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Session E. Gastrointestinal (colorectal) cancer

E07 DPYD c.1905 + 1G > A and c.2846A > T and UGT1A1*28 allelic variants as predictors of toxicity: Pharmacogenetic translational analysis from the phase III TRIBE study in metastatic colorectal cancer

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Background: Adverse drug reactions (ADRs) caused by fluoropyrimidines depend, at least in part, from DPD deficiency resulting from the loss-of-function mutations c.1905 + 1G > A and c.2846A > T. Moreover, irinotecan ADRs appear frequently in patients bearing the *UGT1A1**28 variant, associated with reduced UGT1A1 expression. In this study, we analyse the association between *DPYD* and *UGT* variants with ADRs by 5-fluorouracil and irinotecan in subjects enrolled within the phase III TRIBE study, whose final results have been recently reported.

Methods: Out of 508 randomized patients, blood samples for pharmacogenetic analyses were available for 440 patients. DNA was extracted from 200 µl of blood and analyses of *DPYD* c.1905 + 1G > A, c.2846T > C and *UGT1A1**28 was performed by a Pyrosequencing platform (Qiagen, USA). The study was approved by the local Ethics Committee.

Results: Each of the *DPYD* c.1905 + 1GA and c.2846AT genotypes were found in 5 out of 440 subjects, with a combined frequency of 2.2%. c.1905 + 1GA and c.2846AT had the same impact on ADRs and, taken together, patients bearing these variants (N = 10) had an increased risk of G3/4 neutropenia (OR: 4.14, p = 0.043) and stomatitis (OR: 10.36, p = 0.003) as compared to wild-type patients. Five out of 10 DPYD mutant patients experienced a G4 ADR after the first cycle of therapy. *UGT1A1**28/*28 was found in 39/436 patients (8.9%); these patients had an increased risk of G3/4 neutropenia as compared to both *1/*1 (OR: 3.81, p < 0.001) and *1/*28 (OR: 2.28, p = 0.022) genotypes. Patients bearing *DPYD* c.1905 + 1GA, c.2846AT and *UGT1A1**28/*28 (N = 49) had an increased risk of G3/4 neutropenia (OR: 2.98, p < 0.001), febrile neutropenia (OR: 2.78, p = 0.023) and G3/4 stomatitis (OR: 6.83, p < 0.001). No significant correlation with G3/4 diarrhea was found.

Conclusions: *DPYD* c.1905 + 1GA, c.2846AT and *UGT1A1**28/*28 are associated with a higher risk of G3/4 ADRs also in the TRIBE trial, underscoring the predictive role of *DPYD* and *UGT1A1* variants across various fluoropyrimidine and irinotecan-containing schedules, and therefore their potential usefulness in treatment tailoring.