Use of proton pump inhibitors and cyclin-dependent kinase 4/6 inhibitors in patients with endocrine-resistant metastatic breast cancer

Hitoshi Kawazoe[1], Kaori Takahashi[1], Ryuji Uozumi[2], Toru Mukohara[3], Tetsu Hayashida[4], Midori Iwabe[5], Hirotoshi Iihara[6], Kanako Kusuhara-Mamishin[7], Yuko Kitagawa[4], Masami Tsuchiya[5], Mika Kitahora[6], Aiko Nagayama[4], Shinkichi Kosaka[8], Yoshimi Asano-Niwa[9], Tomoko Seki[4], Koji Ohnuki[10], Akio Suzuki[6], Fumiko Ono[4], Manabu Futamura[9], Tomonori Nakamura[1]

[1]Division of Pharmaceutical Care Sciences, Center for Social Pharmacy and Pharmaceutical Care Sciences, Keio University Faculty of Pharmacy, [2]Department of Industrial Engineering and Economics, Tokyo Institute of Technology, [3]Department of Medical Oncology, National Cancer Center Hospital East, [4]Department of Surgery, Keio University School of Medicine, [5]Department of Pharmacy, Miyagi Cancer Center, [6]Department of Pharmacy, Gifu University Hospital, [7]Department of Pharmacy, National Cancer Center Hospital East, [8]Department of Surgery, National Hospital Organization Mito Medical Center, [9]Department of Breast Surgery, Gifu University Hospital, [10]Department of Breast Surgery, Miyagi Cancer Center

Keio University 1858 CALAMVS GLADIO FORTIOR

ABSTRACT

Introduction: Proton pump inhibitors (PPIs) reduce the bioavailability of several anticancer drugs. The impact of PPIs co-administered with cyclin-dependent kinase 4 and 6 inhibitors is controversial. We aimed to clarify whether the concomitant use of PPIs impacts palbociclib and abemaciclib effectiveness in breast cancer treatment.

Methods: This multicenter, retrospective, observational study, conducted across four medical institutions in Japan, consecutively included patients with endocrine-resistant metastatic breast cancer, receiving palbociclib or abemaciclib between December 2017 and August 2022. Propensity score-matched analyses were performed. Treatment efficacy and safety with and without PPIs were compared. Progression-free survival and overall survival were estimated using the Kaplan-Meier method and compared using a log-rank test. A Cox proportional hazards model was used to estimate the hazard ratio.

Results: The study included 240 patients. After 1:1 matching, 112 patients were treated with and without PPIs. The median progression-free survival period was 1.2 years in the PPI group and 1.3 years in the non-PPI group (hazard ratio, 1.19; 95% CI, 0.70-2.02). The median overall survival period was 3.6 years in the PPI group, whereas it was not reached in the non-PPI group (hazard ratio, 1.23; 95% CI, 0.61-2.47). Consistent results were obtained for subgroups receiving palbociclib (n = 177) and abemaciclib (n = 63) without propensity score matching. Adverse event incidence and severity were similar in both groups.

Conclusions: The effectiveness of cyclin-dependent kinase 4/6 inhibitors is unlikely to be affected by concomitant PPI use. Future prospective pharmacokinetic studies are warranted.

INTRODUCTION

- The use of cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors plus endocrine therapy is the standard treatment for first- or second-line treatment of pre- and postmenopausal patients with hormone receptor-positive and human epidermal growth factor receptor type 2 (HER2)-negative metastatic breast cancer (mBC).
- Drug-drug interactions between CDK4/6 inhibitors and proton pump inhibitors (PPIs) is a controversial issue because of their positive and negative impacts and inconsistency among reports [1-7].
- Additionally, several studies were not specified treatment lines, the corresponding patient eligibility criteria, and the sensitivity to endocrine therapy of the patients.
- The present study aimed to clarify whether concomitant PPI use impacts the effectiveness of CDK4/6 inhibitors in patients with hormone receptor-positive and HER2-negative endocrine-resistant mBC using real-world data.

METHODS AND MATERIALS

Patients

This multicenter, retrospective, observational study, conducted across four medical institutions in Japan. Data retrieved from electronic medical records included consecutive patients with endocrine-resistant mBC who received palbociclib and abemaciclib between December 2017 and August 2022.

The study protocol was representatively approved by the Ethics Committees of the Keio University School of Medicine (approval number: 20221136).

Data Collection

Patient characteristics at baseline, medication history, progression and/or death, and adverse events were collected.

PPI group was defined as PPI administration covered the entire or more than half of the treatment period with CDK4/6 inhibitors.

Statistical Analysis

Progression-free survival (PFS) and overall survival (OS) were estimated using the Kaplan–Meier method and compared using a log-rank test.

Propensity score-matched analyses were performed. Propensity scores of concomitant PPI use were estimated using a logistic regression model based on the following clinically selected covariates: age, performance status, disease site, number of metastases, and previous lines of endocrine treatment.

All *P*-values were two-sided, and the significance level was set at 0.05.

RESULTS

- After 1:1 matching, 112 patients were treated with and without PPIs.
- The median PFS was 1.2 (95% CI, 0.7–1.7) and 1.3 (95% CI, 1.1–2.5) years in the PPI and non-PPI groups, respectively (*P* = 0.53) (**Figure 2**).
- The median OS was 3.6 (95% CI, 2.8–not reached) years in the PPI group, whereas it was not reached in the non-PPI group (*P* = 0.57). (**Figure 3**).
- The proportion of adverse events of grade 3/4 was similar for each CDK4/6 inhibitor, regardless of PPI use (**Table 2**).

Figure 1. Patient enrollment flowchart

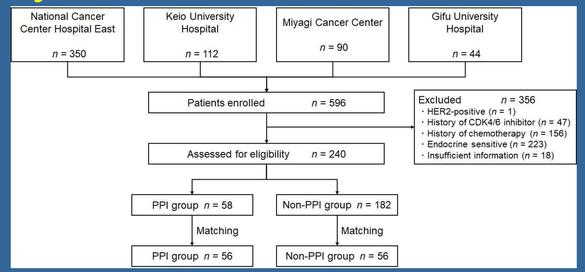


Table 1. Patient characteristics

	PPI (*n* = 56)	Non-PPI (*n* = 56)
Age (years), median (IQR)	71 (60–75)	70 (62–75)
Sex, *n* (%)		
Female	55 (98)	55 (98)
Male	1 (2)	1 (2)
Menopause, *n* (%)		
Premenopause	8 (14)	4 (7)
Postmenopause (or male sex)	48 (86)	52 (93)
Performance status, *n* (%)		
0–1	52 (93)	53 (95)
2	4 (7)	3 (5)
Treatment line, *n* (%)		
1st, 2nd	39 (70)	41 (73)
≥ 3rd	17 (30)	15 (27)
Number of metastases, median (IQR)	2 (1–3)	2 (1–3)
Metastatic site, *n* (%)		
Visceral	34 (61)	36 (64)
Non-visceral	22 (39)	20 (36)
CDK4/6 inhibitor, *n* (%)		
Palbociclib capsule	33 (59)	25 (45)
Palbociclib tablet	10 (18)	10 (18)
Abemaciclib	13 (23)	21 (38)
PPI used, *n* (%)		
Omeprazole	3 (5)	
Lansoprazole	25 (45)	
Rabeprazole	8 (14)	
Esomeprazole	10 (18)	
Vonoprazan	10 (18)	

Table 2. Grade 3/4 adverse events

	Palbociclib (*n* = 78)		Abemaciclib (*n* = 34)	
	PPI (*n* = 43)	Non-PPI (*n* = 35)	PPI (*n* = 13)	Non-PPI (*n* = 21)
Hematological toxicity				
Neutrophil count decreased	36 (84)	31 (89)	7 (54)	4 (19)
White blood cell count decreased	20 (47)	11 (31)	2 (15)	0
Anemia	5 (11)	3 (9)	1 (8)	3 (14)
Platelet count decreased	4 (9)	1 (3)	0	0
Febrile neutropenia	0	0	1 (8)	0
Non-hematological toxicity				
Diarrhea	1 (2)	0	3 (23)	4 (19)
Pneumonitis	3 (7)	2 (6)	0	2 (10)
AST level increased	0	2 (6)	1 (8)	2 (10)
ALT level increased	0	1 (3)	1 (8)	2 (10)
Stevens–Johnson syndrome	0	0	1 (8)	0
Skin ulceration	1 (2)	0	0	0
Malaise	0	1 (3)	0	0
Skin infection	0	1 (3)	0	0
Appendicitis	0	1 (3)	0	0
Nausea	0	0	0	1 (5)
Anorexia	0	0	1 (8)	0

Figure 2. Kaplan–Meier survival curves for PFS

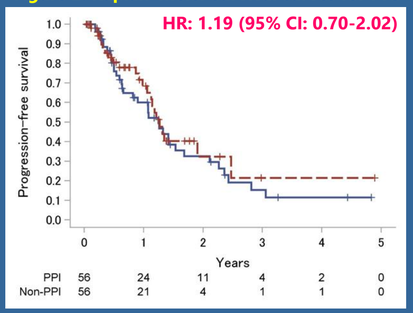
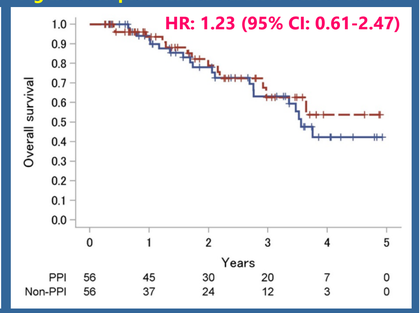


Figure 3. Kaplan–Meier survival curves for OS



DISCUSSION

- Under fasting conditions, co-administration of PPIs and palbociclib capsules decreased the palbociclib mean area under the concentration-time curve from time 0 to infinity by 62%; however, under fed conditions, it decreased by only 13% [8]. If patients take palbociclib capsules appropriately after meals, the effect of PPIs on palbociclib blood levels may not be clinically significant.
- No data on adherence to CDK4/6 inhibitors or PPIs were obtained; we used prescription history. Additionally, we were unable to perform quantitative or qualitative assessments to establish the patterns of drug timing.

CONCLUSIONS

- This study suggests that the effectiveness of CDK4/6 inhibitors is unlikely to be affected by concomitant PPI use in Japanese patients with hormone receptor-positive and HER2-negative endocrine-resistant mBC.
- Further examination is needed to determine whether PPI prescriptions should be adjusted for patients on palbociclib or abemaciclib.

REFERENCES

[1] *ESMO Open* 2021; **6**: 100231.
[2] *BMC Cancer* 2022; **22**: 516.
[3] *JAMA Netw Open* 2023; **6**: e2324852.
[4] *Breast* 2022; **66**: 157-61.
[5] *J Cancer Ther* 2022; **13**: 266-74.
[6] *Medicina* 2023; **59**: 557.
[7] *Clin Breast Cancer* 2023; **23**: 658-63.
[8] *Clin Pharmacol Drug Dev* 2017; **6**: 614-26.