gastrointestinal tumours, non-colorectal

PROTON PUMP INHIBITOR (PPIs) THERAPY MAY IMPAIR CAPECITABINE (CAPE) EFFICACY IN METASTATIC GASTROESOPHAGEAL CANCER (GEC), RESULTS FROM THE TRIO-013/LOGIC TRIAL

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Aim: Cape is used to treat GI and other malignancies. Oral drug absorption often relies on pH-dependent solubility. Many GEC patients (pts) take PPIs for symptom control, which increases gastric pH and PPIs have been shown to impact other anti-cancer drug activity. TRIO-013 is a phase III randomized trial of cape + oxaliplatin (CapeOx) with lapatinib or placebo in HER2-positive metastatic GEC. Outcomes in both arms were comparable with modern GEC studies, but adding lapatinib did not improve progression free (PFS) or overall survival (OS). This ad hoc study analysed PPI effects in both arms.

Methods: Study data were reviewed. PPI use was documented by medication records. Given reported improvement on survival in younger (<60 years), Asian, and female pts, age, gender, stage (metastatic/advanced), histology (intestinal/diffuse), and race were controlled in Cox proportional hazards modeling. Comparisons of PFS and OS were made between PPI vs. no-PPI.

Results: 545 pts were randomized 1:1 between CapeOx + lapatinib or placebo. 229 pts received PPIs (42.0%), split evenly between arms. High cape dose intensity was maintained in both arms and yet CapeOX toxicity was lower than expected. In placebo arm, PPI pts had poorer median PFS, 4.2 vs. 5.7 mo (hazard ratio [HR] 1.55, 95% CI 1.29-1.81, p = 0.0008); and OS, 9.2 vs. 11.3 mo (HR 1.34, 95% CI 1.04-1.64, p = 0.04) vs. no-PPI pts. In multivariate analysis considering age, race, stage, and gender, PPI-pts had poorer PFS (HR 1.64, 95% CI 1.38-1.90, p = 0.0002) and OS (HR 1.36, 95% CI 1.06-1.66, p = 0.03). In the lapatinib arm, PPIs had less effect on PFS (HR 1.08, p = 0.54) and OS (HR 1.26, p = 0.10). However in multivariate analysis, there was a significant difference in OS (HR 1.36, 95% CI 1.06-1.66, p = 0.03).

Conclusions: PPIs negatively impacted cape efficacy possibly by raising gastric pH leading to altered cape solubility and absorption. These results are consistent with erlotinib and sunitinib studies. Whether PPIs affected lapatinib is unclear given concurrent cape use. Given cape’s prevalence in breast and colon cancer, further studies are underway.

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