Letter to the Editor

Clinical Cancer Research

A CDD Polymorphism as Predictor of Capecitabine-Induced Hand–Foot Syndrome—Letter

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In their recently published clinical study (1), Caronia and colleagues investigated various polymorphisms affecting 5 key enzymes implicated in the pharmacogenetics of the widely prescribed drug capecitabine as putative markers for treatment-related toxicities. They conclude, from this candidate-gene approach, that severe hand–foot syndrome (HFS) could be attributed to the deleted allele of rs3215400 across the cytidine deaminase (CDD) promoter.

Because this deleted allele was associated with increased CDD gene expression and enhanced transcription, extensive CDD phenotype could also explain the higher incidence of capecitabine-induced HFS, although surprisingly, no data on its impact on other toxicities (e.g., hematologic) were made available. At our institute, we have found evidence of lethal toxicity from capecitabine intake, which occurred in a woman with an extensive CDD phenotype (2), thus showing that CDD deregulation could indeed be associated with life-threatening toxicities in capecitabine-treated patients. As outlined by Caronia and colleagues, genotype-to-phenotype relationships with CDD are, however, far from being clear, and the relevance of the 79 A>C polymorphism for anticipating severe toxicities from gemcitabine treatment remains in question (3). Such debate is not surprising, given the numerous events that interfere with establishment of genotype-to-phenotype relationships, as many polymorphisms have yet to be discovered; also, CDD epigenetics are far from being elucidated (3). Concerning the relevance of the rs3215400 genetic variation, similar conflicting results are available in light of a previous study that failed to find an association between this very polymorphism and HFS (4). Caronia and colleagues provide *in silico* evidence that the C deletion abolishes a binding site for the transcriptional regulator E2F, leading to enhanced CDD transcription *in vitro*. However, according to dbSNP, the allelic frequency of this variant is surprisingly high (0.564 vs. 0.436 for the C allele) and does not match the frequency of the extensive phenotype recorded in our own patients (3). Consequently, and because no single-nucleotide polymorphism entirely accounts for the variability in CDD activity among patients, haplotype analysis might be a more powerful way to predict CDD transcription, as suggested by other studies (5).

In conclusion, we believe that, along with dihydropyrimidine dehydrogenase (DPYD) impairment, screening for CDD polymorphisms, including rs3215400, is probably of interest as a means to identify patients at risk of developing HFS upon capecitabine intake. However, in light of our own expertise, we consider that a functional approach (e.g., phenotyping patients) is another mandatory step to fully address the issue of CDD status determination and its actual impact on capecitabine-related severe toxicities.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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