EDITORIAL |

DPYD Variants to Predict 5-FU Toxicity: The Ultimate Proof

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Based upon the evidence that pyrimidinemia was familial and caused by a genetic deficiency in the dihydropyrimidine dehydrogenase gene (*DPYD*) (1), the seminal discovery on the heritability of 5-fluorouracil (5-FU) toxicity (2) opened the gate to the flood of studies on the genetic predisposition to severe toxicity in patients treated with fluoropyrimidines. In this issue of the Journal, Lee et al. (3) report the results of a pharmacogenetic study in colorectal cancer patients treated with 5-FU–based therapy in the adjuvant setting. It provides the ultimate evidence for variation in the *DPYD* locus as a major determinant of patient safety. *2A and D949V are two *DPYD* variants with a strong effect size (odds ratios [ORs] of 15.21 and 9.10, respectively) for "5-FU-related" grade 3 or higher toxicities, with a strong association also for all grade 3 or higher toxicities. Hence, the occurrence of these heritable variants poses a considerable risk for patients and a challenge to patient management to preserve dose intensity.

This is the largest single study of 5-FU pharmacogenetics, where *DPYD* genotype results are available from 2600 patients. Moving forward, phase III trials of this size will be more the exception than the rule, but there is no doubt that trials conducted within cooperative groups (like this one) will continue to be incubators of practice-changing discoveries (4). The genotyped patient population is homogeneous, in terms of disease stage and treatments. Population heterogeneity coupled with a less than 0.1% frequency of these two alleles, led to several conflicting results on their predictive role. In the pharmacogenetics field as a whole, a plethora of small underpowered studies claimed the validation of heritable biomarkers of drug response, leading to inconsistent results and very few markers in the clinic (5).

For *2A and D949V, all the tenets of a clinically applicable pharmacogenetic marker are met. First, the variants are functional, resulting in either an inactive dihydropyrimidine dehydrogenase enzyme (*2A) or an enzyme with reduced activity (D949V). Second, because 5-FU catabolism by dihydropyrimidine dehydrogenase is a major pathway of 5-FU clearance, carriers of *2A and D949V have higher exposure to 5-FU. Third, as a consequence of the relationship between 5-FU pharmacokinetics and toxicity, carriers of *2A and D949V have a higher risk of adverse reactions. Unlike many other claimed associations, there is a clear link between the DNA change, the pharmacology of the drug, and the clinical effect.

In other relatively large studies, *2A had only a limited predictive role in patients treated with 5-FU monotherapy (n = 683) (6), while it had a strong effect (in addition to D949V) when 5-FU was given in combination (n = 487) (7). In colorectal cancer patients treated with capecitabine-based therapy in the adjuvant setting, the combination of both *2A and D949V led to an odds ratio of 5.5 for capecitabine-related toxicities (8). It can be postulated that

therapies in combination with fluoropyrimidines might enhance the risk of toxicity in *DPYD*-deficient patients, increasing the sensitivity of highly-replicating normal cells when pyrimidine catabolism is altered by an inactive dihydropyrimidine dehydrogenase. An additional deficient variant (*13) was also tested in Lee et al. (3), but conclusions on its clinical value could not be drawn, probably because of its frequency being even lower than *2A and D949V.

Despite the laudable efforts of the US Food and Drug Administration (FDA) to introduce pharmacogenetic language to drug labels, there is only a handful of genetic tests for safety of cancer drugs, which are only sporadically used by clinicians (9). Is it because there is still insufficient evidence for their clinical utility? Or because clinicians prefer to stick to traditional (nongenetic) practice without having to deal with a genetic test, the implications of which they cannot fully understand? Or is it because recommendations on their use are imprecise and generally inconsistent? Genotyping is now affordable and cheap, and patient genotypes are already preemptively stored in electronic medical records at major institutions applying exome or genome sequencing to their patients. Often third parties are likely to reimburse pharmacogenetic testing if guidelines exist on the use of the test results. However, scientific societies and regulatory bodies have only partially embraced the use of *DPYD* genetic testing. Their recommendations have been described in detail elsewhere (10). They span from the American Society of Clinical Oncology and the National Comprehensive Cancer Network not mentioning *DPYD* testing to the FDA and the European Medicines Agency listing *DPYD* deficiency as a contraindication to treatment with fluoropyrimidines.

Dosing recommendations are available from the Clinical Pharmacogenetics Implementation Consortium (11) and the Dutch Pharmacogenetics Working Group (12). In these guidelines, a fluoropyrimidine would be contraindicated in deficient homozygous patients for either one of *2A, D494V, and *13 (one deficient allele in each chromosome, complete deficiency). In the study of Lee et al. (3), the only patient with complete deficiency (a compound heterozygous for *2A and D494V) died because of complications of severe toxicity (a grade 5 event) after cycle 1. Moreover, in heterozygous patients (one deficient allele only, partial deficiency), it is recommended they receive at least a 50% dose reduction of the fluoropyrimidine at first cycle, with upward titration in subsequent cycles. The Solomonic decision (ie, cutting the starting dose by half) for *DPYD* heterozygotes is based upon the effect of these variants on 5-FU clearance, rather than formal dose-finding studies like the ones conducted for irinotecan in patients with different *UGT1A1* genotypes (13,14), which are difficult to perform for these *DPYD* variants due to their low frequency.

Because disease-free survival is not worse in *DPYD*-deficient patients in this study, lessons should be learned from the results of Lee et al. (3) on how to individualize treatment and manage toxicity in heterozygous, *DPYD*-deficient patients for whom a fluoropyrimidine is still a viable option. While *2A carriers were less likely to complete all 12 cycles than noncarriers (56.0% vs 74.5%, P = .04), the *2A status was not associated with a considerably higher percentage of patients receiving dose modifications (80.0% for carriers, 74.3% for noncarriers, P = .65). Information about differences in dose intensity between carriers vs noncarriers was not provided by Lee et al. (3), and more granular data on the overall management of therapy on *DPYD*-deficient patients was needed from this study, including the necessary percentage reduction in dosing and the use of supportive therapy, so that tailored approaches could be used in the future.

In light of the current results, clinicians are strongly encouraged to consider testing for *2A and D949V in patients treated with either 5-FU– or capecitabine-based regimens. Understanding the implications of *DPYD* deficiency will lead to a more precise management of cancer patients treated with these agents.

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Note

The author has no conflicts of interest to disclose.

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