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

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Abstract

Background Proton pump inhibitors (PPIs) are widely used in cancer patients to mitigate adverse gastrointestinal events. However, drug-drug interactions (DDIs) between PPIs and palbociclib (PPIs-palbociclib interaction) have not been sufficiently investigated. In vitro studies have shown that a DDI exists between palbociclib and PPIs, which could have a detrimental effect on breast cancer patients (mBC) treated with palbociclib.

Methods The study was a prospective, observational, single-arm, open-label, non-randomized clinical trial involving 105 patients with HER2-negative advanced/metastatic breast cancer, treated with palbociclib + adjuvant endocrine therapy, and stratified by PPIs use (PPI+ or PPI−). The primary end points were progression-free survival (PFS) and overall survival (OS) at 6 months. Patients were followed up for 12 months. The study was planned as a Phase II study to provide sufficient power to detect a difference in PFS of 2 months.

Results A total of 112 patients were enrolled. 56 belonged to the “no concomitant PPIs” group while 56 to the “concomitant PPIs” group. Survival analysis indicated that PPIs use had a significant detrimental impact on PFS (HR: 0.56, p<0.0001). The multivariate analysis confirmed the use of concomitant PPIs as the only independent negative predictor for shorter PFS (p<0.0001). No statistically significant differences were found between the two groups concerning OS.

Background and Aim

Palbociclib is an oral cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor and is a small molecule able to prevent DNA synthesis by inhibiting the G1-to-S-phase progression (Lancet 2020; 395: 417-427). Palbociclib is a weak base with pH-dependent solubility that rapidly decreased to values below 0.5 mg/ml as pH increased above 4.5 (i.e., the gastric pH typically falls below 2). The drug’s solubility is measured in vitro and in vivo, during the progression of a particular tumor, and is significantly associated with tumor progression and the development of drug resistance (ESMO 2021 Annual Meeting).

Patients and methods

Patients were stratified into 2 groups: PPI−: no concomitant PPIs; or PPI+: concomitant PPIs. The primary end points were PFS and OS. The study was planned as a Phase II study to provide sufficient power to detect a difference in PFS of 2 months.

Figure 1: PFS of patients assuming palbociclib-endocrine therapy (ET) ± PPIs

Figure 2: PFS of patients stratified as per PPIs over endocrine sensitivity

Results

A total of 112 patients were enrolled in the study, 56 of which did not receive any PPI during palbociclib treatment and 56 received concomitant PPI treatment, 71 patients were endocrine sensitive and were administered with combination of palbociclib and letrozol, and 41 were defined as endocrine resistant/rare 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 a dose of 75 mg dosage. No statistically significant differences were found comparing the “no concomitant PPIs” vs “concomitant PPIs” based on their clinical characteristics. Clinical characteristics 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 patients assuming PPIs had a shorter PFS relative to patients assuming palbociclib and endocrine therapy alone (14.9 vs 37.8 months; p<0.0001, Figure 1). The univariate analysis included patients’ age, number of metastatic sites at baseline, endocrine sensitivity or resistance, ECOG, metastatic status, visceral disease and palbociclib dose reduction. Age, ECOG, and endocrine sensitivity or resistance resulted to be significantly associated to PFS (p=0.04, p=0.02 and p=0.01, respectively). The multivariate analysis confirmed the use of concomitant PPIs as the only independent predictive biomarker for shorter PFS (HR: 2.73–95%CI: 1.42–4.75; p=0.0002).

To evaluate the effective role of PPIs over endocrine sensitivity in PFS determination, patients were stratified in 4 groups: endocrine sensitive patients and no concomitant PPIs, endocrine sensitive patients and concomitant PPIs, endocrine resistant patients and no concomitant PPIs, endocrine resistant patients and concomitant PPIs.

PFS was significantly longer in endocrine sensitive patients with no concomitant PPIs compared to the other 3 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 3). No correlation with adverse events such as gastroesophageal reflux, neutropenia, anemia and thrombocytopenia were reported.

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 PPI with caution in these patients, or administer H2-antagonists or PPI for very short periods.