UGT1A1 (TA)n Polymorphisms

Indications for Ordering

- Dosage planning for individuals
  - Who will receive high-dose irinotecan (>150 mg/m^2)
  - With a personal or family history of sensitivity to irinotecan
  - Who have experienced neutropenia while receiving irinotecan
- Confirm suspected diagnosis of Gilbert syndrome

Test Description

Polymerase chain reaction/fragment analysis

- Alleles tested
  - **36* (TA)5
  - **1* (TA)6
  - **28* (TA)7
  - **37* (TA)8

Tests to Consider

UDP Glucuronosyltransferase 1A1 (*UGT1A1*) Genotyping 0051332

Disease Overview

Pathophysiology

- Uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) enzyme is responsible for the clearance of drugs (eg, irinotecan) and endogenous substances (eg, bilirubin)
- Irinotecan is a topoisomerase I inhibitor
  - Interrupts DNA replication in cancer cells, causing cell death
- Prodrug is metabolized to active metabolite SN-38
  - 100-1,000 times more cytoxic than parent drug
  - Inactivated by UGT1A1
- Decreased UGT1A1 activity reduces ability to metabolize SN-38 to inactive form

Treatment issues

- Irinotecan (CPT-11, Camptosar)
  - Approved for treatment of metastatic colorectal cancer
  - May be used in metastatic lung, brain, and breast cancer
- Irinotecan is associated with severe diarrhea and neutropenia in 20-35% of individuals
  - Toxicity of irinotecan is associated with specific *UGT1A1* genotype variants

Genetics

Gene – *UGT1A1*

Variants

- Polymorphic TA repeat in the TATA element of the 5' promoter region of *UGT1A1* may consist of
  - 5, 6, 7, or 8 repeats
    - 6 is common number of repeats – also known as *UGT1A1*1* (TA)6
- *UGT1A1* variants are also associated with
  - Gilbert syndrome (benign familial hyperbilirubinemia)
  - Crigler-Najjar syndrome (rare form of nonhemolytic jaundice)

Allele frequency

Allele	Caucasians	Asians	African Americans
**1* (TA)6	0.61	0.84	0.47
**28* (TA)7	0.39	0.16	0.43

Test Interpretation

Sensitivity/specificity

- Analytical sensitivity – >99%
- Clinical sensitivity/specificity – risk of irinotecan toxicity by genotype (Marcuello, 2004)

TA genotype	Diarrhea risk	Neutropenia risk	Irinotecan dosing
6/6 (**1/*1*)	17%	15%	Standard
6/7 (**1/*28*)	33%	27%	Based on clinical findings
7/7 (**28/*28*)	70%	40%	Dose reduction recommended

Results

- **36* (TA)5 and **37* (TA)8 are reported
  - Dosing recommendations are less clear for these alleles
- No significant risk of irinotecan toxicity is associated with *UGT1A1* genotype when using low-dose therapy (eg, 15-75 mg/m^2 for 5 days for 2 consecutive weeks)
- Homozygosity for the **28* (TA)7 allele is associated with Gilbert syndrome

Limitations

- Variants other than those targeted will not be detected
- Clinical significance of the rare **36* (TA)5 and **37* (TA)8 alleles in predicting irinotecan toxicities is not well established
- Genetic and nongenetic factors other than *UGT1A1* may contribute to irinotecan toxicity and efficacy
- Diagnostic errors can occur due to rare sequence variations

Reference

Marcuello E, Altés A, et al. UGT1A1 gene variations and irinotecan treatment in patients with metastatic colorectal cancer. Br J Cancer. 2004;91(4):678-682