Understanding Thiopurine Drug Toxicity Testing

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In this *Expert Edge* Q&A, Dr. Johnson-Davis discusses thiopurine drug toxicity testing, which provides vital information for patients with autoimmune disorders, inflammatory bowel disease, and organ transplants. Thiopurine S-methyltransferase (TPMT) is an enzyme encoded by the *TPMT* gene that inactivates thiopurine drugs, which suppress the body's immune system.

Expert Edge

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Q: Why should TPMT enzyme activity be evaluated prior to thiopurine drug therapy?

A: Mutations in the *TPMT* gene can cause TPMT deficiency. The TPMT enzyme is used to metabolize (turn off) thiopurine drug activity. TPMT and xanthine oxidase are involved in purine metabolism; together, they inactivate 90 percent of a drug dose, while only 10 percent of the dose is converted to metabolites that stop inflammation and T-cell proliferation.

Because xanthine oxidase does not exist in bone marrow, the risk for life-threatening bone marrow toxicity depends on TPMT enzyme activity. Patients with low TPMT activity are at increased risk for thiopurine drug-induced toxicity when treated with a standard drug dose, while patients with high TPMT activity may be undertreated.

Q: What is the best way to utilize *TPMT* genotyping or phenotyping tests?

A: *TPMT* genotyping or phenotyping should be performed prior to thiopurine administration to predict the risk of developing severe bone marrow toxicity. For the phenotype (enzyme) assay, patients should not be on thiopurine therapy.

If a patient is on thiopurine therapy, the thiopurine drug metabolite assay can be ordered to assess TPMT activity by measuring levels of 6-methylmercaptopurine and 6-thioguanine nucleotides to determine if the patient has normal metabolism.

The genotype assay can also be ordered post thiopurine drug therapy. If a patient is identified as having low or intermediate TPMT activity, dose adjustments should be made to minimize the risk for bone marrow toxicity and optimize therapy.

Q: What are the limitations of genotype and phenotype testing?

A: Several drugs can alter or inhibit TPMT enzyme activity, which may lead to falsely low results (e.g., TPMT activity in red blood cells can be masked if the patient has received a recent blood transfusion). Saliva genotype assays have been proposed to overcome this limitation.

Conventional *TPMT* genotyping assays are designed to target the most common single-nucleotide polymorphisms (SNPs); however, the test doesn't detect rare alleles.

Q: What is the evidence that genotype and phenotype testing improves patient outcomes?

A: Genetically low TPMT activity was first linked to thiopurine drug-associated, life-threatening toxicities in 1989; since then, multiple studies have confirmed this association.

Based on consistent clinical evidence, the Clinical Pharmacogenetics Implementation Consortium (CPIC) has issued guidelines with strong recommendations for considering alternative agents or drastically reducing doses for patients carrying low or deficient TPMT alleles prior to drug therapy.

TPMT gene and related thiopurines drugs (i.e., thioguanine, mercaptopurine, and azathioprine) were also listed in the table of pharmacogenetic biomarkers in drug labeling by the U.S. Food & Drug Administration.