

ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

Section Editor: Mark J. Ratain, MD

UGT1A1 Genotyping in Patients Undergoing Treatment With Irinotecan

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H&O What is UGT1A1?

FI The *UGT1A1* gene encodes for UDP-glucuronosyl-transferase 1A1, the enzyme responsible for the conjugation of bilirubin. Studies published in the 1990s reported a correlation between a *UGT1A1* polymorphism and Gilbert syndrome, a mild and benign hyperbilirubinemia known to occur in 2–12% of the general population.

H&O What are the characteristics of this polymorphism?

FI The *UGT1A1* polymorphism that was found to be associated with Gilbert syndrome involves an insertion and deletion in the TATA box of the promoter of the *UGT1A1* gene. Specifically, 4 different repeats have been identified: 5, 6, 7, and 8 TA repeats. The 6 and 7 TA repeats are fairly common, while the 5 and 8 TA repeats are less common, found only in individuals of African background. An increased number of repeats is associated with reduced expression of the gene; individuals with 7 TA repeats have a reduced expression of *UGT1A1* compared to individuals with the 6 TA repeat polymorphism. The 7 TA allele is classified as the UGT1A1*28 allele.

H&O What is the clinical relevance of this polymorphism to the treatment of cancer patients with irinotecan?

FI A retrospective study to address this question was conducted in Japan and published in 2000 by Ando and colleagues in *Cancer Research*. According to the report, *UGT1A1* polymorphisms were associated with an increased risk of severe toxicity among patients being treated with irinotecan. Patients were stratified if they had

experienced severe toxicity or not. This study included several different regimens, including variations in dose levels of irinotecan and different therapeutic combinations. Despite this heterogeneity, there was a strong correlation between the presence of the 7 TA repeat *UGT1A1* polymorphism and the severity of toxicity.

H&O What were the specific toxicities observed?

FI The toxicities associated with irinotecan are primarily myelosuppression (neutropenia), and gastrointestinal problems (diarrhea). In the Japanese study, severe neutropenia and diarrhea both correlated with the presence of *UGT1A1* polymorphism.

H&O Has a prospective study evaluating this connection been done?

FI Yes. A prospective study was conducted in Chicago in refractory patients receiving irinotecan monotherapy every 3 weeks at a fixed dose, and the findings were published in the *Journal of Clinical Oncology* in 2004. We found that there was a strong correlation between the presence of the 7 TA allele and the occurrence of severe neutropenia. The prevalence of grade IV neutropenia was 0% among patients with the 6/6 genotype, 12.5% among those with the 6/7 genotype, and 50% among those with the 7/7 genotype.

Interestingly, this study also found a correlation between the levels of total bilirubin measured before the administration of irinotecan and the nadir neutrophil count. Bilirubin was highly correlated with the nadir neutrophil count, suggesting that bilirubin, in the absence of the information on the UGT1A1*28 allele, could be used as an indicator for the toxicity risk.

H&O How has the connection between UGT1A1 polymorphism and irinotecan-associated toxicity been addressed by the US Food and Drug Administration?

FI In November 2004, a US Food and Drug Administration (FDA) Advisory Committee along with representatives from Pfizer met to evaluate whether the irinotecan product label should be revised to incorporate these data. At this meeting it was decided that the label should be

revised to include a statement that patients with the 7/7 genotype who are undergoing irinotecan therapy are at high risk for severe neutropenia, and that these patients should be treated with a lower dose of irinotecan, although the specific level has not been determined. In addition, the label states that patients with other *UGT1A1* genotypes, such as the 6/7 TA repeat, are likely to be at increased risk of severe neutropenia, but may be able to tolerate the standard dose of irinotecan. Two subsequent studies of irinotecan combined with other agents (Rouits et al., 2004; Marcuello et al., 2004) have confirmed the findings of the study conducted at the University of Chicago.

H&O Should all irinotecan therapy candidates be screened for the 7/7 genotype?

FI The product label does not recommend screening for this polymorphism. However, a genetic test can be requested so that a patient can be genotyped prior to therapy. A commercially available test manufactured by Third Wave Technologies has been approved by the FDA as the standard test for *UGT1A1* polymorphism. The test is available through the University of Chicago Genetic Services (Director, Dr. Soma Das). There are potential issues regarding reimbursement for this test of which physicians should be aware.

H&O For patients with *UGT1A1* polymorphisms, how might the therapeutic approach be altered?

FI For colorectal cancer patients, there are other therapeutic regimens that are as effective as irinotecan-based therapy. If a patient is 7/7 homozygous, an alternative regimen might be more beneficial.

H&O What percentages of patients have the most common and serious *UGT1A1* polymorphisms?

FI Among patients with the *UGT1A1* 6 and 7 TA repeat polymorphisms, approximately 50% are homozygous for the 6/6 allele, approximately 40% are heterozygous 6/7, and approximately 10% are homozygous for the 7/7 allele. There are many ethnic variations, and the percentages are different among patients of Asian ethnicity, since there is a lower frequency of the TA 7 allele among this population compared with others.

H&O What is the exact connection between *UGT1A1* polymorphisms and the occurrence of irinotecan toxicity?

FI This connection is related to the metabolism of the active metabolite of irinotecan, SN-38, a topoisomerase-1 inhibitor, which is 100- to 1,000-fold more potent than irinotecan. SN-38 is glucuronidated to an inactive product (SN-38G) by *UGT1A1*. Patients who are deficient for *UGT1A1* due to the presence of the 7/7 genotype have a much higher exposure to the active metabolite after irinotecan administration. Inactivation of SN-38 is reduced in patients with the 7/7 genotype because of reduced expression of the enzyme in the liver, the main site of SN-38 metabolism.

In the study conducted at the University of Chicago, plasma levels of the active metabolite and the glucuronide of the active metabolite were also measured. It was found that there was an increased exposure to the active metabolite among patients with the 7/7 genotype, intermediate exposure to the active metabolite among patients with the 6/7 heterozygous genotype, and lower levels of exposure among patients with the 6/6 genotype. Thus it appears that there is a mechanism at play whereby patients with the 7/7 genotype are exposed to higher levels of the active metabolite, which is active in the tumor but also toxic to normal tissues.

Suggested Reading

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