Background: The multikinase inhibitor regorafenib (REG) is currently registered for the treatment of colorectal cancer (CRC), gastrointestinal stromal tumors (GIST), and hepatocellular carcinoma. REG exhibits a pH-dependent solubility, and therefore acid reducing drugs such as proton pump inhibitors (PPIs, e.g. esomeprazole) might reduce REG absorption by increasing the stomach pH as was shown for many other kinase inhibitors (van Leeuwen, Lancet Oncol, 2014). We performed a randomized, 3-phase, cross-over trial to compare the exposure of REG alone to REG with esomeprazole (concomitantly or 3 hours prior to REG intake) in CRC and GIST patients.

Methods: Patients were randomized into 2 sequence groups consisting of 3 phases: REG intake alone, REG with concomitant esomeprazole (for 5 days), and REG 3 hours preceded by esomeprazole (for 5 days). Pharmacokinetic (PK) blood sampling was performed at the 21st, 49th and 77th day of the trial. All patients were treated with REG 120 mg at steady-state. Primary endpoint was the relative difference (RD) in geometric means for REG AUC0-24h. A linear mixed model was used to analyze log-transformed area under the curve (AUC). For multiple testing a Bonferroni correction was applied.

Results: A total of 14 patients were evaluable for the primary endpoint. Exposure (AUC0-24h) to REG alone was: 55.9 μg*h/mL (CV: 40.3%). For REG with concomitant esomeprazole or with esomeprazole 3 hours prior AUC0-24h was: 53.2 μg*h/mL (CV: 33.5%) and 53.6 μg*h/mL (CV: 42.6%) respectively. No significant differences were identified when REG alone was compared to REG with concomitant esomeprazole (RD: -3.9%, 95% CI: -20.5–16.1%, p = 1.0) or REG with esomeprazole 3 hours prior (RD: -4.1%, 95% CI: -22.8–19.2%, p = 1.0). Furthermore, no significant differences were observed in other PK parameters of REG and its active metabolites M-2 and M-5 (i.e. Cmax, Tmax). Most common adverse events ≥ grade 2 were hypertension (71%), fatigue (43%) and hand foot skin reaction (36%).

Conclusions: The use of esomeprazole concomitantly or 3 hours prior to REG intake did not alter REG pharmacokinetics. Our results indicate that PPIs like esomeprazole can be combined with REG without the appearance of a significant drug interaction.

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