Common and rare DPYD variants are predictive for 5FU/capecitabine (SFU) toxicity: The MRC COIN and COIN-B trials


1Medical Oncology, Clatterbridge Cancer Center, Wirral, UK, 2Clinical Trials Unit, MRC, London, UK, 3CRUK/MRC Oxford Institute for Radiation Oncology, University of Oxford, Oxford, UK, 4Division of Cancer and Genetics, Cardiff University, Cardiff, UK, 5Hammersmith Hospital, Imperial College Healthcare NHS Trust, London, UK

Background: Rare genetic variants in DPYD increase toxicity and screening for them prevents serious complications by upfront reduction in SFU dose; however, most patients with severe toxicities do not have a rare mutation. We have previously shown that 2 common DPYD variants were associated with toxicity in patients with advanced colorectal cancer treated on COIN & COIN-B (abstract 3509, ASCO 2013): Cys29Arg [rs1801265] (Minor Allele Frequency (MAF) 0.21) and Val732Ile [rs1801160] (MAF 0.04). We have now genotyped 4 rare variants using the same cohort.

Methods: Blood samples were available from 2183 patients treated with first line oxaliplatin-5FU + cetuximab. We assayed IVS14 + 1G>A [rs3918290], Asp949Val [rs67376798], Lys259Glu [rs45589337] and Ser534Asn [rs1801158] using KASPar. Primary endpoint was dose reduction or delay in chemotherapy in the first 12 weeks of treatment due to any toxicity except neuropathy. Secondary endpoints were grade ≥2 versus grade <2 for neutropenia, leucopenia, Nausea & Vomiting (N&V), diarrhoea, stomatitis, Hand-Foot Syndrome (HFS) and infection.

Results: Two rare variants were associated with toxicity (OR 95% CI): Asp949Val with neutropenia 3.2 (1.2-8.2) P = 0.019, N&V 3.4 (1.5-7.3) P = 0.002, diarrhoea 4.6 (2.1-10.1) P < 0.001 and infection 5.3 (1.3-24.2) P = 0.024; IVS14 + 1G>A with leucopenia 5.3 (1.9-14.9) P = 0.002, diarrhoea 4.4 (1.7-11.0) P = 0.002, stomatitis 4.6 (1.7-12.6) P = 0.003, HFS 3.8 (1.2-11.8) P = 0.021 and infection 19.2 (5.0-73.8) P < 0.001. MAF was 0.007 and 0.005, respectively. The effect on toxicity for our 2 common variants was not as marked (OR 95% CI): Cys29Arg 0.8 (0.7-1.0) P = 0.008 (protective) and Val732Ile 1.6 (1.1-2.1) P = 0.006 for the primary endpoint.

Conclusions: We have validated 2 mutations, Asp949Val and IVS14 + 1G>A, as predictors for 5FU toxicity in a large cohort of patients and recommend they should be screened for. Our data suggest that common DPYD variants are also associated with toxicity but not to the same level seen with rare ones. While the presence of a single common variant is not an indication for dose modification, the presence of multiple variants in a patient might be. Further work is needed to establish what combinations of common DPYD variants would necessitate SFU dose alteration.

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