# Population PK/PD model of capecitabine to predict neutrophil dynamics incorporating pharmacogenetic evaluation of ABC gene polymorphisms.

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**[Objetivo]** The aims of the current work are (i) to develop a population PK/PD model able to account for the neutropenic effects after the oral administration of capecitabine (CAP) in colorectal cancer patients with different polymorphisms of the ABC gene, and (ii) to optimize the dosing strategy based on the established PK/PD relationship for each sub-group of population enrolled.

**[Metodos]** A prospective observational post-authorization study between February 2015 and August 2016 was carried out in the Doctor Peset University Hospital of Valencia in patients with colorectal cancer. CAP was administered in different schedules with doses between 850-1250 mg/m$^2$ orally twice a day. Plasma measurements of CAP, 5-DFUR and 5-FU were obtained at 1h, 2h and 3h post-administration. A single observation of neutrophil count levels was measured between day 15-24 post-administration.

**[Resultados y Discusión]** 48 patients were included in our study in which 432 plasma levels of CAP, 5-DFUR and 5-FU were collected. First-order absorption and metabolism was assumed from CAP to 5-FU through 5-DFUR and first-order elimination processes were assumed for CAP and 5-FU. The clearance values of CAP, 5'-DFUR and 5-FU were 294, 26.8 and 8.97 L/h, respectively. The apparent volume of distribution of CAP (V2) was 449 L, while V3 (5-DFUR) and V4 (5-FU) were fixed at 1L. A total of 85 covariates were collected in the dataset (78 polymorphisms and 7 biochemical, treatment-related and demographic variables). The final PK model incorporates the following covariates: oxaliplatin on absorption lag time, rs6720173 on clearance of 5-DFUR and rs2271862 on clearance of 5-FU. A reduction of 14%, 19%, and 66% in the IIV of each parameter was estimated when PK base and final parameter estimates were compared. 370 neutrophil count observations from 48 patients were included in the PK/PD model development. The base structural PK/PD model included the standard features published by Friberg et al [1]. The baseline absolute neutrophil count level ($E_0$) was 3.54 x19$^9$ cells/mL and a first-order proliferation rate constant ($k_{prol}$) equal to 1.48x10$^{-2}$ h$^{-1}$ (MTT=270 h). IIV was included in all PD parameters. The final PK/PD model included oxaliplatin as a significant covariate on $k_{prol}$, showing a 2.84-fold $k_{prol}$ increase in patients receiving oxaliplatin. The results of the optimal dosing analysis suggest dose levels 500 and 1000 mg bid orally provide less than 20% of patients with $AUC_{168-192}$ greater than 30 mg·h/L with an incidence of neutropenia G3/4 less than 20%,

irrespective of the co-administration of oxaliplatin. On the other hand, M rs2271862-W and M-M sub-groups would be able to receive a dose of CAP in the range of 500 and roughly 2500 mg bid orally, as the probability of AUC>30 and incidence of neutropenia G3/4 is less than 20% both. The administration of CAP as a single agent would not show incidence of neutropenia G3/4 higher than 20% at any dose level, whereas in combination therapy with oxaliplatin, dose ≥1500 mg bid orally might overcome the safety threshold.

**[Conclusiones]** A model-based dosing strategy has been successfully applied to select the optimal dosing schedule of capecitabine in colorectal cancer patients with different polymorphisms of ABC gene (rs2271862) based on the probability of neutropenia G3/4 incidence.