582, and rs1045642 were significantly associated with severe neutropenia and early dose-limiting toxicity (DLT) on day 14 of palbociclib treatment [20]. Moreover, patients carrying the rs1128503–rs2032582T(A)–rs1045642T variant haplotype were at an increased risk of hematologic toxicity and early dose reduction. The same study also reported that the CYP3A4 allele was significantly associated with early DLT in the univariate analysis. However, as the *CYP3A4* variant is extremely rare in East Asian populations, this may explain the absence of such an association in the current study. These discrepancies may reflect population-specific pharmacogenomic differences due to genetic backgrounds.

Strengths and limitation

This study had several strengths. First, it represents one of the few pharmacogenetic investigations focusing on the risk of severe neutropenia in Japanese patients with HR-positive/HER2-negative advanced breast cancer treated with palbociclib and endocrine therapy. By targeting a single ethnic population in Asia, this study minimized genetic heterogeneity and enabled a more precise evaluation of genotype–phenotype associations. Second, both clinical and genetic variables were comprehensively assessed using multivariate analysis, allowing for the identification of independent risk factors for severe SN. In particular, the identification of the *ABCG2* rs2231142 polymorphism as a significant predictor highlights the importance of transporter-mediated drug disposition in the development of drug toxicity. Third, the use of real-world clinical data enhanced the generalizability of the findings. Unlike randomized controlled trials, real-world cohorts reflect a broader spectrum of patient characteristics, including comorbidities and variability in treatment schedules. Finally, this study integrated clinical indicators, such as baseline neutrophil count, with pharmacogenomic insights to provide a more comprehensive understanding of individual susceptibility to palbociclib-induced hematologic toxicity. Importantly, dose adjustments based on these risk factors may help reduce adverse events and improve treatment continuity, thereby contributing to safer and more effective therapeutic strategies in clinical settings.

This study had at least three limitations. First, it was a single-center, retrospective study with a limited sample size, which may have reduced the statistical power to detect modest genetic effects in the study population. One possible reason for this is that in May 2018, the Ministry of Health, Labour, and Welfare issued a safety communication regarding the risk of interstitial pneumonia associated with abemaciclib, a drug belonging to the same class. Following the issuance of this warning, the number of patients receiving the drug temporarily decreased, resulting in fewer cases than expected. Second, there was a potential issue with multiple tests. We analyzed seven genetic variants and several confounding factors. In addition, a conventional significance level of 0.05 was used for the multivariate models. This threshold may be acceptable because this study was exploratory and intended as a pilot to inform future research. Therefore, the findings should be interpreted with caution because of the potential for type I errors. Third, pharmacokinetic data were unavailable, preventing a direct assessment of drug exposure. Nevertheless, because we conducted a single-center study, the treatment setting, timing of blood sampling, and adverse event assessments were standardized, thereby reducing data variability and minimizing inter-institutional confounding compared with multicenter studies. This methodological uniformity can be regarded as a strength of the present study. Based on the present findings, we plan to conduct a pharmacokinetics and pharmacodynamics study in patients with low baseline neutrophil counts and those carrying the *ABCG2* rs2231142 polymorphism to directly evaluate the relationship between genotype, drug exposure, and toxicity.

Future prospective studies with larger sample sizes are warranted to validate the current findings and facilitate their translation into clinical applications. Incorporating pharmacokinetic analyses is essential to directly evaluate the relationship between genotype, drug exposure, and toxicity. Furthermore, genome-wide association studies hold promise for identifying novel predictors of CDK4/6i–related toxicities. In clinical practice, integrating both genetic and clinical factors into screening strategies may facilitate the implementation of personalized medicine. This integrative approach may ultimately enable safer, more effective, and individualized treatment for patients receiving CDK4/6i, including palbociclib.

Conclusion

In this exploratory study, we identified a significant association between *ABCG2 rs2231142* and the development of severe neutropenia, in addition to baseline ANC. These findings may serve as a reference for optimizing the selection and management of CDK4/6i for future breast cancer treatment.

Statements / Declarations

Conflict of interest

The authors declare no conflicts of interest related to this study.

Ethical approval

The study protocol was approved by the Institutional Review Boards (IRBs) of both the NCC and University of Shizuoka in September 2023 (approval numbers: 2023-159 and 5-41). This study used clinical data and DNA samples from participants registered in the NCC Biobank. All participants provided written informed consent at the time of biobank enrollment for the use of their biological samples and clinical information in the research. The IRBs approved the use of these materials for this study without requiring additional informed consent. This study was conducted in accordance with the Ethical Guidelines for Life Sciences and Medical Research Involving Human Subjects published by Japan's Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labour and Welfare, Japan, and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Clinical trial number

Not applicable

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Author contributions

KM: Investigation and methodology, writing-original draft, had full access to the data and take responsibility for the integrity of data and adherence to the study protocol.HN: Project administration, conceptualization, investigation and methodology, formal analysis, writing-review and editing; had full access to the data and take responsibility for the integrity of data and adherence to the study protocol. SaMi: Conceptualization, formal analysis, Statistical analysis, writing-review and editing; had full access to the data and take responsibility for the integrity of data and adherence to the study protocol. ShMa: Investigation had full access to the data and take responsibility for the integrity of data and adherence to the study protocol. TM: Supervision and methodology. KI: Supervision. DT: Conceptualization, methodology, formal analysis, writing-review and editing; had full access to the data and take responsibility for the integrity of data and adherence to the study protocol.

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Date availability

Most of the data generated or analyzed in this study are included in this published article and its supplementary information files. Other datasets related to the current study are available from the corresponding author upon reasonable request.

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Tables

Tables 1 to 3 are available in the supplementary files section

Supplementary Files

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