Novel Genetic Variants in Carboxylesterase 1 Predict Severe Early-Onset Capecitabine-Related Toxicity

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An important concern with the anticancer drug capecitabine (Cp), an oral prodrug of 5-fluorouracil, are dose-limiting adverse effects, in particular hand-foot syndrome (HFS) and diarrhea. Here we evaluated the association of genetic variability in all enzymes of the Cp-activation pathway to 5-fluorouracil with Cp-related early-onset toxicity in 144 patients receiving Cp. We identified a haplotype encompassing five variants in the carboxylesterase 1 (CES1) gene region including an expression quantitative trait locus associated with early-onset Cp-toxicity (Haplotype A3: ORadditive = 2.2, 95% CI 1.2-4.0, Padjusted = 0.012; ORrecessive = 10.3, 95% CI 2.1-49.4, Padjusted = 0.0038). Furthermore, the association of two linked cytidine deaminase (CDA) promoter variants (c.1-451C>T: ORdominant = 4.3, 95% CI 1.3-14.2, Padjusted = 0.017; and c.1-92A>G: ORdominant = 4.4, 95% CI 1.3-14.5, Padjusted = 0.015) with Cp-related diarrhea was replicated. This first study identifying an association of genetic variation in CES1 with Cp-related toxicity provides further evidence for the existence of a functional noncoding CES1-variant with a possible regulatory impact.