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Opinion Article

Pharmacogenetics Variants in *DPYD* and the Risk of Fluoropyrimidine Toxicity in Cancer Therapy

Juliana Ortega*

Department of Molecular Oncology and Pharmacogenetics, National University of Córdoba, Córdoba, Argentina

DESCRIPTION

Fluor pyrimidines, including 5-Fluorouracil (5-FU) and its oral prodrug capecitabine, are essential chemotherapeutic agents for treating a wide range of solid tumors such as colorectal, breast and gastric cancers. While effective, these agents are associated with severe toxicities in a subset of patients, ranging from microsites and neutropenia to life-threatening gastrointestinal or hematologic complications. Pharmacogenetics variations in the Dihydropyrimidine Dehydrogenase (*DPYD*) gene have been identified as a major contributor to this interindividual variability in drug tolerance.

In a recent prospective study conducted at the Córdoba Oncology Research Institute, 348 patients undergoing 5-FU or capecitabine treatment were screened for the four key *DPYD* variants. Approximately 7% of patients carried one of the deleterious alleles and over 75% of them experienced grade 3 or higher toxicities despite receiving standard dosing. In contrast, patients with wild-type genotypes had a significantly lower incidence of adverse events, reinforcing the role of *DPYD* polymorphisms in fluoropyrimidine intolerance.

Based on such compelling data, several international bodies, including the European Medicines Agency (EMA) and Clinical Pharmacogenetics Implementation Consortium (CPIC), now recommend pre-treatment *DPYD* genotyping to identify patients at risk. For heterozygous variant carriers, dose reductions of 25–50% are advised, while complete deficiency may necessitate alternative therapies altogether. These recommendations have been implemented in national healthcare guidelines in countries such as the Netherlands, France and the UK.

In Argentina, *DPYD* testing is increasingly being adopted in major oncology centers, although it is not yet standard across all public hospitals. The Pharmacogenomics Unit at the National University of Córdoba has developed an in-house validated panel for rapid genotyping of the four high-risk variants, offering results within 48 hours. This initiative has already prevented numerous cases of avoidable hospitalization due to fluoropyrimidine toxicity.

From a Pharmacoproteomic standpoint, measurement of DPD enzyme activity in Peripheral Blood Mononuclear Cells (PBMCs) provides an additional functional assessment. While genotyping predicts potential risk, enzyme assays can capture the combined effect of genetics, epigenetics and environmental influences. Integrating both methods may offer the highest predictive accuracy in clinical decision-making.

In clinical oncology, patients with *DPYD* variants often require careful dose titration, intensive monitoring and personalized supportive care strategies. Furthermore, there is growing interest in using uridine triacetate, an FDA-approved antidote for 5-FU toxicity, in *DPYD*-deficient patients who inadvertently receive standard dosing. However, its availability and cost remain limiting factors in many healthcare systems.

Recent pharmacoeconomic evaluations have demonstrated that routine *DPYD* genotyping prior to initiating fluoropyrimidine therapy is cost-effective. Preventing a single hospitalization from severe toxicity often offsets the cost of several hundred genetic tests. More importantly, genotype-guided dosing can preserve patient quality of life and enable continuation of effective chemotherapy without delay.

DPYD variants significantly increase the risk of fluoropyrimidine-related toxicity and preemptive genetic screening offers a practical strategy to personalize chemotherapy. As pharmacogenomics continues to gain ground in oncology, incorporating *DPYD* genotyping into routine practice can improve safety, optimize dosing and enhance treatment outcomes for cancer patients receiving fluoropyrimidine-based regimens.

***Correspondence to:** Juliana Ortega, Department of Molecular Oncology and Pharmacogenetics, National University of Córdoba, Córdoba, Argentina, E-mail: j.ortega.oncopharm@univcordoba.ar

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