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ORIGINAL RESEARCH

Drug-drug interactions between palbociclib and proton pump inhibitors may significantly affect clinical outcome of metastatic breast cancer patients

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Background: Proton-pump-inhibitors (PPIs) are frequently prescribed for the management of anticancer drug-related gastrointestinal symptoms. Palbociclib is a weak base with pH-dependent solubility and potential drug-drug interaction at the absorption level may affect clinical pharmacokinetics. The current study was aimed at investigating the effect of co-administration of PPIs and palbociclib on progression-free survival (PFS) in metastatic breast cancer (mBC) patients.

Patients and methods: Patients affected by estrogen receptor-positive, human epidermal growth factor receptor 2-negative mBC, who were candidates for first-line treatment with palbociclib, were enrolled in this retrospective observational study. Patients were defined as 'no concomitant PPIs' if no PPIs were administered during palbociclib treatment, and as 'concomitant PPIs' if the administration of PPIs covered the entire or not less than two-thirds of treatment with palbociclib. All clinical interventions were made according to clinical practice.

Results: A total of 112 patients were enrolled in the study; 56 belonged to the 'no concomitant PPIs' group and 56 to the 'concomitant PPIs' group. Seventy-one patients were endocrine-sensitive and received palbociclib and letrozole, and 43 were endocrine-resistant and were treated with palbociclib and fulvestrant. The most prescribed PPI was lansoprazole. Patients taking PPIs had a shorter PFS than those taking palbociclib and endocrine therapy alone (14.0 versus 37.9 months, $P < 0.0001$). Multivariate analysis confirmed concomitant PPIs as the only independent predictive factor for shorter PFS ($P = 0.0002$). PFS was significantly longer in estrogen-sensitive mBC with no concomitant PPIs compared with patients taking PPIs or estrogen-resistant patients, with and without PPIs ($P < 0.0001$). No correlation with adverse events was found when considering grade >2 hematological toxicities [Common Terminology Criteria for Adverse Events (CTCAE) scale].

Conclusions: The present study demonstrates that concomitant use of PPIs in mBC patients treated with palbociclib has a detrimental effect on PFS. Therefore, it is recommended to prescribe PPIs with caution in these patients, strictly adhering to the indications in the summary of product characteristics (RCP).

Key words: breast cancer, palbociclib, proton pump inhibitors, drug-drug interactions, PFS

INTRODUCTION

Proton pump inhibitors (PPIs) are widely used in cancer patients (with a prevalence of 20%-55%) to mitigate symptoms associated with gastroesophageal reflux disease, although there may be pharmacologic interactions since a substantial number of targeted drugs exhibit pH-dependent solubility.[1] Therefore, drug-drug interactions (DDI) at the absorption level should be considered as a possible cause of treatment failure in cancer patients.[2] As a matter of fact, gastric pH elevation by PPIs was found to significantly reduce the oral bioavailability of many anticancer drugs, particularly those with exponentially decreasing solubility in the pH range 1-4.[3,4] Whether or not these changes may be clinically relevant depends on the type of anticancer drug involved.[5] Prolonged acid suppression by PPIs in cancer patients was found to reduce the antitumor efficacy of

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capecitabine[6,7] and pazopanib,[8] whereas it did not seem to influence clinical outcomes in patients treated with epidermal growth factor receptor (EGFR) inhibitors.[9-11]

Palbociclib is an oral cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor able to suppress DNA synthesis by inhibiting the progression of cells from G1 to S phase.[12] Palbociclib demonstrated clinical efficacy in combination with fulvestrant or aromatase inhibitors as first- or second-line treatment of premenopausal and postmenopausal, hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer (mBC) patients.[13,14] Palbociclib is a weak base with pH-dependent solubility that rapidly decreases to values $<$0.5 mg/ml as pH increases above 4.5 (i.e. gastric pH typically achieved by PPIs). Coadministration of multiple doses of rabeprazole was found to reduce palbociclib mean area under the concentration-time curve (AUC) and maximum plasma concentration (C_{max}) by 62% and 80%, and 13% and 41% under fasting and fed conditions, respectively.[15]

Studies on ribociclib examining solubility, physiologically-based pharmacokinetic modeling, clinical trial data, and population pharmacokinetics suggest that drug absorption is unlikely to be affected by changes in gastric pH that occur following food intake or concomitant use of PPIs.[16,17] To our knowledge, no data are available on DDIs between abemaciclib and PPIs or palbociclib and PPIs other than rabeprazole.

The current study is aimed at investigating the effect of concomitant PPIs (mainly lansoprazole) on palbociclib progression-free survival (PFS) in patients treated as first-line for estrogen-positive, HER2-negative mBC.

PATIENTS AND METHODS

Hormone receptor-positive, HER2-negative mBC patients treated with palbociclib with or without concomitant PPI treatment were enrolled in this observational study. Hormone receptor-positive, HER2-negative BCs were defined as tumors with estrogen and/or progesterone receptors expression $>$1% and HER2-negative (score 0 or 1+ or negative to immuno-histochemistry). Patients were defined as 'no concomitant PPIs' if no PPIs were administered during palbociclib treatment, while 'concomitant PPIs' was used to indicate that the administration of PPIs covered the entire or not less than two-thirds of treatment with palbociclib. According to the duration of previous endocrine response, each patient was classified as endocrine-sensitive (if relapsed at least 12 months after the completion of adjuvant endocrine therapy or with *de novo* advanced breast cancer) or endocrine-resistant (if relapsed on or within 12 months after ending adjuvant endocrine therapy).[18]

All pharmacological and clinical interventions were made according to clinical practice. In particular, palbociclib was administered at a dose of 125 mg orally, once daily for 21 consecutive days, followed by 7 days off, to comprise a complete cycle of 28 days plus fulvestrant or letrozole, according to clinical practice. Palbociclib reduction to 100 or 75 mg was made according to the toxicity profile. Patients were advised to take the dose of lansoprazole (15 mg), esomeprazole (20 mg), omeprazole (10 mg), or pantoprazole (20 mg) in the morning at breakfast. Palbociclib was taken at lunchtime and patients were advised not to take strong inhibitors or inducers of cytochrome P450 3A4 (CYP3A4). The prescribing physician monitored the patient's compliance with the recommendations. Toxicity was graded according to Common Terminology Criteria for Adverse Events (CTCAE v5). The study was approved by the local Ethics Committee and conducted in accordance with the Helsinki Declaration. All patients released a written informed consent.

Statistical analysis

Categorical variables including Eastern Cooperative Oncology Group (ECOG) performance status, lines of treatment, hormone sensitivity, premenopausal versus postmenopausal status, visceral versus bone disease, and number of tumor sites were described by absolute and relative frequencies and quantitative factors by median and range. PFS was defined as the time from treatment start to progression of disease. The Kaplan—Meier method was used to create survival curves and the log-rank test was used to evaluate the differences between curves. The Cox hazard regression method was used to identify independent risk factors for PFS. Differences were considered significant at $P < 0.05$. All statistical analyses were carried out with MedCalc Statistical Software version 14.8.1 (MedCalc Software, bvba, Ostend, Belgium).

RESULTS

A total of 112 patients were enrolled in the study, 56 of whom did not receive any PPI during palbociclib treatment and 56 received concomitant palbociclib-PPI treatment; 71 patients were endocrine-sensitive and were administered a combination of palbociclib and letrozole, and 41 were defined as endocrine-resistant and were treated with the combination of palbociclib and fulvestrant. The majority of patients received palbociclib at a dose of 125 mg (61.6%), 26.8% reduced the dose to 100 mg, and 9.8% of patients needed the 75 mg dose. No statistically significant differences were found comparing the 'no concomitant PPIs' versus 'concomitant PPIs' based on their clinical characteristics. Clinical characteristics of patients and the type of PPI used are reported in Table 1.

The overall population was stratified according to PFS and the use of concomitant PPIs, showing that patients taking PPIs had a shorter PFS with respect to patients taking palbociclib and endocrine therapy alone (14.0 versus 37.9 months, $P < 0.0001$; Figure 1). The univariate analysis included age, number of metastatic sites at palbociclib baseline, endocrine sensitivity or resistance, ECOG, menopausal status, visceral disease, and palbociclib dose reduction. Age, ECOG, and endocrine sensitivity or resistance were significantly associated to PFS ($P = 0.04$, $P = 0.02$ and $P = 0.001$, respectively; Table 2). The

Table 1. Clinical characteristics of patients and their distribution across PPI groups

	Total number of patients ($n = 112$)	Concomitant use of PPIs		*P* value
		No ($n = 56$)	Yes ($n = 56$)	
Age at the diagnosis of metastasis (years), median (range)	63 (35-86)	61.5	63	—
Pre/postmenopause, *n* (%)				0.61
Premenopause	19 (16.96)	11 (19.6)	8 (14.3)	
Postmenopause	93 (83.04)	45 (80.4)	48 (85.7)	
ECOG PS, *n* (%)				0.64
0	84 (75)	44 (78.6)	40 (71.4)	
1	25 (22.3)	11(19.6)	14 (25)	
2	3 (2.7)	1 (1.8)	2 (3.6)	
Disease site, *n* (%)				0.26
Visceral	55 (49.1)	31 (55.4)	24 (42.9)	
Non-visceral	57 (50.9)	25 (44.6)	32 (57.1)	
Type of HT associated to palbociclib, *n* (%)				1
Fulvestrant	39 (34.8)	20 (35.7)	19 (33.9)	
Letrozole	73 (65.2)	36 (64.3)	37 (66.1)	
Endocrine-sensitive or -resistant disease, *n* (%)				1
Sensitive	71 (63.4)	35 (62.5)	36 (64.3)	
Resistant	41(36.6)	21 (37.5)	20 (35.7)	
Dose reduction of palbociclib, *n* (%)				0.21
125 mg	69 (61.6)	36 (64.3)	33 (58.9)	
100 mg	30 (26.8)	11 (19.6)	19 (33.9)	
75 mg	11 (9.8)	8 (14.3)	3 (5.4)	
Unknown	2 (1.8)	1 (1.8)	1 (1.8)	
PPI used, *n* (%)				
Lansoprazole			42 (37.5)	
Omeprazole			11 (9.8)	
Pantoprazole			2 (1.8)	
Esomeprazole			1 (0.9)	

ECOG PS, Eastern Cooperative Oncology Group (ECOG) performance status; HT, hormone therapy; PPIs, proton pump inhibitors.

multivariate analysis confirmed the use of concomitant PPIs as the only independent predictive biomarker for shorter PFS (hazard ratio 2.77; 95% confidence interval: 1.62-4.75; $P = 0.0002$; Table 2). To evaluate the effective role of PPIs over endocrine sensitivity in PFS analysis, patients were stratified into four groups: (i) endocrine-sensitive patients and no concomitant PPIs, (ii) endocrine-sensitive patients and concomitant PPIs, (iii) endocrine-resistant patients and no concomitant PPIs, and (iv) endocrine-resistant patients and concomitant PPIs. PFS was significantly longer in endocrine-sensitive patients with no concomitant PPIs compared with the other three groups ($P < 0.0001$; Figure 2). The worse PFS was identified in the group of endocrine-resistant patients with concomitant use of PPIs (6.3 months; Figure 2). No correlation with adverse events was found considering grade >2 hematological toxicities, since neutropenia, anemia, and thrombocytopenia were equally distributed across the two groups of patients and the majority of patients developed toxicity during the first and/or second cycle of therapy ($P = 0.8$).

DISCUSSION

It has been recognized that among different factors that can influence drug absorption, pH solubility is the most relevant one.[19] In particular, an increase in gastric pH was found to affect the anticancer activity of weakly basic drugs by reducing their bioavailability.[3,20] To our knowledge, this is the first study demonstrating that the use of PPIs in mBC patients treated with palbociclib has a detrimental effect on PFS. Regarding the mechanism underlying the unfavorable impact of PPIs on PFS, it is conceivable that the increase in gastric pH may have lowered palbociclib plasma concentrations affecting treatment efficacy. Indeed, palbociclib is a weak base with pH-dependent solubility that rapidly decreases as pH increases above 4.5. The changes induced on palbociclib pharmacokinetics by rabeprazole in fed condition were considered not clinically relevant,[15] and no restriction for the concomitant use of PPIs are reported in the palbociclib label.[21] At variance with the current study, however, Sun and co-workers[15] did not evaluate the effect of rabeprazole on clinical outcomes. Furthermore, the impact on palbociclib pharmacokinetics by rabeprazole given for 6 days only may have been underestimated, since short-term treatment with PPIs does not elevate the intragastric pH over the whole 24-h range.[14,22] In the current study, PPIs (mainly lansoprazole) were given for the entire or not less than two-thirds of palbociclib treatment, a treatment schedule that most likely induces a larger and more constant elevation of intragastric pH.

Although the absolute threshold level below which the activity of palbociclib may be affected is currently unknown, it has been reported that the free average steady-state concentration (C_{ss}) for palbociclib was similar to the *in vitro* cell potency (IC_{50}), with a C_{ss}/IC_{50} ratio of 0.94.[23] Findings of the current study support the hypothesis that long-term treatment with PPIs may reduce palbociclib plasma levels below the minimum effective concentration, thus affecting its efficacy to some degree. A limitation of

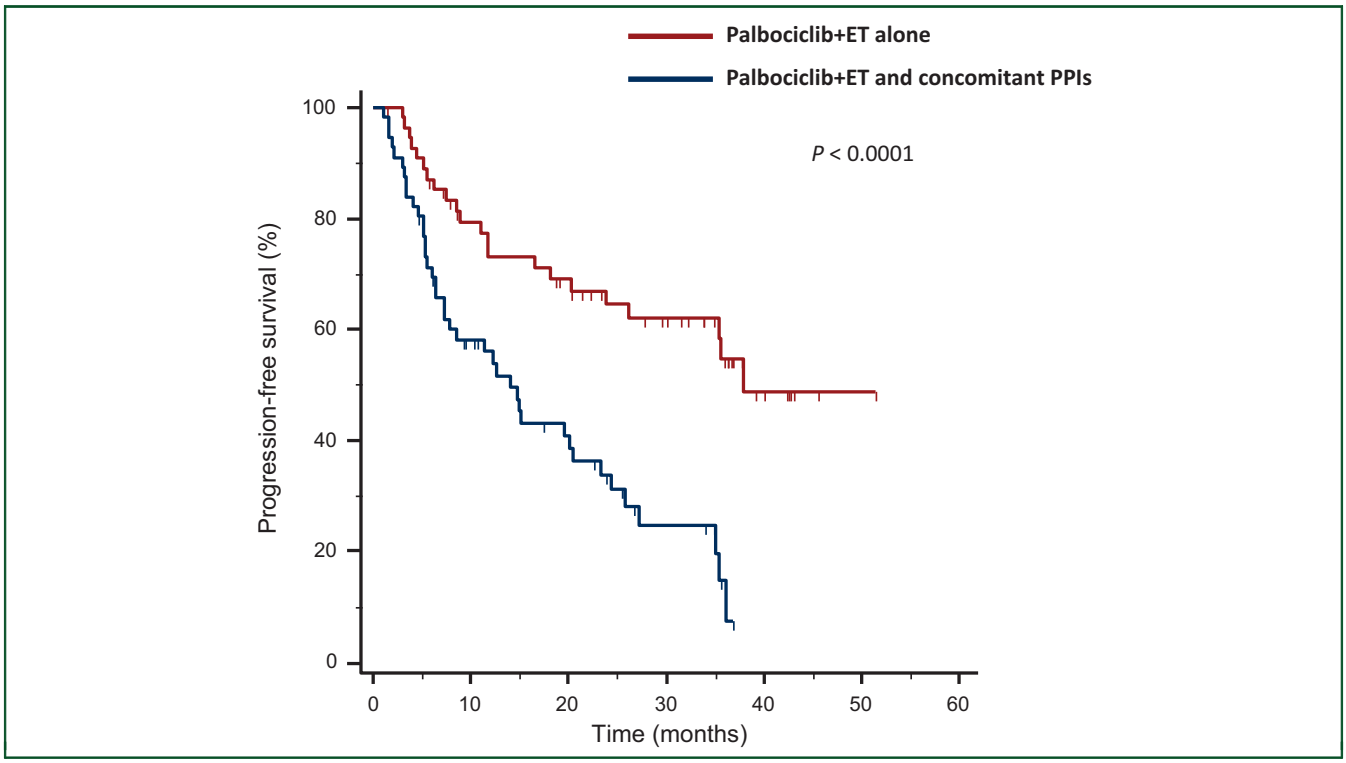

Figure 1. Overall population treated with palbociclib plus endocrine therapy stratified according to progression-free survival and the use of concomitant PPIs.
ET, endocrine therapy; PPIs, proton pump inhibitors.

Table 2. Univariate and multivariate analysis for progression-free survival

Variables	Univariate		Multivariate	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (years)	1.68 (1.01-2.78)	**0.04**	1.46 (0.86-2.47)	0.15
Number of metastatic sites	1.09 (0.85-1.42)	0.48		
Endocrine-sensitive or -resistant disease	2.29 (1.38-3.78)	**0.001**	1.83 (0.93-3.58)	0.08
ECOG PS	1.82 (1.07-3.11)	**0.02**	1.64 (0.94-2.86)	0.07
Pre/postmenopause	1.92 (0.87-4.21)	0.10		
Visceral or non-visceral disease	1.46 (0.88-2.40)	0.14		
Dose reduction	0.91 (0.55-1.52)	0.73		
Concomitant use of PPIs	2.93 (1.71-5.03)	**0.0001**	2.77 (1.62-4.75)	**0.0002**

CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group (ECOG) performance status; PPIs, proton pump inhibitors; HR, hazard ratio. Statistically significant values are reported in bold.

our study is the lack of assessment of changes in palbociclib pharmacokinetics induced by PPIs. It has been reported, however, that short-term treatment with rabeprazole reduces palbociclib C_{max} by 80% and 41% under fasting and fed conditions, respectively.[15]

Several lines of evidence suggest no impact of gastric pH-altering agents on the absorption of ribociclib.[16,17] Samant et al.[16] analyzed steady-state pharmacokinetic parameters of ribociclib (600 mg) during PPI use and found no differences in AUC and C_{max} between the two groups. The different behavior of ribociclib and palbociclib in the acid microenvironment may be due to different dissolution properties. Indeed, ribociclib solubility is >2.4 mg/ml at pH 4.5,[16] whereas that of palbociclib is >0.5 mg/ml only at pH <4.5.[15] In the non-compartmental analysis of clinical data, Samant et al.[16] found that trough concentration (C_{trough}) mean values of ribociclib were 597 and 711 ng/ml in patients taking or not taking PPIs, respectively. Such a reduction in the ribociclib C_{trough} is unlikely, however, to be clinically relevant due to its wide therapeutic index characterized by an average free C_{ss} that largely exceeds the *in vitro* cell potency (C_{ss}/IC_{50} ratio >25).[23] Concerning abemaciclib, the drug shows similarities in pharmacokinetics compared with the other CDK4/6 inhibitors. Perhaps a feature that is worth mentioning is the saturable absorption which justifies, together with the shorter half-life and the smaller volume of distribution compared with ribociclib and palbociclib, a continuous, twice-daily administration.[24]

Another interesting question is whether P-glycoprotein (P-gp) inhibition may have influenced the effects of PPIs on PFS observed in the current study. Indeed, PPIs are known

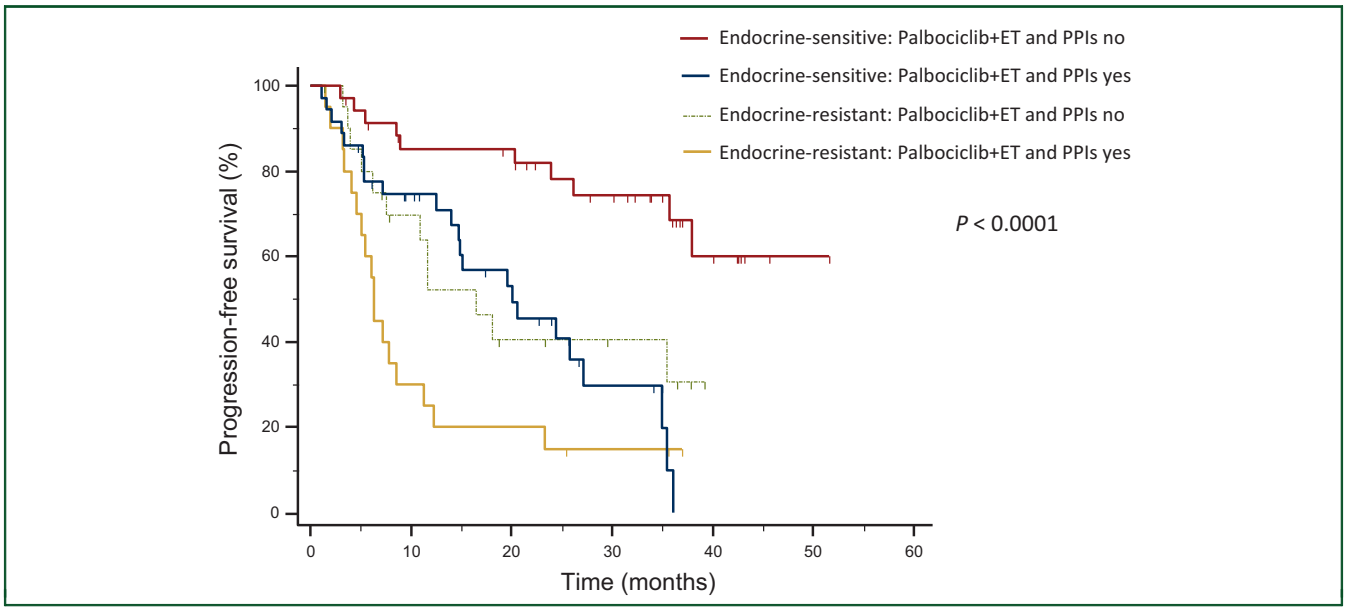

Figure 2. Effect of concomitant PPIs on progression-free survival over endocrine sensitivity.
Patients were stratified in four groups: (1) endocrine-sensitive patients and no concomitant PPIs, (2) endocrine-sensitive patients and concomitant PPIs, (3) endocrine-resistant patients and no concomitant PPIs, and (4) endocrine-resistant patients and concomitant PPIs.
ET, endocrine therapy; PPIs, proton pump inhibitors.

to be moderate inhibitors of P-gp[25] and palbociclib is a P-gp substrate.[26] Furthermore, pantoprazole was found to alter tyrosine kinase inhibitor (TKI) pharmacokinetics by affecting breast cancer resistance protein (BCRP) and P-gp.[22] If P-gp inhibition by PPIs had been the main mechanism of DDI observed in our study, it would have produced an opposite effect to that induced by the increase in gastric pH (i.e. higher palbociclib exposure with evidence of toxicity). This hypothesis does not agree with our data since no statistical differences in the incidence of adverse drug reactions were observed in the presence or absence of PPIs. Accordingly, although rabeprazole was found to inhibit P-gp activity at clinically relevant concentrations, the net effect was the reduction of palbociclib exposure.[15] Therefore, changes in gastric pH caused by PPIs appear to be the main mechanism of interaction with drugs that require an acid microenvironment for dissolution and absorption.[27]

Other examples of DDIs among PPIs and TKIs (i.e. pazopanib, sunitinib, gefitinib, and erlotinib) have been reported.[9,28-33] A meta-analysis on 16 retrospective studies for a total of 372 418 patients with gastrointestinal, renal, and non-small-cell lung cancers, soft tissue sarcomas, or solid tumors of mixed histology, showed a significant impact of PPI treatment on survival outcomes in patients receiving oral anticancer drugs.[34] Another retrospective study on 12 538 patients with lung, renal, liver, pancreatic cancer, and chronic myelogenous leukemia evaluated the impact of concomitant PPI administration on overall survival and treatment discontinuation 90 days and 1 year after the end of the exposure. This work retrospectively demonstrated that the use of PPIs was associated with an increased risk of death in TKI-treated patients.[35]

The main limitation of this study is the retrospective nature. However, our data suggest caution in the long-term use of PPIs in this specific population and a careful assessment of benefits and risk of coadministration of strong acid-reducing agents with anticancer drugs whose solubility is dependent on the pH at the site of absorption. The choice of PPI should also be carefully evaluated. For example, rabeprazole can maintain longer acid suppression than other drugs of the same class; the administration of H2-antagonists instead of PPIs should also be considered. Although increasing the dose of palbociclib in patients using PPIs may be theoretically logical, it is probably not an effective strategy in clinical practice due to possible off-target effects.

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