ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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How to Implement *DPYD* Genotyping Into Practice

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H&O Can you explain what the dihydropyrimidine dehydrogenase (*DPYD*) gene does?

AV The *DPYD* gene encodes the dihydropyrimidine dehydrogenase (DPD) enzyme, which degrades excess thymine and uracil that have not been incorporated into DNA. At least some DPD function is required for people to survive. DPD function is clinically relevant when people are receiving high levels of fluoropyrimidine drugs, specifically 5-fluorouracil (5-FU) and capecitabine. Fluoropyrimidine drugs interfere with the ability of cancer cells to replicate by replacing the body's normal pyrimidine, which is a crucial organic compound that serves as a building block for DNA and RNA.

Back in the 1970s and 1980s, researchers realized that people who had poor DPD function were experiencing toxicities from 5-FU that were related to the body's inability to clear the agent. This was an important finding, especially given that 5-FU remains a mainstay of treatment for many types of cancer, including colon cancer.

H&O How common is DPD deficiency?

AV Complete DPD deficiency is very uncommon, probably affecting no more than 1 in 10,000 patients with cancer. We are much more likely to see partial DPD deficiency, which affects approximately 6% to 8% of the population. Approximately 4% of the Western population has a variant in *DPYD**2A, *DPYD**9B, *DPYD**13, or *DPYD* HapB3. These variants have been reasonably well characterized and clearly put patients at high risk for toxicity. There are hundreds of other less well studied variants, however, and many have not been studied enough to have been assigned a functional status. Therefore, more inclusive genetic variant assays are more likely to identify variants of uncertain significance that, by default, will likely lead to unnecessary dose reductions.

Someone who has 2 nonfunctioning *DPYD* variants will not be able to tolerate fluoropyrimidines at all, whereas someone who has 1 normal allele and 1 nonfunctioning or poorly functioning allele may have half or 75% of the normal function of DPD.

H&O When should *DPYD* genotype testing be conducted?

AV The US Food and Drug Administration (FDA) added a boxed warning to capecitabine in late 2025 and to 5-FU in early 2026 stating that testing for *DPYD* variants should be conducted before treatment is initiated unless immediate treatment is necessary. An advisory group for the European Medicines Agency has also mandated testing for DPD activity.

The recommendations of the National Comprehensive Cancer Network differ depending on the disease site. For example, the guidelines for colon and rectal cancer have been recommending *DPYD* testing for a few years, whereas the breast cancer guidelines have not. Now that the FDA is recommending testing for everyone, each panel will determine exactly how to implement testing.

H&O What are the most serious toxicities that clinicians should anticipate with fluoropyrimidines, and what is the mortality risk?

AV The most dangerous toxicities we see are severe

mucositis, skin toxicities, hand-foot syndrome, and bowel obstruction. We also see cardiac toxicity because fluoropyrimidines can cause coronary vasospasm, even in people who have normal coronary arteries. We do have a specific protocol to follow in case a patient experiences cardiac toxicity due to 5-FU. In some cases, idiosyncratic mortality caused by coronary heart disease that is unrelated to the genetic clearance of 5-FU occurs in patients undergoing 5-FU treatment.

The rate of mortality due to fluoropyrimidines is approximately 3% to 4% and perhaps 2% to 3% in patients with DPD deficiency, but it is difficult to know the true rate because 5-FU and capecitabine are used in combination with other agents. After drugs have been approved, it is very hard to get at these data.

It is important to remember that a patient can experience fluoropyrimidine toxicity even if the test results are normal for all 13 alleles.

H&O What can you walk through what happens pharmacokinetically when a DPD-deficient patient receives a standard dose of 5-FU or capecitabine?

AV A DPD deficiency means that clearance of the drug is slowed, so potentially toxic metabolites begin to accumulate. Patients end up receiving a higher dose of the medication than was planned, resulting in additional organ exposure to the drugs and their byproducts.

H&O What are the dosing recommendations for patients with a DPD deficiency?

AV The dosing recommendations of the Clinical Pharmacogenetics Implementation Consortium suggest reductions ranging from 25% to 75% depending on the patient's gene function.[1] If we test and see that the patient has no activity in one allele and normal activity in the other allele, we estimate that the patient has approximately half the function of the average person, so we might recommend cutting the dose of 5-FU or capecitabine by 50%. If the patient has intermediate function in one allele and normal function in the other allele, we might recommend cutting the dose by 25%. The plan is to escalate the dose if the patient tolerates the first dose well.

We have less information about how to reduce capecitabine dosing because the drug is designed to be converted to active 5-FU after absorption through the gastrointestinal tract. As a result, we do not understand how to reduce doses of capecitabine nearly as well as we do 5-FU doses in patients with decreased DPD function. We need to be very careful about dose reduction.

I have never seen a patient with complete DPD deficiency, but if I did, I would not use 5-FU or capecitabine.

H&O What type of *DPYD* genotype testing should be conducted?

AV One example is Guardant360 Liquid, which is used to test for *DPYD* variants. At least half a dozen other commercial assays are available, and they are all similar. At the University of California, San Francisco, we have our own assay that we use to look at the 13 *DPYD* variants, as well as some pharmacogenomic variants for other drugs. Most commercial assays look at the 4 alleles in which variants occur most commonly, but the most recent recommendation is to test for at least 13 alleles. I personally think the FDA should have mandated a particular test or listed a range of acceptable tests, but it did not. Now that testing is mandatory, companies are working overtime to get their tests up and running. The turnaround needs to be relatively rapid because we do not wish to delay the use of 5-FU in a patient who really needs it.

The European Medicines Agency also does not mandate a specific genetic test. In France, testing is done by administering a fluoropyrimidine load to a patient and then measuring the clearance of the drug. This is the best way to determine the actual metabolic function of the patient's genes, as opposed to just looking at the enzyme or the gene.

It is important to remember that a patient can experience fluoropyrimidine toxicity even if the test results are normal for all 13 alleles.

H&O Do patients with DPD deficiency require more frequent monitoring?

AV Patients with DPD deficiency do require more frequent monitoring, although I would argue that all patients taking capecitabine require more careful monitoring than they currently receive. One of the flaws in the care of patients taking capecitabine is that both patients and doctors underestimate the danger because the drug is administered as a pill rather than given intravenously. In

fact, administering a drug orally is even more dangerous because patients may continue to take it even when they should not. This is unusual, but in our practice we have a nurse contact patients 3 times a week if they are taking capecitabine because we are wary of possible toxicity. I am compulsive about doing this because when things go bad with capecitabine, they can go bad in a hurry. We generally choose 5-FU over capecitabine at our institution because capecitabine is a highly toxic drug for anyone.

We tell our patients on fluoropyrimidine treatment to check in if they experience nosebleeds, diarrhea, or anything else related to mucositis. If we have any concerns about the drug, we start by halting administration rather than reducing the dose. Our threshold for stopping administration is especially low if the patient is on capecitabine. Because 5-FU is administered as a 48-hour infusion, the agent has typically left the patient's system before toxicities appear. For example, gastrointestinal toxicity generally does not start for at least 48 hours after administration.

Not everyone knows this, but we have an antidote for fluoropyrimidine excess called uridine triacetate (Vistogard, BTG Pharmaceuticals). This agent works by competing for fluoropyrimidine metabolites, diminishing the toxicity of the agent. If we initiate this agent within 96 hours after a severe toxic effect, we have a chance to improve the patient's outcome. This drug is expensive and not extremely effective, but providers need to be aware of its availability because it can be helpful if administered early enough.

H&O What do we know about how dose reductions affect efficacy?

AV Many of us have held off on advocating for mandatory testing because we do not understand the extent to which dose reductions affect efficacy. If we reduce the dose of a drug too much on the basis of genomics, are these patients at risk for a worse cancer outcome? This question is especially relevant in colon cancer, in which 5-FU is part of curative treatment.

The recommendation is to escalate the dose after the first dose if the first dose has been reduced. We want to make sure that the patient receives the maximal clinical benefit. Studies have shown that most patients whose initial dose is reduced do not end up undergoing dose escalation. This is an unfortunate side effect of the logistics of chemotherapy.

We should not allow our concerns about toxicity cause us to underuse these important drugs. In a retrospective study from the Mayo Clinic that was conducted approximately 15 years ago, just one treatment-associated death occurred among 2500 patients who received 5-FU, and that patient had a complex heterozygous mutation.[2] No fatal toxicity occurred in the 50-plus other patients who had a *DPYD* variant that should have markedly reduced their DPD activity, even though doses were reduced only after a toxicity occurred. Although patients in this group experienced a greater number of toxicities, their cancer outcomes were the same as those for the rest of the population.

H&O Are any other patients considered to be at increased risk for toxicity from fluoropyrimidines?

AV People with kidney dysfunction are at increased risk of nephrotoxicity from capecitabine. People with irritable bowel disease or other diarrheal syndromes are also at increased risk for toxicity from fluoropyrimidines. By contrast, a condition like coronary vasospasm is unpredictable.

Women are probably more likely than men to experience toxicity from 5-FU, although it is unclear whether men are simply less likely than women to report the symptoms they experience, such as grade 1 nausea.

H&O In what circumstances would you use a fluoropyrimidine right away, before *DPYD* testing?

AV The rare case in which I would use a fluoropyrimidine before testing would be a patient with obstructing colon cancer who needed immediate treatment, or a patient with jaundice because a cancer was blocking the bile ducts. Fortunately, we expect to have a commercial assay for *DPYD* variants available soon that will be able to produce results in 3 or 4 days. We should even have a bedside assay available in a few years.

Disclosures

Dr Venook has no disclosures.

References

1. Pratt VM, Cavallari LH, Fulmer ML, et al. DPYD genotyping recommendations: a joint consensus recommendation of the Association for Molecular Pathology, American College of Medical Genetics and Genomics, Clinical Pharmacogenetics Implementation Consortium, College of American Pathologists, Dutch Pharmacogenetics Working Group of the Royal Dutch Pharmacists Association, European Society for Pharmacogenomics and Personalized Therapy, Pharmacogenomics Knowledgebase, and Pharmacogene Variation Consortium. *J Mol Diagn*. 2024;26(10):851-863.

2. Lee AM, Shi Q, Pavey E, et al. DPYD variants as predictors of 5-fluorouracil toxicity in adjuvant colon cancer treatment (NCCTG N0147). *J Natl Cancer Inst*. 2014;106(12):dju298.