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Genitourinary Cancer

The Effect of Concomitant Proton Pump Inhibitor and Cabozantinib on the Outcomes of Patients with Metastatic Renal Cell Carcinoma

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Cabozantinib • Pharmacology • Proton pump inhibitors • Renal cell carcinoma • Overall survival • Toxicity

Abstract

Introduction. Cabozantinib is an oral tyrosine kinase inhibitor that is approved for the treatment of metastatic renal cell carcinoma (mRCC). Cabozantinib is a weak base that exhibits a pH-dependent solubility profile in vitro which raises concerns about its bioavailability in patients treated with proton pump inhibitors (PPIs). The purpose of this study was to investigate whether PPI use has an impact on the efficacy, safety, and residual concentration (Ctrough) of cabozantinib in patients with mRCC.

Materials and Methods. This is a retrospective review of a prospectively collected electronic database of patients with mRCC who received cabozantinib at Gustave Roussy between February 2014 and December 2018. The Kaplan-Meier method was used for survival analysis and the Cox proportional-hazard model for uni- and multivariate analysis. In parallel, we conducted a pharmacokinetic study of cabozantinib in a distinct cohort of 50 mRCC patients, in which cabozantinib Ctrough was assayed using a validated tandem mass spectrometry–liquid chromatography method.

Results. We identified 99 patients treated with cabozantinib, including 43 patients being PPI users. With a median follow-up of 30.3 months, PPI users showed similar progression-free survival and overall survival outcomes compared with PPI nonusers. Similarly, the incidence of adverse events was not significantly different between the PPI users and nonusers, although PPI users required dose reductions more often. In the independent pharmacokinetic cohort, of whom 21 received PPI concomitantly, Ctrough was similar between the two groups.

Conclusion. In line with the pharmacologic data, the concomitant use of PPI does not significantly impact the efficacy or safety of cabozantinib in patients with mRCC. ***The Oncologist*** 2021;26:389–396

Implications for Practice: Drug interactions, especially between targeted therapies and proton pump inhibitors (PPI), were shown to potentially impact the outcomes of cancer patients. Cabozantinib, a current therapeutic standard in metastatic renal cell carcinoma (mRCC), exhibits a pH-dependent solubility profile, which raises concerns about its bioavailability in patients treated with proton pump inhibitors (PPI). At the present time, there is no evidence regarding the effect of PPIs on cabozantinib's efficacy and safety in patients with mRCC. This study found that the concomitant use of PPI during cabozantinib treatment in mRCC patients does not appear to impact the residual concentration, efficacy, and safety of cabozantinib in a real-life context.

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Introduction

Approximately 400,000 cases of renal cell carcinoma are diagnosed worldwide every year, with nearly a third having advanced-stage or metastatic disease at the time of diagnosis [1, 2] The majority of patients diagnosed with clear-cell metastatic renal cell carcinoma (mRCC) will be treated with vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors (TKIs) and/or immune checkpoint inhibitors in the metastatic setting [3]. These treatment options have yielded substantial response rates and have significantly improved the survival of patients with mRCC [4, 5]. Cabozantinib is an oral VEGFR-TKI that inhibits the activity of c-MET, vascular endothelial growth factor receptor, AXL, and other tyrosine kinases. It is approved in patients with mRCC that had progressed after VEGFR-targeted therapy based on the METEOR trial (NCT01865747), which showed progression-free survival (PFS; hazard ratio [HR], 0.51; 95% confidence interval [CI], 0.41–0.62) and overall survival (OS; HR, 0.66; 95% CI, 0.53–0.83) benefit in comparison with everolimus [6]. Cabozantinib was later approved in the first-line treatment of patients with intermediate/poor-risk mRCC based on the CABOSUN trial (NCT01835158), which showed a longer PFS for cabozantinib in comparison to sunitinib (HR, 0.48; 65% CI, 0.31–0.74) but was not powered to show an OS benefit (HR, 0.80; 95% CI, 0.53–1.21) [7].

Drug interactions, especially with proton pump inhibitors (PPIs), were shown to potentially impact the outcomes of patients treated with TKIs for solid tumors [7–9]. For instance, a retrospective cohort of patients with non-small cell lung cancer treated with the anti-EGFR TKI (erlotinib) showed that OS was negatively impacted by administration of acid-suppressor drugs. Moreover, a detrimental impact of gastric acid suppression in terms of both OS and PFS was demonstrated in patients with soft tissue sarcoma treated with pazopanib. In mRCC, a single retrospective chart review study demonstrated a lower PFS and OS in patients treated with both sunitinib and a PPI.

Cabozantinib is a weak base that exhibits a pH-dependent solubility profile in vitro that raises concerns about its bioavailability in patients treated with PPIs [10]. The concomitant prescription of cabozantinib and PPIs is not rare, as 12%–27% of patients receiving cabozantinib develop dyspepsia as an adverse event of the drug itself [7, 12, 13]. A phase I study performed on healthy volunteers has previously shown that mean plasma peak concentration (Cmax) and overall exposure (area under the curve [AUC] 0–*t*) did not differ with the addition of omeprazole after a single dose of cabozantinib [14]. As a result, the label of cabozantinib does not warn against the concomitant use of acid-suppressive medication such as PPIs. However, the available data do not report on the clinical implications of the concomitant use of continuous administered cabozantinib and PPIs. For instance, the two pivotal trials of cabozantinib in mRCC, METEOR (NCT01865747) and CABOSUN (NCT01835158), avoided the concomitant use of PPIs and cabozantinib, although PPI usage was allowed at least 2 hours (preferably 4 hours) after taking cabozantinib and at least 14 hours before the next dose of cabozantinib, if possible [6, 7]. The CANTATA trial (NCT03428217), in which cabozantinib is administered with the glutaminase inhibitor telaglenostat or placebo, in contrast, excluded patients who required continued PPI use after randomization. In this article, we investigate the impact of PPIs on the efficacy and safety outcomes of patients with mRCC treated with cabozantinib.

Materials and Methods

Study Design and Outcomes

The mRCC cohort of patients treated at Gustave Roussy prospectively included all adult patients with biopsy-proven mRCC starting February 2014. All adult patients who received cabozantinib at any point during treatment for mRCC were selected from this cohort. These patients are followed-up regularly in consultation every 2 weeks during the first month, then every 4 weeks subsequently with clinical examination and a blood test, and every 12 weeks with an imaging assessment. Details concerning patient characteristics, pathology, prognostic factors based on International mRCC Database Consortium (IMDC) risk groups, previous therapeutic strategies including the history of primary tumor resection, and lines of treatment were collected. The use of PPIs was also collected according to the specific agent used and duration. Patients who received PPIs for at least 3 weeks during the treatment with cabozantinib were considered as PPI users; otherwise, patients were considered PPI nonusers. All the patients included in the pharmacokinetics cohort were evaluated for therapeutic adherence at the time blood draw was performed. Therapeutic adherence was defined by the number of days of cabozantinib intake reported by the patient divided by 28. For the evaluation of response, computed tomography imaging was locally reviewed by the same radiologist (A.B.Z.) according to RECIST version 1.1. Cabozantinib-related adverse events were defined and evaluated according to the Common Terminology Criteria for Adverse Events, version 5.0. Patients with missing concomitant medication information and those receiving a cabozantinib-based combination were excluded from the analysis.

Pharmacokinetics Analysis

We conducted a separate study in an independent cohort of patients treated with cabozantinib for mRCC and enrolled in a routine monitoring pharmacokinetic (PK) study (INDS MR 5612140520). All the patients had already received cabozantinib and a PPI concomitant for at least 30 days at the time of PK analysis. Plasma samples for PK assay were obtained at least 7 hours after the last cabozantinib dose and were analyzed through a validated tandem liquid chromatography–mass spectrometry method. Residual (Ctrough) was estimated by using a standard pharmacological equation (Cmin = Cmeas × 0.5 dosing interval − $24/t_{1/2}$, where Cmin is the estimated residual concentration of cabozantinib and Cmeas is the concentration of cabozantinib measured with liquid chromatography–mass spectrometry), starting from measured cabozantinib concentration.

Statistical Analysis

Descriptive statistics were used to describe patient characteristics, including pathology and lines of treatment and overall response rates (ORR). The χ^2 test , Student *t* test or Mann-

Table 1. Demographic and disease characteristics of the patients at study inclusion

Characteristic	PPI users, *n* = 43 (43.4%)	PPI nonusers, *n* = 56 (56.6%)	*p* value
Age, median (range), yr	62 (30–78)	58 (22–78)	.377
Male gender, *n* (%)	26 (60.5)	41 (73.2)	.179
Histology, *n* (%)			.105
Clear cell RCC	36 (83.7)	39 (69.6)	
Nonclear cell RCC, *n* (%)	7 (16.3)	17 (30.4)	
IMDC risk groups, *n* (%)			.507
Good risk	6 (13.9)	13 (23.2)	
Intermediate risk	28 (65.1)	33 (58.9)	
Poor risk	9(20.9)	10 (17.8)	
Previous nephrectomy, *n* (%)	35 (81.4)	47 (83.9)	.740
Cabozantinib line of treatment, *n* (%)			.130
First and second line	10 (23.3)	21 (37.5)	
Third line and beyond	33 (76.7)	35 (62.5)	

Abbreviations: IMDC, International Metastatic RCC Database Consortium; PPI, proton pump users; RCC, renal cell carcinoma.

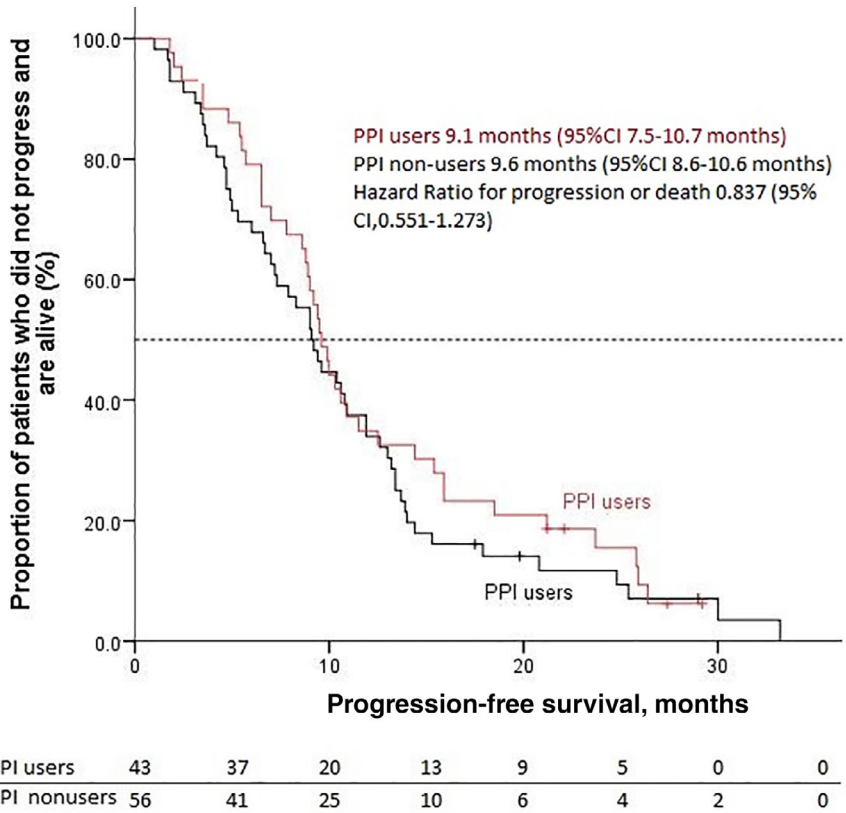

Figure 1. Kaplan-Meier estimates of progression-free survival.
Abbreviations: CI, confidence interval; PPI, proton pump inhibitor.

Withney *U* test was used to assess the difference between the groups as appropriate. Parametric or nonparametric distribution of continuous variables was assessed per Shapiro-Wilk test. The median PFS and OS were estimated using the Kaplan-Meier method. PFS was defined from the date of the cabozantinib initiation to the date of progression or death, and OS was defined from the date of cabozantinib initiation to the date of death. Patients who did not progress and were alive at the time of analysis were censored at the time they were last seen for PFS and OS analyses, respectively. Comparisons according to the patient demographics and disease characteristics were performed with the use of a log-rank test with a two-sided α level. HRs and associated 95% CIs were calculated with the use of a Cox proportional-hazard model for uni- and multivariate analysis. All statistical analyses were performed using IBM SPSS Statistics version 20.

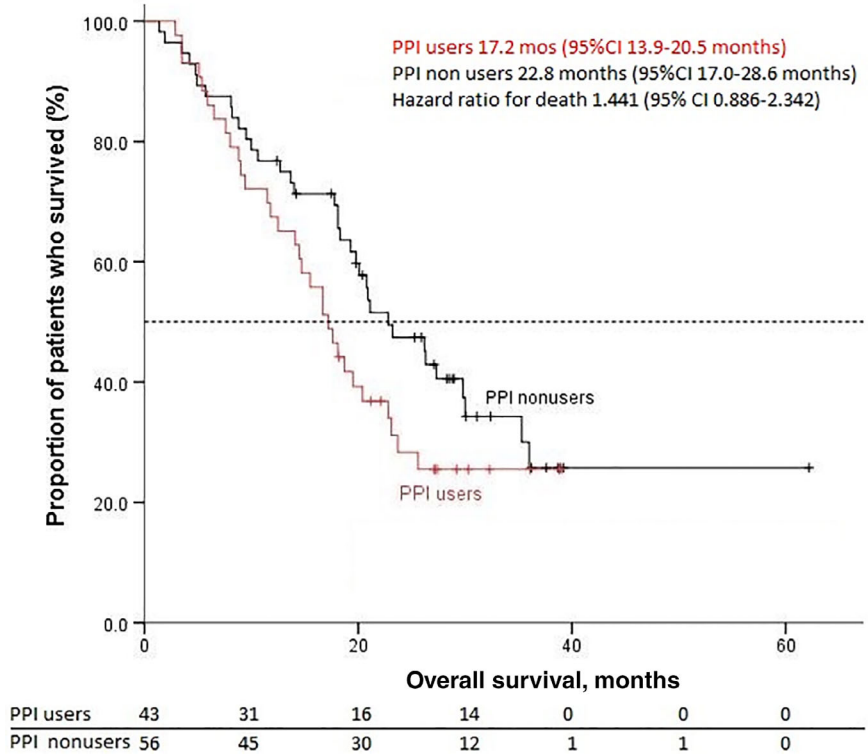

Figure 2. Kaplan-Meier estimates of overall survival.
Abbreviations: CI, confidence interval; PPI, proton pump inhibitor.

Table 2. Efficacy outcomes of cabozantinib in patients with mRCC according to PPI use

Efficacy outcomes	PPI users, *n* = 43 (43.4%)	PPI nonusers, *n* = 56 (56.6%)	*p* value
Overall response rate, *n* (%)	14 (33.4)	21 (38.2)	.674
Disease control rate, *n* (%)	40 (95.2)	49 (89.1)	.464
Median PFS, (95% CI) mo	9.6 (95% CI, 8.6–10.6)	9.1 (95% CI, 7.5–10.7)	.402
HR (95% CI)	0.837 (0.551–1.273)	0.837 (0.551–1.273)	
Median OS, (95% CI) mo	17.2 (95% CI, 13.9–20.5)	22.8 (95% CI, 17.0–28.6)	.138
HR (95% CI)	1.441 (0.886–2.342)	1.441 (0.886–2.342)	

Abbreviations: CI, confidence interval; HR, hazard ratio; mRCC, metastatic renal cell carcinoma; OS, overall survival, PFS, progression-free survival; PPI, proton pump inhibitor; TTF, time-to-treatment failure.

Results

Patient and Disease Characteristics

A total of 103 patients were identified from the electronic records as having received cabozantinib therapy for mRCC. Four patients were excluded from this analysis, as they received cabozantinib-based combinations. Of the 99 eligible patients, median age was 61 years, and most patients were male (67 patients; 67.7%) and had clear cell histology (75 patients; 75.8%). With regard to IMDC risk groups, most patients had an intermediate-risk disease (61 patients; 61.6%), whereas the rest had a poor-risk score (19 patients; 19.2%) or a good-risk score (19 patients, 19.2%). The majority of patients received cabozantinib as a third or further line treatment (68 patients; 68.7%).

Forty-three patients (43.4%) were considered PPI users. The most widely used PPI was omeprazole at 40 mg daily dose (23 patients; 53.5%), followed by esomeprazole at 40 mg (13 patients; 29.3%), pantoprazole at 20 mg (3 patients; 6.9%), lansoprazole at 30 mg (3 patients; 6.9%), and rabeprazole (1 patient; 2.2%). No other acid suppressor agents such as histamine 2 receptor antagonists were administered. The majority of PPI users (60.5%) received PPIs for a preexisting medical condition (such as gastro-esophageal reflux disease, hiatal herniation, and symptomatic dyspepsia), whereas a minority (17 patients, 39.5%) were prescribed PPIs to manage cabozantinib-related adverse events (such as nausea, vomiting, or both). The baseline characteristics were generally well balanced between the concomitant PPI users (56 patients; 56.6%) and PPI nonusers (43 patients; 43.4%, Table 1).

Effect of PPI Use on Efficacy Outcomes

With a median follow-up of 30.3 months from cabozantinib initiation, 82 events of treatment failure, 92 events of progression or death, and 67 deaths had occurred. The median TTF was 12.7 months (95% CI, 9.5–16.0), the median PFS was

Table 3. Adverse events and reasons for treatment discontinuation

	PPI users, *n* = 43 (43.4%)		PPI nonusers, *n* = 56 (56.6%)		
Adverse events	**Grade 1–2, *n* (%)**	**Grade 3–4, *n* (%)**	**Grade 1–2, *n* (%)**	**Grade 3–4, *n* (%)**	***p* value**
Diarrhea	27 (64.3)	1 (2.4)	33 (58.9)	0 (0)	.401
Nausea	15 (34.9)	0 (0)	26 (46.4)	2 (3.4)	
Loss of appetite	19 (45.2)	0 (0)	15 (27.3)	2 (3.6)	.106
Dyspepsia	10 (23.8)	0 (0)	11 (2.0)	0 (0)	.652
Mucositis	15 (35.7)	1 (2.4)	21 (38.2)	0 (0)	.510
Vomiting	11 (26.2)	0 (0)	8 (14.5)	3 (5.5)	.131
Increased liver function tests	19 (46.3)	0 (0)	25 (45.5)	0 (0)	.931
Hyponatremia	11 (26.8)	0 (0)	17 (3.9)	0 (0)	.664
Weight loss[a]	21 (53.8)	4 (10.2)	24 (47)	5 (9.8)	.488
Cabozantinib dose reduction	36 (83.7)	36 (83.7)	36 (64.3)	36 (64.3)	.031
Reasons for treatment discontinuation					.587
Progression	20 (46.5)	20 (46.5)	31 (55.4)	31 (55.4)	
Adverse events	11 (25.6)	11 (25.6)	10 (17.9)	10 (17.9)	

[a]Data at every visit unavailable for 9 patients: 5 PPI users and 4 PPI nonusers
Abbreviation: PPI, proton pump inhibitor.

Table 4. Demographic and disease characteristics of the patients included in the independent pharmacokinetics cohort*

Characteristic	**PPI users, *n* = 21 (42%)**	**PPI nonusers, *n* = 29 (58%)**	***p* value**
Age, median (range), yr	58 (40–79)	57 (22–73)	.748
Male gender, *n* (%)	17 (80.9)	23 (79.3)	.354
Histology, *n* (%)			
Clear cell RCC	17 (80.9)	21 (72.4)	.068
Nonclear cell RCC	4 (19.1)	8 (27.6)	
Cabozantinib line of treatment, *n* (%)			.130
First and second line	5 (23.3)	8 (27.6)	
Third line and beyond	16 (76.7)	21 (72.4)	
Median duration of treatment, wk	26.7	39.6	.794
Cabozantinib dose intensity[b]/blood draw, *n* (%), mg per day			.117
20	1 (3.1)	4 (8)	
28.57	7 (21.9)	4 (8)	
30	0	1 (2)	
35.71	0	1 (2)	
40	17 (53)	14 (28)	
42.85	3 (9.4)	8 (16)	
50	0	1 (2)	
60	3 (9.4)	13 (26)	

[a]16 patients are included in both the clinical study set and the pharmacokinetic cohort.
[b]Cumulative cabozantinib dose received in the previous 4 weeks divided by 28.
Abbreviations: IMDC, International Metastatic RCC Database Consortium; PPI, proton pump users; RCC, renal cell carcinoma.

9.4 months (95% CI, 8.6–10.2), and the median OS was 20.1 months (95% CI, 16.4–23.8). Overall, the results were similar when the efficacy outcomes were assessed according to PPI use (for PFS and OS, Figs. 1, 2; Table 2). The ORR and DCR as assessed by blinded, independent central radiologic review were 33.4% and 95.2% in the PPI users group and 38.2% and 89.1% in the PPI nonusers group, respectively.

In univariate analysis, a longer PFS was associated with a good and intermediate-risk IMDC score at cabozantinib start (HR, 0.346; 95% CI, 0.164–0.729; p = .005 and HR, 0.425; 95% CI, 0.231–0.785; p = .006), whereas longer OS was correlated to good IMDC score at treatment start (HR, 0.153; 95% CI, 0.054–0.432, p < .001). In the multivariate analysis, a longer PFS was associated with good and intermediate-risk IMDC score (HR, 0.345; 95% CI, 0.162–0.734, p = .006 and HR, 0.48; 95% CI, 0.253–0.91, p = .025, respectively). A longer OS was associated with a good-risk IMDC score (HR, 0.144; 95% CI, 0.048–0.428; p < .001); a trend for

Table 5. Overview of the published data reporting on the efficacy outcomes of tyrosine kinase inhibitors among mRCC patients with and without concomitant proton pump inhibitor use

Study	TKI	Number of patients	Outcomes (nonusers vs users)	Comment
Ha et al. (2015) [8]	Sunitinib	231, 45 PPI users (19.4%)	mPFS 5.9 vs 4.7 months (p = .04); mOS 15.6 vs 10.2 months (p = .02)	
Lalani et al. (2017) [17]	Sunitinib, axitinib, sorafenib	2,188, 120 PPI users (5.5%)	mPFS 8 vs 5.5 months (p = 0 .902); mOS 21.3 vs 21.1 months (p = .754)	Patients enrolled in clinical trials
McAllister et al. (2018) [16]	Pazopanib	90, 63 PPI users (70%), 66 PPI + H2 antagonist users (73.3%)	mPFS 9.0 vs 11.0 months (p = .85); mOS 28.0 vs 30.1 months (p = .92)	Survival analysis performed by grouping all acid suppressing drug users
Sharma et al. (2019) [18]	Sunitinib	847 mRCC; 22.7% (whole study population including NSCLC, CML, pancreatic cancer and HCC)	HR for death at 90 days 0.99, (95% CI, 0.66–1.49); HR = 0.98, (95% CI, 0.77–1.25)	Medicare retrospective study performed on several diseases. Data for mRCC extrapolated

Abbreviations: CI, confidence interval; CML, chronic myeloid leukemia; HCC, hepatocellular carcinoma; HR, hazard radio; mOS, median overall survival; mPFS, median progression-free survival; mRCC, metastatic renal cell carcinoma; NSCLC, non-small cell lung cancer

a longer OS was observed in patients with an intermediate-risk IMDC score and those who have undergone a previous nephrectomy (HR, 0.529; 95% CI, 0.279–1.003; p = .051 and HR, 0.492; 95% CI, 0.293–1.015; p = .055, respectively). PPI use was not associated with survival in either the univariate or in the multivariate analysis.

Effect of PPI Use on Safety Outcomes

Adverse events attributed to cabozantinib included diarrhea in 61.6% (grade 3–4, 1%), nausea in 43.4% (grade 3–4, 2%), loss of appetite in 36.3% (grade 3–4, 2%), dyspepsia in 21.2% (grade 3–4, not reported), mucositis in 37.4% (grade 3–4, 1%), vomiting in 20.2% (grade 3–4%, 3%), increased liver function tests in 44.4% (grade 3–4, not reported), and weight loss in 57,8% (grade 3, 10 %). Overall, the incidence of the reported adverse events was similar between the PPI users and nonusers. PPI users required dose reductions more often (83.7% vs. 64.3%; p = .041), but the treatment discontinuation did not differ between the two groups (72.1% vs. 73.3%, p = .587; Table 3).

Effect of PPI Use on Cabozantinib Ctrough

Fifty patients treated with cabozantinib were enrolled in the pharmacokinetics study, of whom 21 (42%) received concomitant PPIs for at least 30 days. Therapeutic adherence in this patients' cohort, expressed as proportion of days covered, was 93.5%: 93.2% for PPI users and 94.5% for PPI nonusers. Seven out of 21 patients (33.3%) received PPIs to manage cabozantinib-related adverse events, whereas the rest received PPIs for other medical conditions. Sixteen patients from this cohort were also included in the retrospective survival analysis. The characteristics of the patients did not differ between PPI users and nonusers (Table 4). The most widely used PPI was omeprazole at 40 mg (10 patients; 47.6%), followed by lansoprazole at 30 mg (5 patients; 23.8%), esomeprazole at 40 mg (4 patients; 19.1%), and pantoprazole at 20 mg (2 patients; 9.5%). No patient in this cohort was treated with other acid-suppressive agents (e.g., histamine 2 receptor antagonists). A total of 82 plasma samples were considered as evaluable for this analysis: 32 obtained from PPI users and 50 from PPI nonusers. There was no significant difference between the two groups of patients (see supplemental online Fig. 1).

Discussion

We hypothesized that the efficacy outcomes of cabozantinib in patients with mRCC could be lower in PPI users because the solubility of cabozantinib is decreased in a higher gastric pH. From a chemical point of view, cabozantinib can be present either in an ionized or a nonionized form, depending on the gastric pH and the acid-base dissociation constant of the drug [15]. Ionized forms normally dissolve easier than nonionized forms, thus leading to a wider absorption; however, the concomitant use of PPI increases the gastric pH, and thus it may potentially decrease the drug absorption [14]. The results of this analysis showed that PPI use does not negatively impact the efficacy and safety of cabozantinib in patients with mRCC.

The available evidence reporting on the effect of concomitant PPIs with other TKIs in mRCC remains inconclusive. A retrospective study including 90 patients with mRCC treated with pazopanib, of whom 66 concomitantly received an acid-suppressing drug, showed similar efficacy outcomes between PPI users and nonusers (median PFS 9.0 vs 11.0 months [p = .85] and median OS 28.0 vs 30.1 months [p = .92]) [16]. Another retrospective study including 231 patients with mRCC treated with sunitinib, of whom 45 were PPI users, showed a shorter survival among PPI users (median PFS 5.9 vs 4.7 months [p = .04] and median OS 15.6 vs. 10.2 months [p = .02]) [8]. A large retrospective study of 2,188 patients with mRCC treated with sunitinib, axitinib, or sorafenib, of whom 120 patients were PPI users, showed similar efficacy between PPI users and nonusers (median PFS 5.5 vs. 8.0 months [p = .902] and median OS 21.1 vs. 21.3 [p = .754]) [17]. In a large SEER-Medicare retrospective study performed on 12,538 patients with cancer aged more than 65 years receiving concomitantly a PPI and a TKI for various oncological indications (such as erlotinib for non-small cell lung cancer, dasatinib and nilotinib for chronic myeloid leukemia, and sorafenib and

sunitinib for mRCC), the concomitant use of PPIs and TKIs was reported in 22.7%. This study showed a higher risk of death at 90 days and 1 year for PPI users (HR, 1.16; 95% CI, 1.05–1.28 and HR, 1.10; 95% CI, 1.04–1.17, respectively). However, when the analysis was restricted to 847 patients receiving sunitinib for mRCC, no difference in 90-day and 1-year survival was demonstrated (HR, 0.99; 95% CI, 0.66–1.49 and HR, 0.98; 95% CI, 0.77–1.25 respectively) [18]. Table 5 gives an overview of the published data reporting on the efficacy outcomes of tyrosine kinase inhibitors among patients with mRCC with and without concomitant PPI use.

Our analysis did not show a significant difference in the median PFS or OS between PPI users and nonusers. This is consistent with the available cabozantinib pharmacokinetics data that did not demonstrate a reduction in the AUC of cabozantinib in healthy volunteers treated with esomeprazole [14]. No relevant differences were noted in terms of safety between the two groups although a higher proportion of PPI users required dose reduction of cabozantinib, which did not seem to impact the clinical efficacy. A plausible explanation for our observation is the prescription of cabozantinib in the morning and the PPI in the evening, which may diminish the impact of the PPI on the absorption of cabozantinib. The effect of PPI may last longer than 12 hours, but the absorption of cabozantinib might not have been affected in a clinically significant manner that would influence the patient outcomes [19].

In our cohort, the median Ctrough of cabozantinib did not differ between PPI users and nonusers. Our pharmacokinetic results are consistent with those deriving from the phase I pharmacokinetic study of cabozantinib, which did not demonstrate a relevant difference in terms of Cmax and AUC 0–infinity in healthy volunteers treated with a single oral dose of cabozantinib before and after the use of PPI [13].

The rate of PPI use in the clinical trial of TKIs in patients with mRCC compares differently to those in the real-world setting [17]. The results of this study are relevant to the daily clinical practice because the prevalence of PPI use (43.4%) parallels that of patients in the clinical setting, as almost 20% of patients take PPIs at baseline and 21.2% (our series) of patients develop dyspepsia attributed to cabozantinib prescription [20]. As such, it is more plausible that our cohort represents the patients encountered in daily practice having more competing comorbidities and requiring polymedications [21].

To our knowledge, this study is the first to specifically report on the impact of PPI use on the outcomes of cabo zantinib in patients with mRCC. The data set is prospectively collected, the imaging assessment is blindly and centrally reviewed, and the details about the specific PPI and schedule are available. More broadly, our study results are in line with previous clinical experiences of concomitant PPI and TKI use in mRCC patients. The clinical efficacy and safety outcomes of our patients are comparable with those of patients enrolled in the pivotal clinical trials and the largest retrospective series currently published [6, 7, 22, 23]. Nevertheless, solid conclusions are limited by the relatively small sample size, the retrospective nature of the study, and the lack of standardized indications for PPIs, which are prescribed at the discretion of the treating oncologist. Furthermore, therapeutic adherence was assessed prospectively for the patients included in the pharmacokinetics cohort and through patient self-reporting, a therapeutic adherence tool that may be biased by patients' over-reporting of drug adherence [24]. However, the self-reported adherence rates to cabozantinib were comparable between the PPI users and nonusers; therefore the impact of the therapeutic adherence in this cohort can be considered negligible. Taking into consideration the pharmacologic data and the safe use of PPIs with other TKIs may suggest that PPIs do not impact the efficacy or safety of cabozantinib. The current development of cabozantinib as a drug is centered on combination regimens with either immune-checkpoint inhibitors or CB 839, a glutaminase inhibitor. It is noteworthy that our results cannot be extrapolated to cabozantinib-based combinations with immune checkpoint inhibitors (nivolumab in the CheckMate 9ER [NCT03141177], nivolumab plus ipilimumab in COSMIC-313 [NCT03937219], and atezolizumab in CONTACT 03 [NCT03170960]) [24–27]. Thus, PPIs may influence the efficacy of immune checkpoint inhibitors by modifying the gut microbiota [28, 29]. Conversely, PPI use is not allowed for patients enrolled in the phase II trial CANTATA in which cabozantinib is administered with placebo or CB 839.

Conclusion

Approximately 43% of patients with mRCC used PPIs during cabozantinib treatment. The concomitant use of PPIs did not significantly impact the efficacy and safety of cabozantinib in patients with mRCC. The pharmacologic cohort did not identify significant differences associated with PPI use. Thus, clinicians may consider allowing patients to remain on concomitant PPIs for clinically appropriate indications.

Author Contributions

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Disclosures

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