

Influence of pharmacogenetic polymorphisms on 5-fluorouracil and irinotecan efficacy and tolerance in patients treated for advanced colorectal cancer.

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Abstract: **Introduction:** The purpose of the present study was to determine genetic and pharmacokinetic factors to tailor 5-FU and Irinotecan administration and determine the impact of individual dose-adjustment in first-line chemotherapy of advanced colorectal cancer. Patients and **Methods:** from 90 patients with metastatic colorectal cancer treated with fluorouracil, leucovorin and irinotecan (FOLFIRI), 1) blood DNA samples were collected: thymidilate synthetase, dihydropyrimidine dehydrogenase, methylene tetrahydrofolate reductase and UGT 1A1 germinal polymorphisms; 2) dihydrouracil/uracil plasma ratio and 5-FU plasma clearance were determined. They were investigated and correlated for tolerance and efficacy. The initial 5-FU dose was 2,500mg/m² then tailored using pharmacokinetic monitoring. Statistical analysis used the χ^2 test, linear regression analysis and the Kaplan-Meier method. **Results:** This treatment was well tolerated with few severe toxic side-effects (8.7%). The overall response rate was 42.3%, the median overall survival and median progression-free survival were 28 and 10 months respectively. UGT 1A1 7/7 (13.4%) and certain DPD genotypes (5%) were statistically correlated with a higher risk of toxicity (26% and 100% grade III-IV neutropenia and diarrhoea) and UGT 1A1 7/7 a lower response rate (17%). The overall survival time of the patients with 3R/3R TS genotype associated with MTHFR C/C for 677 C>T or A/A for 1298A>C (20 patients=22%) was not statistically different than the other genotype. **Conclusions:** This protocole was efficient and well tolerated thank to 5-FU dose adjustment that lowered the incidence of severe toxic side-effects. For CPT11, the risk of severe toxicity was statistically higher for 7/7 group and consecutively associated with a lower response rate. DPD SNP's and UGT 1A1 genotyping combined to individual dose-adjustment with a pharmacokinetic follow-up must be considered in FOLFIRI to optimize response rate and decrease severe adverse side effects.