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Irinotecan Therapy and *UGT1A1* Genotype

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Introduction

Irinotecan (brand name Camptosar) is a topoisomerase I inhibitor widely used in the treatment of cancer. It is most frequently used in combination with other drugs to treat advanced or metastatic colorectal cancer. However, irinotecan therapy is associated with a high incidence of toxicity, including severe neutropenia and diarrhea (1).

Irinotecan is converted in the body to an active metabolite known as SN-38, which is then inactivated and detoxified by a UDP-glucuronosyltransferase (UGT) enzyme encoded by the *UGT1A1* gene. The UGT enzymes are responsible for glucuronidation, a process that transforms lipophilic metabolites into water-soluble metabolites that can be excreted from the body.

The risk of irinotecan toxicity increases with genetic variants associated with reduced UGT enzyme activity, such as *UGT1A1*28*. The presence of this variant results in reduced excretion of irinotecan metabolites, which leads to increased active irinotecan metabolites in the blood. Approximately 10% of North Americans carry 2 copies of the *UGT1A1*28* allele (homozygous, *UGT1A1 *28/*28*), and are more likely to develop neutropenia following irinotecan therapy (1, 2, 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" (Table 1) (1).

The Dutch Pharmacogenetics Working Group (DPWG) of the Royal Dutch Association for the Advancement of Pharmacy (KNMP) recommends starting with 70% of the standard dose for homozygous carriers of the *UGT1A1*28* allele. If the patient tolerates this initial dose, the dose can be increased guided by the neutrophil count. They state that no action is needed for heterozygous carriers of the *UGT1A1*28* allele (e.g., *UGT1A1 *1/*28*) (Table 2) (4). In addition, the French National Network of Pharmacogenetics (RNPGx) has proposed a decision tree for guiding irinotecan prescribing based on the *UGT1A1* genotype and irinotecan dose (Table 3) (5).

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Table 1. FDA (2017) Drug Label for Irinotecan. Therapeutic Recommendations based on *UGT1A1* Genotype. Dosage and Administration.

Genotype	Recommendations
*UGT1A1 *28/*28*	When administered as a single-agent, a reduction in the starting dose by at least one level of irinotecan hydrochloride injection, USP[1] 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 see Therapeutic Recommendations based on Genotype for more information from the FDA. Table adapted from (1).

Table 2. DPWG (2014) Recommendations for Irinotecan and *UGT1A1* Genotype.

Phenotype / genotype	Recommendations
UGT1A1 intermediate metabolizer (IM)	NO action is needed for this gene-drug interaction.
UGT1A1 poor metabolizer (PM)	Start with 70% of the standard dose If the patient tolerates this initial dose, the dose can be increased, guided by the neutrophil count.
*UGT1A1 *1/*28*	NO action is needed for this gene-drug interaction.
*UGT1A1 *28/*28*	Start with 70% of the standard dose If the patient tolerates this initial dose, the dose can be increased, guided by the neutrophil count.

Please see Therapeutic Recommendations based on Genotype for more information from the DPWG. Table is adapted from (4).

Table 3. RNPGx (2017) Recommendations for Irinotecan and *UGT1A1* Genotype.

Dose of irinotecan	Recommendation
low doses (<180 mg/m^2/week)	Presence of the *UGT1A1*28* allele is not a major risk factor (little difference in risk of hematological or digestive toxicity irrespective of the genotype)
180—230 mg/m^2 spaced by 2—3-week intervals	Patients who are homozygous for the *UGT1A1*28* allele have a higher risk of hematological and/or digestive toxicity than patients who are heterozygous or non-carriers. For these *28/*28* patients, a 25-30% dose reduction is recommended, especially if the patient presents other risk factors for toxicity. Dose can be adjusted for subsequent cycles depending on the tolerance.
240 mg/m^2 or higher spaced by 2—3-week intervals	Homozygous *UGT1A1*28* patients have a greatly increased risk of hematological toxicity (neutropenia) compared with other genotypes, contraindicating administration at this higher dose and leading to discussion of a standard dose depending on the associated risk factors. Administration of an intensive dose (240 mg/m^2) is recommended only for *1/*1* patients, or for *1/*28* patients who have no other risk factors and who benefit from intensive surveillance.

Please see Therapeutic Recommendations based on Genotype for more information from the RNPGx. Table is adapted from (5).

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 advanced or 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 [also known as leucovorin], Fluorouracil, IRInotecan).

Irinotecan is a semisynthetic derivative of the antineoplastic agent camptothecin, which derives its name from the Camptotheca tree where it was first isolated. Like camptothecin, irinotecan is an inhibitor of the nuclear

[1] USP stands for the United States Pharmacopeia. The USP establishes standards that promote safe medication use (e.g., procurement, prescribing, transcribing, order entry, preparation, dispensing, administration, and monitoring of medications).

enzyme, topoisomerase I. This enzyme catalyzes a number of nuclear processes; regulation of 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 bind to the topoisomerase to form a cleavable complex. Once the DNA is sufficiently relaxed and the passage of strands has been completed, topoisomerase re-ligates the broken DNA strands and allows for transcription to proceed (7, 8).

Irinotecan is a pro-drug, and is converted by carboxylesterase enzymes to the active metabolite SN-38, which is 100–1000 times more potent that its parent drug, after administration by intravenous injection (9). The SN-38 metabolite exerts its cytotoxic effects by binding to the cleavable complex to form a ternary 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 causing irreparable DNA damage and subsequent cell apoptosis. (10, 11).

SN-38 is lipophilic, and it needs to be inactivated by undergoing phase II metabolism (glucuronidation). The resulting conjugated SN-38 glucuronide is water-soluble, and is mainly excreted through the bile, with about 30% excreted by the kidneys (12).

Irinotecan-based combination therapy has been found to be superior in overall response and survival when compared with the use of 5-fluorouracil/leucovorin therapy alone for patients with metastatic colorectal cancer (3). However, the use of irinotecan is limited by a high incidence of unpredictable and severe dose-limiting toxicity, including severe neutropenia, fever, and diarrhea (13). The rate of grade 3 or 4 adverse events is around 20-25% (14). Approximately 7% of patients who present with severe neutropenia and fever following treatment with irinotecan will die from these complications (3, 15, 16, 17, 18).

Gene: *UGT1A1*

The UGT enzymes (uridine diphosphate-glucuronosyltransferase, or UDP-glucuronosyltransferase) are a superfamily of enzymes that metabolize a wide range of lipophilic molecules such as bilirubin, steroids, toxins, and drugs—including irinotecan's active metabolite, SN-38. These enzymes mediate the process of 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 polymorphic, and genomic processes, such as copy-number variations, variant splicing, and epigenetic factors, likely contribute to their diversity. As a result, the substrates that the UGT enzymes catalyze are particularly variable (19).

The UGT superfamily contains at least 117 enzymes divided into 4 families, of which UGT1A is a member (20). The *UGT1A* gene locus, located on chromosome 2q37, is complex—it encodes multiple genes and pseudogenes, and alternatively spliced isoforms also exist (21).

The *UGT1A* locus contains multiple alternative first coding exons, each of which has its own promoter site, enabling the transcription of 9 unique UGT1A enzymes (22). One of these transcripts is *UGT1A1*, which encodes UGT1A1, the bilirubin-UGT enzyme. Whereas many UGT enzymes overlap in the substrates they glucuronidate, UGT1A1 is the only enzyme that glucuronidates bilirubin (23).

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 data suggests that one copy of *28 allele results in about a 35% decrease in transcriptional activity, and 2 copies (**28/*28*, homozygous) results in about a 70% decrease (24, 25).

The jaundice may be mild, as seen in Gilbert syndrome, or severe, as seen in Crigler-Najjar syndrome. Crigler-Najjar syndrome presents in 2 forms called type 1 and type 2. 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 135 genetic variants of *UGT1A1* have been reported (23, 26). *UGT1A1*1* is the wild-type allele 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) (27, 28). 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 (19, 27).

The *UGT1A1*28* [$(TA)_7TAA$] variant contains an extra thymine-adenine (TA) repeat within the TATA box promoter region (7 TA repeats compared with 6 in the wild-type allele) (29). 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 (30).

Another variant allele, UGT1A1*37 [$(TA)_8TAA$], has 8 TA repeats at this site, and results in reduced promoter activity of the gene to levels lower than the UGT1A1*28 allele. In contrast, the UGT1A1*36 [$(TA)_5TAA$] allele only has 5 repeats and is associated with increased promoter activity 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.

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 intravenous irinotecan therapy (28). The rate of severe neutropenia in **28/*28* homozygous patients is as high as 36%, and is strongly associated with a higher hospitalization rate (7, 31, 32).

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 (8, 33).

Another variant allele, *UGT1A1*6*, is more prevalent in Asian populations, with an allele frequency of around 15–30% in Chinese, Korean, and Japanese populations (24, 34, 35). In this variant, there is a switch of amino acids, from a glycine to an arginine at position 71 within a coding region (p.Arg71Gly). Individuals who are homozygous for this allele have reduced UGT1A1 enzyme activity, which can cause Gilbert syndrome and prolonged neonatal jaundice (36, 37, 38, 39). This variant also appears to be an important predictor of severe toxicity to irinotecan therapy in Asian populations (35, 40, 41, 42, 43, 44, 45, 46, 47).

In addition to genetic variations in the *UGT1A1* gene, several other genetic markers may influence the risk of irinotecan toxicity. These include genetic variation in the adenosine triphosphate (ATP)-binding cassette (ABC) transporter genes, *ABCC1* and *ABCB2* (43, 48, 49), the solute carrier (*SLC*) transporter genes (48, 50, 51), the transforming growth factor (*TGFB*) gene (52), and the xenobiotic-sensing receptor, *NR1I2* (53).

The emerging data suggests that other variant alleles may have a protective effect. The newly discovered marker rs11563250 (NM_001287395.1:c.-1068A>G), located in the 3′-flanking region of *UGT1A1*, 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 also have the *UGT1A1*1/*1* genotype (54).

Genetic Testing

The NIH's Genetic Testing Registry provides examples of the genetic tests currently available for irinotecan response and for the *UGT1A1* gene.

Genetic testing can be used to optimize irinotecan dosing. For example, 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 (55, 56, 57, 58, 59).

- If the patient prefers maximizing quality of life: genotyping might allow lower dosing for **28/*28* genotype (7, 31, 32).

Genotyping may also enable irinotecan to be added to the treatment of other gastrointestinal tumors without the risk of hematologic toxicity (60). Genotyping may also be used as part of the management of Gilbert syndrome (15).

In the USA, the common **1* and **28 UGT1A1* alleles comprise 98–99% of genotypes (61). Routine genotyping typically tests for *UGT1A1 *1/*1, *1/*28*, and **28/*28 genotypes* (also known as *6/6*, *6/7*, and *7/7*, respectively).

Routine screening does not rule out other *UGT1A1* polymorphisms that are more common in specific populations (7). For example, the *UGT1A1*6* allele is common in Asian populations, and in Japan, a reduced dose of irinotecan is recommended for individuals with *UGT1A1 *6/*6*, **6/*28*, and **28/*28* genotypes (62). In addition, routine screening does not identify patients who are being under-dosed and could potentially tolerate a much higher dose of irinotecan.

The adoption of preemptive *UGT1A1*28* genotyping to increase irinotecan safety and efficacy in clinical practice is still limited and often not covered by health insurance, despite the significant costs of treating irinotecan-related toxicities (63, 64).

Part of the reason that healthcare providers forgo testing may be because the standard dose of irinotecan used in FOLFIRI is low (180 mg/m^2). A phase II trial is currently determining whether dosing irinotecan based on genotype, as part of a FOLFIRI treatment regime, is effective and safe. The standard irinotecan dose of 180 mg/m^2 is being used for patients with the *28/*28* genotype, a dose of 260 mg/m^2 is being used for patients with the **1/*28* genotype, and a dose of 310 mg/m^2 is being used for patients with the **1/*1* genotype (65).

Therapeutic Recommendations based on Genotype

This section contains excerpted[2] information on gene-based dosing recommendations. Neither this section nor other parts of this review contain the complete recommendations from the sources.

[2] 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.

2017 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, USP treatment.

In a study of 66 patients who received single-agent Irinotecan Hydrochloride Injection, USP (350 mg/m^2 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, USP 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.

UGT1A1 Testing

A laboratory test is available to determine the *UGT1A1* status of patients. Testing can detect the *UGT1A1 6/6*, *6/7* and *7/7* genotypes.

Please review the complete therapeutic recommendations that are located here: (1).

2017 Recommendations from the French National Network of Pharmacogenetics (RNPGx)

Interpreting Results

The RNPGx has proposed a decision tree for guiding irinotecan prescription based on the *UGT1A1* genotype and the protocol's theoretical dose:

- for low doses (< 180 mg/m^2 /week), presence of the *UGT1A1*28* allele is not a major risk factor (little difference in risk of hematological or digestive toxicity irrespective of the genotype);
- for doses in the 180—230mg/m^2 spaced by 2—3-week intervals, patients who are homozygous for the *UGT1A1*28* allele have a higher risk of hematological and/or digestive toxicity than patients who are heterozygous or non-carriers. For these **28/*28* patients, a 25% to 30% dose reduction is recommended, especially if the patient presents other risk factors for toxicity. Dose can be adjusted for subsequent cycles depending on the tolerance;
- for doses of 240mg/m^2 or higher spaced by 2—3 weeks intervals, homozygous *UGT1A1*28* patients have a greatly increased risk of hematological toxicity (neutropenia) compared with other genotypes, contraindicating administration at this higher dose and leading to discussion of a standard dose depending on the associated risk factors. Administration of an intensive dose (240 mg/m^2) is recommended only for *1/*1 patients, or for *1/*28 patients who have no other risk factors and who benefit from intensive surveillance.

[...]

The first-intention of this strategy for analysis of *UGT1A1* status is to detect the *28 variant, the most common deficiency variant observed in the Caucasian population, to be performed before initiating treatment. Referring to the level of evidence classification for RNPGx recommendations detailed in the article by Picard et al. in this issue, *UGT1A1* genotyping is advisable for a standard dose (180—230mg/m^2) and essential for intensified dose (> 240 mg/m^2).

Thus, individualized treatment can be proposed based on the *UGT1A1* genotype, with either a dose reduction for **28/*28* homozygous patients, or possibly dose intensification for non-carriers of the *28 allele.

For the other *UGT1A1* alleles, genotyping is performed by a limited number of laboratories and is considered a second- intention test.

Moreover, the RNPGx suggests that this analysis could be performed concomitantly with other genetic explorations for colorectal cancer patients (search for *KRAS*, *BRAF* mutations. . .) and constitutional (search for *DYPD* variants) in order to guarantee optimal irinotecan therapy within adequate delay for optimal hospital practices.

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

2014 Recommendations from the Dutch Pharmacogenetics Working Group (DPWG) of the Royal Dutch Association for the Advancement of Pharmacy (KNMP)

UGT1A1 Intermediate Metabolizers (IM)
NO action is needed for this gene-drug interaction.
This genetic variation (IM) is more common in Western populations than the wild-type (*1/*1). This means that treatment is largely geared to patients with this genetic variation. Adjustment of the treatment is therefore not useful.

UGT1A1 Poor Metabolizers (PM)
Genetic variation reduces conversion of irinotecan to inactive metabolites. This increases the risk of serious, life-threatening adverse events.
Recommendation:
1. Start with 70% of the standard dose
If the patient tolerates this initial dose, the dose can be increased, guided by the neutrophil count.

UGT1A1 *1/*28
NO action is needed for this gene-drug interaction.
This genetic variation (*1/*28) is more common in Western populations than the wild-type (*1/*1). This means that treatment is largely geared to patients with this genetic variation. Adjustment of the treatment is therefore not useful.

UGT1A1 *28/*28
Genetic variation reduces conversion of irinotecan to inactive metabolites. This increases the risk of serious, life-threatening adverse events.
Recommendation:
1. Start with 70% of the standard dose
If the patient tolerates this initial dose, the dose can be increased, guided by the neutrophil count.

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

Nomenclature of selected *UGT1A1* variants

Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
*UGT1A1*1*	$(TA)_6TAA$	NM_000463.2:c.-53_-52TA[7]	Not applicable—variant occurs in a non-coding (TATA box promoter) region	rs8175347
*UGT1A1*6*	211G>A Gly71Arg	NM_000463.2:c.211G>A	NP_000454.1:p.Gly71Arg	rs4148323

Table continued from previous page.

Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
*UGT1A1*36*	$(TA)_5TAA$	NM_000463.2:c.-53_-52TA[6]	Not applicable—variant occurs in a non-coding (TATA box promoter) region	rs8175347
*UGT1A1*28*	$(TA)_7TAA$	NM_000463.2:c.-53_-52[8]	Not applicable—variant occurs in a non-coding (TATA box promoter) region	rs8175347
*UGT1A1*37*	$(TA)_8TAA$	NM_000463.2:c.-53_-52TA[9]	Not applicable—variant occurs in a non-coding (TATA box promoter) region	rs8175347

*UGT1A1*1* is the wild-type allele and is associated with normal enzyme activity.
Note: The *UGT1A1*28* variant has 8 TA repeats, as shown by the "[8]" in the official HGVS term, "NM_000463.2:c.-53_-52[8]". In the medical literature, the term "$(TA)_7TAA$" is commonly used. Here, 7 of the TA repeats are shown in parentheses "$(TA)_7$", followed by the 8th repeat "(TAA)".
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).

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