Germline TYMS genotype is highly predictive in patients with advanced colorectal and gastroesophageal cancer independent of fluoropyrimidine pharmacology: Results from two prospective translational studies

M. Joerger1, A.D.R. Huitema2, H. Boot3, A. Cats1, V. Doodeman4, P. Smits4, L. Vainchtein2, H. Rosing2, I. Meijerman5, M. Zueger6, T.T. Cerny1, J.H.M. Beijnen2, J. Schellens7

1Dept. of Oncology, Kantonsspital St. Gallen, St. Gallen, SWITZERLAND
2Department of Pharmacy & Pharmacology, Slotervaart Hospital/The Netherlands Cancer Institute, Amsterdam, NETHERLANDS
3Department of Gastroenterology, Antoni van Leeuwenhoek Hospital/The Netherlands Cancer Institute, Amsterdam, NETHERLANDS
4Department of Molecular Biology, Slotervaart Hospital/The Netherlands Cancer Institute, Amsterdam, NETHERLANDS
5Faculty of Science, Department of Pharmaceutical Sciences, Utrecht University, Utrecht, NETHERLANDS
6Division of Clinical Pharmacology and Toxicology, University Hospital, Basel University, Basel, SWITZERLAND
7Department of Clinical Pharmacology, Antoni van Leeuwenhoek Hospital/The Netherlands Cancer Institute, Amsterdam, NETHERLANDS

Aim: Germline gene polymorphisms may impact clinical outcome in patients with gastrointestinal malignancies, but there are no data on the interaction between chemotherapy pharmacokinetics (PK) and gene polymorphisms, to assess their independent predictive value.

Methods: Two studies prospectively assessed 44 gene polymorphisms in 16 genes (TYMS, MTHFR, GSTP1, -M1, -T1, DPYD, XRCC1, XRCC3, XPD, ERCC1, RECQ1, RAD54L, ABCC1, ABCG2, UGT1A1) by Sanger sequencing in 64 patients with advanced colorectal cancer (CRC) receiving capecitabine/oxaliplatin chemotherapy, and 76 patients with advanced gastroesophageal (GE) cancer receiving epirubicin/cisplatin/capecitabine (ECC) chemotherapy, respectively. Plasma concentrations of all anticancer drugs were sampled for up to 24 hours, analyzed using validated LC-MS/MS (capecitabine), HPLC (epirubicin) and flameless atomic absorption spectrometry (platinum), and results submitted to population PK analysis using non-linear mixed effects modeling. We calculated the association between gene polymorphisms, anticancer drug exposure, radiological tumor response, progression-free survival (PFS), overall survival (OS) and chemotherapy-related toxicity using appropriate statistical tests.

Results: Patients with a low clearance of the active metabolite 5FU had an increased risk of neutropenia in both groups (p<0.05), and a higher risk of hand-foot syndrome (HFS) in patients receiving ECC (p=0.002). Mutant variants of DPYD T85C, T1896C, IVS14+1G>A and A2846T were associated with diarrhea (p<0.05), mutant variants DPYD T85C, T1896C and A2846T with HFS (p<0.02). The TYMS high-expression genotype (promoter variants 2R/3G, 3C/3G or 3G/3G) was significantly associated with worse PFS in the CRC (HR=2.0, p=0.006) and GE group (HR=6.55, p<0.001) and worse OS in the GE group (p<0.001). In the CRC group, GSTP1 mutant variant was significantly associated with an improved PFS (HR=0.55, p=0.001) and OS (HR=0.60, p=0.002).

Conclusions: Carriers of the TYMS high-expression genotype have a markedly inferior outcome when receiving capecitabine-based chemotherapy for advanced colorectal or gastroesophageal cancer. Therapeutic targeting of this molecularly-defined subgroup of patients should be explored to improve their prognosis.

Disclosure: All authors have declared no conflicts of interest.