Drug-drug interactions between pazopanib and proton pump inhibitors may significantly affect clinical outcome of patients affected by metastatic renal cell carcinoma

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Abstract

Background Proton pump inhibitors (PPIs) are widely used in cancer patients to mitigate adverse gastroesophageal events polypharmacy-associated. However, pharmacokinetic data showed that concomitant administration of pazopanib and PPIs leads to decreased plasma concentrations and exposure of pazopanib by 40% (Cancer Chemother Pharmacol 2013;71:1635–1643).

The current study aimed at investigating the effect of concomitant PPIs on pazopanib progression free survival (PFS) in patients affected by metastatic renal cell carcinoma (mRCC).

Patients and Methods mRCC patients candidate to pazopanib as first line treatment were enrolled in this retrospective observational study. Patients were defined as «no concomitant PPIs» if no PPIs were administered during pazopanib, and as «concomitant PPIs» if the administration of PPIs covered the entire or not less than 2/3 of treatment with pazopanib. All clinical interventions were made according to clinical practice.

Results A total of 126 patients were enrolled; median PFS to pazopanib was 12 months. Fifty-nine patients belonged to «no concomitant PPIs» during pazopanib treatment and 67 to the «concomitant PPIs» group. Most prescribed PPIs were lansoprazole and pantoprazol. The overall population was stratified according to PFS, showing no difference in the two groups (p=0.95). Patients were then stratified based on median PFS as «short» (n=70) and «long» (n=56) responders. In the long responders group, there was a significant difference in terms of PFS in patients assuming vs not assuming PPIs, being 24.7 vs 45.5 months, respectively (p=0.03). Multivariate analysis included gender, age, ECOG, nefrectomy, radiotherapy, number of metastatic sites, and IMDC score and confirmed the use of concomitant PPIs as the only independent predictive factor for shorter PFS (p=0.04).

Conclusions This study demonstrates that concomitant use of PPIs in mRCC patients treated with pazopanib forlong time has a detrimental effect on PFS. Therefore, it is recommended to prescribe PPIs with strict compliance with the registered indications and for short periods, or use alternative gastroprotective procedures.

Background and Aim

The clinical pharmacokinetics of many tyrosine kinase inhibitors (TKIs) is characterized by pH-dependent solubility, and co-treatment with gastric acid suppressants in patients taking these types of molecules may decrease drug exposure and efficacy (Clin Pharmacol Ther. 2012;92(2):203-13). A pooled analysis conducted on metastatic renal cell carcinoma (mRCC) patients within phase II and III clinical trials showed that the use of proton pump inhibitors (PPIs) did not appear to negatively affect the efficacy and safety of selected antiangiogenic drugs, including sunitinib, axitinib, and sorafenib (Clin Genitourin Cancer. 2017;15(6):724-732). In a pharmacokinetic study carried out in a small cohort of patients with solid tumors treated with pazopanib and esomeprazole, the area under the concentration-time curve (AUC) and maximum concentration (Cmax) of pazopanib were reduced by 40% and 42%, respectively (Cancer Chemother Pharmacol. 2013;71(6):1635-4). Furthermore, it has been demonstrated that the minimum concentration (Cmin) levels of pazopanib were lower in patients who received PPIs, as compared with non-users (Int J Cancer. 2021;148(11):2799-2806). The current study aimed at investigating the effect of concomitant PPIs on pazopanib progression free survival (PFS) in patients affected by mRCC.

Patients and methods

mRCC patients candidate to pazopanib as first line treatment were enrolled in this retrospective observational study. Patients were defined as «no concomitant PPIs» if no PPIs were administered during pazopanib, on the contrary, patients were classified as «concomitant PPIs» if the administration of PPIs covered the entire or not less than 2/3 of treatment with pazopanib.

All pharmacological and clinical interventions were made according to clinical practice. Pazopanib and PPis were administered as per drug label.

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 Ethic Committee and conducted in accordance with the Helsinki Declaration. All alive patients released a written informed consent.

Statistics

Categorical variables including ECOG, nefrectomy, radiotherapy, number of metastatic sites, and IMDC score were described by absolute and relative frequencies, while quantitative factors by median and range. PFS was defined as the time from treatment start to progression disease. The Kaplan–Meier method was used to create survival curves and 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 performed with MedCalc Statistical Software version 14.8.1 (MedCalc Software, bvba, Ostend, Belgium).

Results

A total of 126 patients were enrolled; median PFS to pazopanib was 12 months. Fifty-nine patients belonged to «no concomitant PPIs» during pazopanib treatment and 67 to the «concomitant PPIs» group. No statistically significant differences were found comparing the «no concomitant PPIs» vs «concomitant PPIs» based on their clinical characteristics.

Most prescribed PPIs were pantoprazol (46.3%) and lansoprazole (31.3%).

The overall population was stratified according to PFS based on the administration of pazopanib and PPIs. The results showed no difference in the two groups, with a median of PFS 8.9 vs 13.7 months (p=0.95) in patients assuming vs not assuming concomitant PPIs (**Figure 1**).

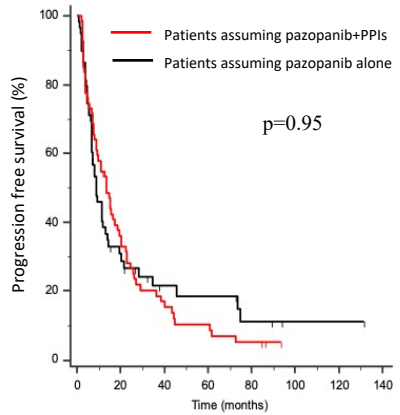

Figure 1: PFS of patients assuming pazopanib +/- PPIs

Results

Based on median PFS, patients were stratified as «short» (PFS<12 months; n=70) and «long» (PFS>12 months; n=56) responders. Patients divided in the two groups were again stratified accordingly to PPIs yes/no assumption. Interestingly, in the long responders group, there was a significant difference in terms of PFS in patients assuming vs not assuming PPIs, being 24.7 vs 45.5 months, respectively (n= 35 vs 21, p=0.03; **Figure 2A**). No significant difference was found in the short respoders group (p=0.5; **Figure 2B**).

Multivariate analysis included gender, age, ECOG, nefrectomy, radiotherapy, number ofmetastatic sites, and IMDC score and confirmed the use of concomitant PPIs as the only independent predictive factor for shorter PFS (p=0.04).

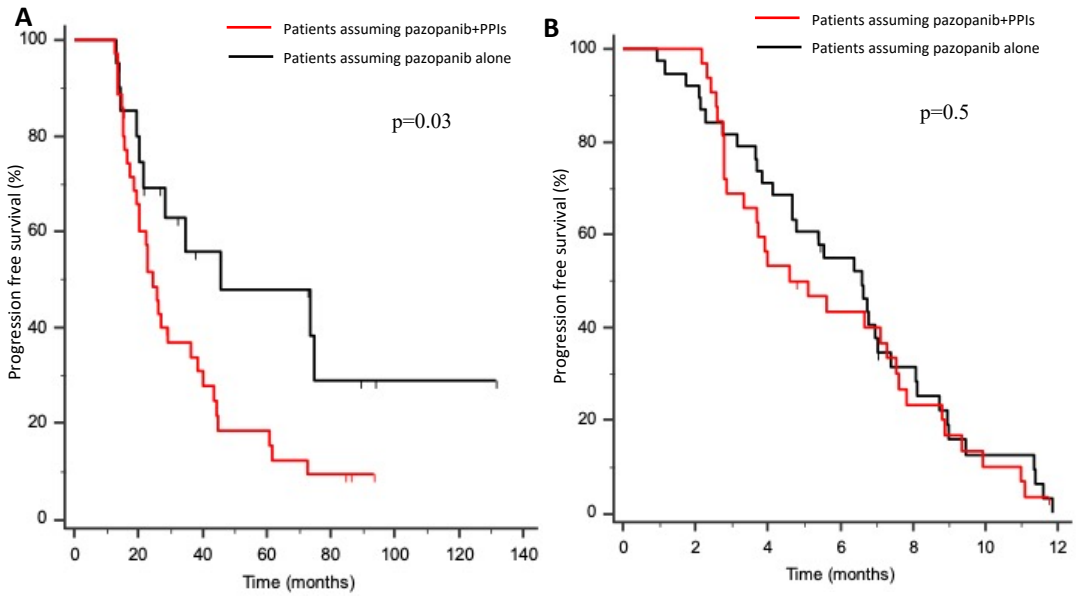

Figure 2: A) PFS of «long responders» patients assuming pazopanib +/- PPIs; **B**) PFS of «short responders» patients assuming pazopanib +/- PPIs;

Conclusions

This study demonstrates that concomitant use of PPIs in mRCC patients treated with pazopanib for long time has a detrimental effect on PFS. Therefore, it is recommended to prescribe PPIs with strict compliance with the registered indications and for short periods, or use alternative gastroprotective procedures.

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