COMMENTARY

Universal Pretreatment *DPYD* Genotyping in Fluoropyrimidine Candidates: Still Controversial but With Clear Instructions for Practitioners, at Last!

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Fluorouracil (FU) and its oral prodrugs, capecitabine and tegafur, are the backbone of numerous combination regimens for the treatment of solid neoplasms, despite severe-to-fatal toxicities associated with their administration. The cause for the adverse drug reactions was often found in the reduction or the lack of dihydropyrimidine dehydrogenase (DPD) activity because of *DPYD* gene allelic variants.[1] Several studies have been performed to define an appropriate strategy for identifying patients at major risk of severe or lethal toxicities, including the universal pretreatment *DPYD* genotyping in patients who are candidates for fluoropyrimidine treatment. Although this approach remains controversial, in this issue of *JCO Oncology Practice*, Innocenti et al[2] provide a timely, precise, and accurate guide to help practitioners decide whether patients require *DPYD* genotyping prior to starting fluoropyrimidine-based chemotherapy. Indeed, their aim is to give updated information on the *DPYD* genetic tests in terms of which patients need the test, which kind of test should be performed and where, and when testing should be done in relation to chemotherapy. The guidelines will help oncologists to have informed discussions with their patients.

For some authors, the analysis of *DPYD* variants alone is only moderately predictive of DPD deficiency. Therefore, DPD phenotyping, such as the dihydrouracil:uracil ratio, could be considered the most appropriate method to screen for DPD deficiency, either on its own or in association with genotyping.[3] However, in recent years, the genetic analysis of *DPYD* allelic variants took place until recommendations from the European Medicines Agency (EMA) advised performing genetic tests on all patients who are candidates for fluoropyrimidines.[4] The success and diffusion of genetic tests for *DPYD* in contrast to other methods (ie, pharmacokinetics, plasma uracil, and drug monitoring[5]) are likely due to the relative ease of collecting samples for genetic testing, the performance of tests, and their lower costs if compared with those related to the management of fluoropyrimidine-related toxicities.[6] Nonetheless, some uncertainties linger.

As demonstrated by Schwab et al,[7] *DPYD* genetic variants are one of many factors that may influence fluoropyrimidine tolerability. Besides the presence of *DPYD* alleles with reduced enzyme activity, female sex, folate intake, and a higher rate of drug infusion may also increase the risk of toxicities. These characteristics may explain how pharmacogenetic tests of *DPYD* cannot prevent all toxicities, as Innocenti et al[2] stress in their discussion of the specificity and sensitivity of DPD genetic testing. Thus, the performance of *DPYD* testing and the absence of known *DPYD* allelic variants associated with severe toxicities should not induce a false sense of security in oncologists and patients. Moreover, the impact of reduced DPD activity on the severity of treatment-induced toxicities may be dependent on the fluoropyrimidine administered and its dose.[8] In the presence of a reduced (but not completely absent) DPD enzyme activity, low doses are recommended, and this may be more easily manageable in the daily practice with the use of an oral prodrug.[9]

The issue of severe-to-fatal toxicities associated with fluoropyrimidine administration has an indissoluble bond with another question relevant to treatment efficacy. Although the noninferior efficacy of a reduced dosage of FU has been shown in patients with colorectal cancer and *DPYD* allelic variants in a randomized prospective clinical trial,[10] no similar data are available for other tumor types such as breast or head and neck cancer. Moreover, if a reduced starting FU dosage could be correctly suggested based on *DPYD* genotyping, it should be pursued with the objective of personalizing the FU dose. This may be escalated based on reported toxicities and individual tolerance or, if possible, individual drug pharmacokinetics to ensure the best adherence to the treatment while pursuing its therapeutic efficacy. Finally, another issue is the level of recommendations for *DPYD* genetic tests. The recent EMA document that highly recommends the pharmacogenetic analysis of *DPYD* gene in a patient candidate to fluoropyrimidines is reasonable given the unquestionable safety reasons. Therefore, to

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avoid any medical or legal issues, oncologists are asked to plan a pretreatment screening for their patients with all the characteristics identified by Innocenti et al.[2] These recommendations will require all laboratories to adopt proper testing procedures that include all the allelic variants associated with partially reduced or absent enzyme activity. If a hospital's laboratory cannot implement such tests in their methodologies, an easy flow to perform the test in other institutions should be put in place to guarantee the cure and the safety of patients undergoing treatment.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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