

Irinotecan Therapy and *UGT1A1* Genotype

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Introduction

Irinotecan is a topoisomerase inhibitor that is widely used in the treatment of cancer. It is often used in combination with other drugs to treat metastatic colorectal cancer. However, irinotecan therapy is associated with a high incidence of toxicity, including severe neutropenia and diarrhea (1, 2).

Irinotecan is metabolized and inactivated by an UDP-glucuronosyltransferase enzyme encoded by the gene *UGT1A1*. UDP-glucuronosyltransferase enzymes are part of the glucuronidation pathway that transforms small lipophilic molecules, such as certain drugs like irinotecan, into water-soluble, excretable metabolites. Variants of this gene, such as *UGT1A1**28, are associated with reduced enzyme activity and an increased risk of irinotecan toxicity. Approximately 10% of North Americans are homozygous for the *UGT1A1**28 allele and are more likely to develop neutropenia following irinotecan therapy (3).

The FDA-approved drug label for irinotecan states that “when administered as a single-agent, a reduction in the starting dose by at least one level of irinotecan hydrochloride injection should be considered for patients known to be homozygous for the *UGT1A1**28 allele. However, the precise dose reduction in this patient population is not known and subsequent dose modifications should be considered based on individual patient tolerance to treatment” (3). A guideline from the Dutch Pharmacogenetics Working Group (KNMP) mentions “although results are not consistent, there is sufficient evidence that a reduction in the initial dose by 30% is required for regimens containing >250 mg/m² of irinotecan prescribed to homozygous carriers of the *UGT1A1**28 allele. This is in agreement with the Food and Drug Administration–mandated label change. No dose reduction is recommended for heterozygous carriers of the *UGT1A1**28 allele because

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dose reduction might result in under treatment” (Table 1) (4). A guideline from the Evaluation of Genomic Applications in Practice and Prevention (EGAPP™) Working Group (published in 2009, prior to the FDA statement or KNMP guideline) states that “the evidence is currently insufficient to recommend for or against the routine use of *UGT1A1* genotyping in patients with metastatic colorectal cancer who are to be treated with irinotecan, with the intent of modifying the dose as a way to avoid adverse drug reactions (severe neutropenia)” (5).

Table 1. *UGT1A1* phenotypes and the therapeutic recommendations for Irinotecan therapy

Genotype	Genotype details	Therapeutic (dose) recommendation
*1/*28	One active allele and one reduced activity allele	No dose adjustment.
*28/*28	Two reduced activity alleles	Dose more than 250 mg/m ² : reduce initial dose by 30%. Increase dose in response to neutrophil count. Dose less than or equal to 250 mg/m ² : no dose adjustment.

The strength of the irinotecan therapeutic recommendations scored 3/4 (moderate quality of evidence). Table is adapted from Swen J.J., Nijenhuis M., de Boer A., Grandia L. et al. Pharmacogenetics: from bench to byte - an update of guidelines. *Clinical pharmacology and therapeutics*. 2011;89(5):662–73 (4).

Drug: Irinotecan

Irinotecan is used to treat colorectal cancer, which is the third most common cancer worldwide (6). It is often used in combination with other drugs to treat patients with metastatic colorectal cancer when the cancer has recurred or has progressed following initial treatment. A common irinotecan-based combination therapy is referred to as FOLFIRI (FOLinic acid, Fluorouracil (also known as leucovorin), IRInotecan).

Irinotecan is a semisynthetic derivative of the antineoplastic agent camptothecin, which takes its name from the tree where it was first isolated (Camptotheca). Like camptothecin, irinotecan inhibits the nuclear enzyme, topoisomerase I. This enzyme catalyzes a number of nuclear processes, such as regulating DNA supercoiling, replication, recombination, and repair.

Topoisomerase I decreases the torsional strain in the helical strands of DNA by making single strand breaks in the DNA. Single strands of DNA pass through the breaks and they bind to the topoisomerase to form a cleavable complex. Once the DNA is sufficiently relaxed and the passage of strands has been completed, the topoisomerase re-ligates the broken DNA strands and allows for transcription to proceed (7, 8).

Irinotecan is a pro-drug. After it is administered by intravenous injection, it is metabolized to its active form, SN-38, which is 100–1000 times more potent than its parent drug (9). It is inactivated by undergoing phase II metabolism (glucuronidation) in the liver. The resulting conjugated SN-38 glucuronide is water soluble, and is mainly excreted through the bile, with about 30% excreted by the kidneys (10).

SN-38 exerts its cytotoxic effects by binding to the cleavable complex to form a ternary complex (drug-topoisomerase-DNA complex). This complex is thought to prevent the re-ligation of the single strand breaks, which interrupts the moving DNA replication fork. The arrest of replication and the interaction between replication enzymes and the ternary complex introduces lethal double-stranded breaks in DNA. Because the DNA damage cannot be repaired, the cells undergo apoptosis (11, 12).

Irinotecan-based combination therapy has been found to be superior in overall response and survival when compared to the use of 5-fluorouracil/leucovorin therapy alone (2). However, the use of irinotecan is limited by a high incidence of unpredictable and severe toxicity, including severe neutropenia, fever, and diarrhea. Approximately 7% of patients who present with severe neutropenia and fever following treatment with irinotecan will die from these complications (2, 13-16).

Gene: *UGT1A1*

The uridine diphosphate glucuronosyltransferase (UDP-glucuronosyltransferase, or UGT) enzymes are a superfamily of enzymes that metabolize a wide range of molecules such as bilirubin, steroids, toxins, and drugs—including irinotecan. These enzymes are responsible for glucuronidation, which is a phase II metabolic pathway during which glucuronic acid is conjugated to specific targets to convert them to water-soluble metabolites that can then be eliminated from the body.

The UGT genes are often polymorphic, and genomic processes, such as copy-number variations, variant splicing, and epigenetic factors, are likely to contribute to their diversity. As a result, the metabolic pathways the UGT enzymes catalyze are particularly variable (17).

The UGT superfamily contains 117 enzymes that are divided into four families, and *UGT1A* is one of these families (18). The *UGT1A* gene locus, located on chromosome 2q37, is complex—it encodes multiple genes and pseudogenes, and alternatively spliced isoforms also exist (19).

The *UGT1A* locus contains multiple alternative first coding exons, each of which has its own promoter site, enabling the transcription of nine unique *UGT1A* enzymes (20). One of these transcripts is *UGT1A1*, which encodes the bilirubin-UGT enzyme (bilirubin uridine diphosphate glucuronosyl transferase enzyme). Whereas many UGT enzymes overlap in the substrates they glucuronidate, *UGT1A1* is the only enzyme that glucuronidates bilirubin (21).

Bilirubin is a yellow waste product produced during the catabolism of heme, a constituent of hemoglobin. When old or damaged red blood cells are broken down in the spleen, their hemoglobin is broken down to heme, which is then converted into bilirubin. The *UGT1A1* enzyme converts this toxic, insoluble form of bilirubin (unconjugated bilirubin) to its nontoxic form (conjugated bilirubin). Because conjugated bilirubin is water-soluble, it can be dissolved in bile and eliminated with solid waste. If bilirubin is not eliminated

and instead, accumulates to high levels (hyperbilirubinemia) it can cause a yellowish discoloration of the skin and eyes, a condition known as jaundice.

Variants of the *UGT1A1* gene that decrease UGT1A1 enzyme activity can lead to jaundice. The jaundice may be mild, as seen in Gilbert's syndrome, or severe, as seen in Crigler-Najjar syndrome. Crigler-Najjar syndrome is divided into two types. Type 1 is the extremely severe form where affected individuals can die in childhood due to kernicterus (bilirubin-induced brain injury), although they may survive for longer with treatment. Type 2 is less severe; the affected individuals are less likely to develop kernicterus and most survive into adulthood.

Currently, over 113 genetic variants of *UGT1A1* have been reported (21). *UGT1A1**1 is the wild-type allele and is associated with normal enzyme activity. The most common variant allele is *UGT1A1**28, which is commonly found in African-Americans (0.42 – 0.45 allele frequency) and Caucasians (0.26–0.31), and is less common in Asian populations (0.09–0.16) (22, 23).

The *28 variant contains an extra thymine-adenine (TA) repeat within the TATA box promoter region (seven TA repeats compared to six in the wild-type allele). This extra (TA) repeat decreases the rate of transcription initiation of the *UGT1A1* gene, leading to decreased enzyme activity and decreased glucuronidation of bilirubin to about 30% of wild-type levels (24). A different allele, *UGT1A1**37, has eight TA repeats at this site, and results in reduced promoter activity to levels lower than that of promoters with the *UGT1A1**28 allele. In contrast, the allele *UGT1A1**36 has only five repeats, and is associated with increased promoter activity of the gene and a reduced risk of neonatal hyperbilirubinemia, a common and typically benign condition. Both *UGT1A1**36 and *UGT1A1**37 occur almost exclusively in populations of African origin, with estimated allele frequencies of 0.03–0.10 and 0.02–0.07, respectively.

Within Caucasian and African American populations, the *UGT1A1**28 variant is a common cause of Gilbert syndrome, and is also a cause of Crigler-Najjar syndrome types 1 and 2 (17, 22). The *UGT1A1**28 variant is also associated with drug toxicity.

Approximately 10% of the North American population is homozygous for the *28 allele (*28/*28 genotype, also known as *UGT1A1* 7/7 genotype) and are at an increased risk of neutropenia following injections of irinotecan treatment (23). The rate of severe neutropenia in *28/*28 homozygous patients is as high as 36%, and is strongly associated with a higher hospitalization rate (25-27).

There is less evidence to support a link between *UGT1A1* genotype and irinotecan treatment-related diarrhea, and there is conflicting data on whether an individual's *UGT1A1* genotype influences their response to irinotecan therapy (5, 28).

Another variant allele, *UGT1A1**6, is more prevalent in Asian populations, with an allele frequency of around 0.13% in Chinese, Korean, and Japanese populations (29). In this variant, there is a switch of amino acids, from a glycine to an arginine at position 71 within a coding region (Arg71Gly). Individuals who are homozygous for this allele have

reduced *UGT1A1* enzyme activity, which can cause Gilbert syndrome and prolonged neonatal jaundice (30-33). This variant also appears to be an important predictor of severe toxicity to irinotecan therapy in Northeastern Asian populations (34).

Emerging data suggests that other variant alleles may have a protective effect. The newly discovered marker rs11563250, located in the 3'-flanking region of *UGT1*, has a major A allele (rs11563250A) and a relatively common variant G allele (rs11563250G, found in 12% of the population). Carriers of the G allele have a lower risk of irinotecan-induced neutropenia. They also tend to have lower total plasma bilirubin levels, suggesting that this variant is associated with an enhanced capacity for glucuronidation. Evidence suggests that carriers of rs11563250G could tolerate a higher dose of irinotecan, especially if they have the *UGT1A1**1/*1 genotype (35).

Genetic Testing

Genetic testing to determine the *UGT1A1* status of patients is available (36). Genotyping is used to optimize irinotecan dosing to prevent side effects when treating patients with metastatic colorectal cancer, and may also be used as part of the management of Gilbert syndrome (36). Routine genotyping usually tests for *UGT1A1* 6/6, 6/7, and 7/7 genotypes (*1/*1, *1/*28, and *28/*28 respectively).

Because the *UGT1A1**28 variant allele is associated with severe neutropenia following irinotecan therapy, the use of genotyping in selective cases may make the following patient choices possible:

- If the patient prefers aggressive treatment: genotyping might allow higher dosing for *1/*1 and *1/*28 genotypes.
- If the patient prefers maximizing quality of life: genotyping might allow lower dosing for *28/*28 genotype (25-27).

The common *1 and *28 *UGT1A1* alleles comprise 98–99% of the genotypes found in the U.S. Caucasian population. However, routine genotyping of *UGT1A1* does not rule out other *UGT1A1* polymorphisms that might be more common in other populations (27). In addition, currently routine screening does not identify patients who would tolerate an even higher irinotecan.

Therapeutic Recommendations based on Genotype

This section contains excerpted¹ information on gene-based dosing recommendations. Neither this section nor other parts of this review contain the complete recommendations from the sources.

¹ The FDA labels specific drug formulations. We have substituted the generic names for any drug labels in this excerpt. The FDA may not have labeled all formulations containing the generic drug.

Statement from the US Food and Drug Administration (FDA): Individuals who are homozygous for the *UGT1A1**28 allele (*UGT1A1* 7/7 genotype) are at increased risk for neutropenia following initiation of irinotecan hydrochloride injection treatment.

In a study of 66 patients who received single-agent irinotecan hydrochloride injection (350 mg/m² once-every-3-weeks), the incidence of grade 4 neutropenia in patients homozygous for the *UGT1A1**28 allele was 50%, and in patients heterozygous for this allele (*UGT1A1* 6/7 genotype) the incidence was 12.5%. No grade 4 neutropenia was observed in patients homozygous for the wild-type allele (*UGT1A1* 6/6 genotype).

When administered as a single-agent, a reduction in the starting dose by at least one level of irinotecan hydrochloride injection should be considered for patients known to be homozygous for the *UGT1A1**28 allele. However, the precise dose reduction in this patient population is not known and subsequent dose modifications should be considered based on individual patient tolerance to treatment.

Please review the complete therapeutic recommendations that are located here: (3).

Summary of recommendations from the Pharmacogenetics Working Group of the Royal Dutch Association for the Advancement of Pharmacy (KNMP): The *UGT1A1**28 allele is associated with irinotecan toxicity. Although results are not consistent, there is sufficient evidence that a reduction in the initial dose by 30% is required for regimens containing >250 mg/m² of irinotecan prescribed to homozygous carriers of the *UGT1A1**28 allele. This is in agreement with the Food and Drug Administration–mandated label change. No dose reduction is recommended for heterozygous carriers of the *UGT1A1**28 allele because dose reduction might result in undertreatment (Table 1).

Please review the complete therapeutic recommendations that are located here: (4).

Summary of Findings on *UGT1A1* Genotyping to Predict Response to Irinotecan, from the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group:

In 2009, the independent Evaluation of Genomic Applications in Practice and Prevention (EGAPP™) Working Group evaluated the use of *UGT1A1* genotyping to determine the best dose of irinotecan to prevent side effects when treating patients with metastatic colorectal cancer. The Working Group determined that there was not enough evidence to conclude whether *UGT1A1* genotyping should be used for this purpose. The balance of benefits and harms of *UGT1A1* genotyping to guide irinotecan use could not be determined from the available evidence.

(Note that the EGAPP recommendation statement was published prior to the FDA statement or KNMP guidelines and may not have considered evidence available to those groups.)

The EGAPP recommendation statement was based on the following key points from the evidence review:

- *UGT1A1* genotyping results appear accurate for the common variants.
- Observational studies identified associations between *UGT1A1* genotype results and the occurrence of certain side effects, as well as a potential impact on treatment effectiveness.
- The EGAPP Working Group (EWG) found no evidence that demonstrated that targeted dosing of irinotecan based on *UGT1A1* genotyping leads to improved patient outcomes.
- Even if targeted dosing were shown to be highly effective, it is not clear that benefits (reduced side effects) would outweigh harms (unresponsive tumors) (27).

Please review the complete therapeutic recommendations that are located here: (5).

Nomenclature

Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
<i>UGT1A1</i> *1	A(TA) ₆ TAA	NM_000463.2:c.-53_-52[6]	Not applicable—variant occurs in a non-coding (TATA box promoter) region	rs8175347
<i>UGT1A1</i> *28	A(TA) ₇ TAA	NM_000463.2:c.-53_-52[7]	Not applicable—variant occurs in a non-coding (TATA box promoter) region	rs8175347
<i>UGT1A1</i> *6	211G>A Arg71Gly	NM_000463.2:c.211G>A	NP_000454.1:p.Gly71Arg	rs4148323

For an overview of the haplotypes for *UGT1A1*, please see the PharmGKB's [haplotype translation table](#).

Guidelines for the description and nomenclature of gene variations are available from the Human Genome Variation Society (HGVS): <http://www.hgvs.org/content/guidelines>.

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Tests in GTR by Condition

Irinotecan response

Tests in GTR by Gene

UGT1A1 gene