SMART Approach

Pharmacogenetic Considerations for Irinotecan Therapy

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1. Overview

Pharmacogenetic testing provides a valuable tool for personalizing irinotecan therapy, which is often used to treat pancreatic cancer, as well as many others such as colorectal cancer. Genetic variability in Uridine diphosphate glucuronosyl transferase 1A1 (*UGT1A1*), which contributes to the metabolism of irinotecan, has been shown to significantly influence the risk of experiencing severe toxicity. Emerging evidence has demonstrated assessing patients for genetic variation in *UGT1A1* can help to minimize adverse effects and clinical guidelines for genotype-guided irinotecan dosing are available. Here is a brief summary of the current guidelines and recommendations:

- *UGT1A1* is responsible for the inactivation of irinotecan's active metabolite SN-38. Decreased *UGT1A1* activity leads to increased concentrations of SN-38
- UGT1A1 poor metabolizers have an increased risk of experiencing severe irinotecan-associated toxicities, particularly neutropenia and diarrhea.
- About 15 in 100 individuals is a UGT1A1 poor metabolizer, although some biogeographic groups, such as African American/Afro-Caribbean, this phenotype is much more prevalent.
- Current evidence supports irinotecan dose reductions in UGT1A1 poor metabolizers can help to reduce the risk of severe toxicities.
- Additional research is needed to assess genotype-guided dose adjustments for irinotecan among different chemotherapy regimens

2. Pharmacogenetics of Irinotecan

Irinotecan is a camptothecin derivative that demonstrates anticancer activity in many solid tumors including pancreatic and colorectal cancer, among others. Irinotecan is a prodrug that is converted predominantly by carboxylesterases (CES) in the liver and intestines to the active metabolite SN-38, which has 100 to 1000-fold higher activity compared to irinotecan.[1] SN-38 is inactivated by further enzymatic conversion into SN-38 glucuronide (SN-38G) via *UGT1A1.*[2]

Multiple different clinical groups provide *UGT1A1*-genotype- irinotecan dosing guidance, including the U.S. Food and Drug Administration (FDA) and the Dutch Pharmacogenomics Working Group (DPWG), among others (Table 1).[2–8] Although there is some variability in the recommendations, all agree that if a patient is a known UGT1A1 poor metabolizer the irinotecan dose should be reduced by ~30%. UGT1A1 poor metabolizers convert SN-38 to SN-38G less efficiently, leading to higher concentrations and an increased risk for developing severe neutropenia or diarrhea.

This article summarizes the relationship between the gene *UGT1A1* and irinotecan, existing dosing recommendations, and future areas of research to provide awareness to clinicians.

UGT1A1 Variation

The *UGT1A1* gene is located on chromosome 2, which encodes for the uridine diphosphate glucuronosyltransferase (UGT) 1A1 enzyme. *UGT1A1* is highly polymorphic, with more than 100 reported genetic variants.[9] UGT1A1 activity is critical for the conjugation of bilirubin, and the preliminary discovery of genetic variation was often associated with cases of hyperbilirubinemia and/or jaundice.[10–12] Two common decreased function variants in this gene, *UGT1A1*28* (rs4148323) and *UGT1A1*6* (rs3064744) have been extensively studied. *UGT1A1**28 is an extra repeat in the promoter TATA box, resulting in 7 TA repeats instead of the expected 6 repeats.[12] Testing for this variant may sometimes report the number of TA repeats as the genotype; a result of 7/7 would be synonymous with a *UGT1A1* *28/*28 genotype. The *UGT1A1**6 allele is a single nucleotide polymorphism in exon 1 of the gene that cause an

Abbreviations used in this paper: CES, carboxylesterases; CPIC, Clinical Pharmacogenetics Implementation Consortium; FDA, Food and Drug Administration IM, intermediate metabolizer; NM, normal metabolizers, PM, poor metabolizer; UGT1A1, uridine diphosphate glucuronosyl transferase 1A1

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Table 1: PGx–Based Recommendations for Irinotecan / *UGT1A1*

Guidelines and Administrative authorities	Phenotype	Recommends *UGT1A1* testing prior to irinotecan	PGx Recommendation	Year
FDA Drug Label[3]	PM	Yes	Consider reducing the starting dosage by at least one level (~20%). Decrease liposomal irinotecan to 50 mg/m^2	2022
FDA Table of Pharmacogenetic Associations[4]	IM or PM	No	Increased drug exposure could lead to increased risk of adverse events Consider dose reduction in PMs per drug labeling recommendation	2024
DPWG[2]	IM	Yes	No action required	2023
	PM		Reduce initial dose by 30%	
NCCN[8]	PM (by association with Gilbert's disease)	No	Irinotecan should be used with caution in patients with Gilbert's disease or elevated serum bilirubin.	2024
EMA[7]	PM	Yes	A reduction to 50 mg/m2 is recommended for liposomal irinotecan	2024
RNPGX/GPCO-Unicancer[5]	PM	Yes Advised for dosing 180—230 mg/m^2, considered essential for dosing >240 mg/m^2	Recommends an initial 25-30% dose reduction	2017
AIOM and SIF[6]	PM	Yes	Recommends a dose reduction of 30%	2019

FDA: Food and Drug Administration, DPWG: Dutch Pharmacogenomics Working Group, NCCN: National Comprehensive Cancer Network, EMA: European Medicines Agency, RNPGX/GPCO- Unicancer: French National Network of Pharmacogenetics/ Group of Clinical Onco-pharmacology, AIOM: Italian Association of Medical Oncology, SIF: Italian Society of Pharmacology

amino acid change from glycine to arginine and is found almost exclusively in patients with Asian ancestry.[11]

Three phenotypes have been established for *UGT1A1* in relation to medication metabolism. Normal metabolizers (NM) are individuals with no decreased function alleles (e.g. *1/*1), intermediate metabolizers (IM) are individuals with one decreased function allele (e.g. *1/*28 or *1/*6), and poor metabolizers (PM) are individuals with two decreased function alleles (e.g. *28/*28, *6/*6).[13] The frequencies of *UGT1A1* phenotypes vary significantly among biogeographic groups. Notably, the *UGT1A1* poor metabolizer phenotype is the most commonly observed *UGT1A1* phenotype in African American and Latino populations and is also commonly identified in other groups (Figure 1).[14]

Current Issues to Consider

- The *UGT1A1* poor metabolizer phenotype is common across multiple biogeographical groups highlighting the significant impact personalized treatment can have for irinotecan to minimize the risk of severe adverse events (Figure 1).
- There is currently no CPIC guideline for irinotecan, however, many other organizations provide genotype-guided recommendations. Although dose reductions are consistently recommended for *UGT1A1* poor metabolizers, the recommended adjustments differ among the publishing organizations.
- Most studies to date have been performed in colorectal cancer patients receiving FOLFIRI and did not identify an increased risk of toxicity in *UGT1A1* intermediate metabolizers. However, emerging evidence suggested intermediate metabolizers may have an increased toxicity risk. Consideration for the chemotherapy regimen for identifying at risk patients and determining the irinotecan dose adjustment may further reduce the risk of severe toxicity.[37]

UGT1A1 and Irinotecan Toxicity

The presence of each decreased function *UGT1A1* allele results in a ~25% reduction in the conversion of SN-38 to SN-38G and the reduction of activity is greatest in UGT1A1 PM with two decreased function alleles.[15] Pharmacokinetic studies have shown SN-38 metabolism is significantly slower in UGT1A1 poor metabolizers, resulting in up to a 200% increase in exposure.[15–20]

Numerous retrospective studies have evaluated the impact the increase in SN-38 exposure has on irinotecan toxicities for multiple administration strategies (i.e. monotherapy or combination regimens). Multiple meta-analyses have shown that UGT1A1 poor metabolizers have an increased risk for experiencing neutropenia and/or diarrhea when receiving irinotecan treatment, regardless of regimen. In these meta-analyses, the odds of developing neutropenia were reported to be four to six-fold higher in UGT1A1 poor metabolizers, while the risk of diarrhea was estimated as two to four-fold greater in these patients.[21–24]

The majority of available literature evaluating *UGT1A1*-irinotecan was performed in colorectal cancer patients receiving FOLFIRI and did not find associations between UGT1A1 IM and increased toxicity risk.[25–28] In fact, there have been multiple prospective studies that have concluded that UGT1A1 IM likely tolerates higher doses of irinotecan within this regimen. However, there is an increasing amount of evidence that irinotecan toxicity is also increased in UGT1A1 intermediate metabolizers when administered as part of a three-agent regimen with both fluoropyrimidine and oxaliplatin that may need to be considered.[29–31]

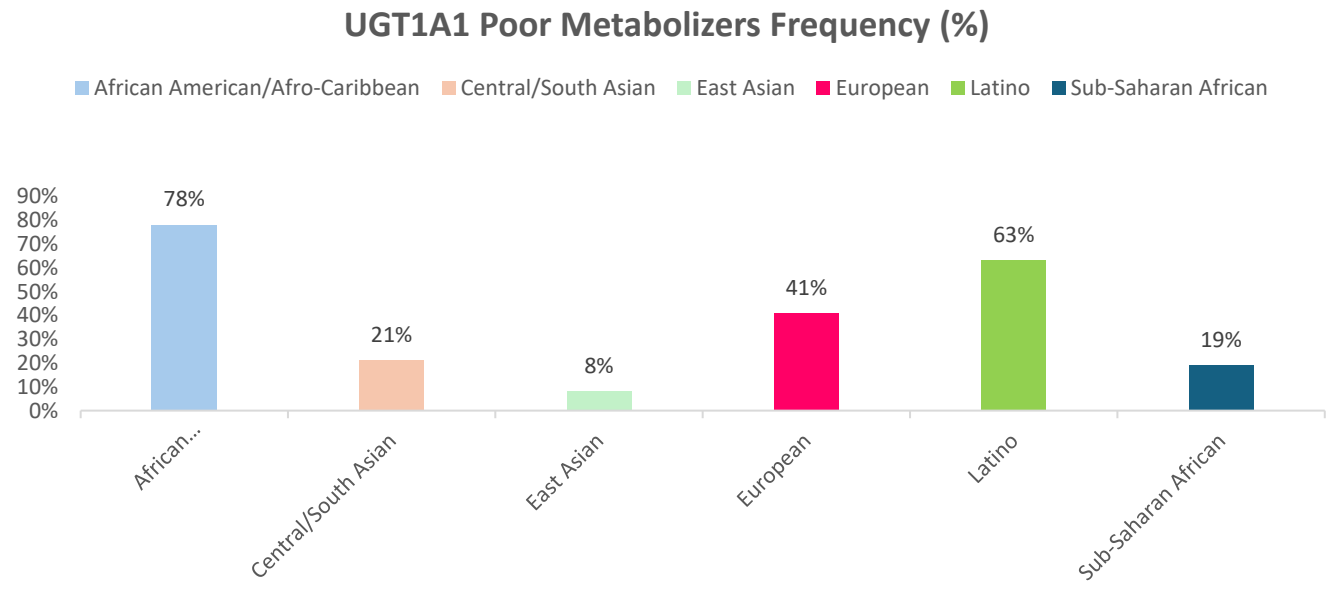
Evidence for UGT1A1-genotype-guided dosing

The impact of *UGT1A1*-genotype-guided dose reductions on irinotecan pharmacokinetics and toxicity rates has been evaluated in a variety of prospective methods. Pharmacokinetic studies have shown that irinotecan dose reductions in UGT1A1 PMs result in a lower SN-38 exposure more comparable to a UGT1A1 NM receiving standard dosing.[25,32,33]

Prospective studies of irinotecan dose reductions in UGT1A1 PM have also demonstrated reductions in severe adverse events. In one study, participants who were UGT1A1 PMs received a preemptive median 30% dose reduction and had comparable rates of febrile neutropenia to UGT1A1 NM and significantly lower rates compared to historical UGT1A1 PM controls where genotype-guided dosing was not used.[33] A preemptive dose reduction is supported by other studies where rates of severe toxicity were similar to or lower in UGT1A1 PMs who received irinotecan dose reductions compared to UGT1A1 NM and IM, although the exact irinotecan dose reduction varied among studies.[34]

Multiple organizations provide *UGT1A1*-guided irinotecan dosing recommendations. The primary pharmacogenetic dosing resources in the United States include the Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Food and Drug Administration (FDA). The FDA does indicate *UGT1A1* genotyping should be considered prior to prescribing irinotecan, and if the patient is a UGT1A1 poor metabolizer the dose should be reduced by at least one dose level (~20%) or to 50 mg/m2 for the liposomal formulation.[3] This aligns with the recommendations from the National Comprehensive Cancer Network to consider irinotecan dose reductions in patients with a history of Gilbert's disease (i.e. *UGT1A1* poor metabolizers).[8] Currently, no CPIC guideline is available although multiple European groups have published guidelines for personalized irinotecan dosing.[2,5–7] The recommendations for performing testing and adjusting doses have some variation, as shown on Table 1.

Figure 1: Estimated frequency of the UGT1A1 Poor Metabolizer phenotype among biogeographical regions[13,14]



However, all resources recommend irinotecan dose reductions when patients are known to be UGT1A1 poor metabolizers, with a ~30% reduction in initial dose being the most recommended.

Other Pharmacogenes

Irinotecan and SN-38 are substrates of additional enzymes, such as carboxylesterases, and transporters such as P-glycoprotein and multidrug-resistant protein. These proteins are also known to have interindividual variability in activity secondary to genetic variation. Some of these genetic variants have been evaluated for associations with irinotecan treatment responses.[35] Variants in transporters important for irinotecan distribution and metabolism have been suggested to have potential protective as well as detrimental impacts on irinotecan toxicities.[15,36] However, these associations have not been consistently replicated and further studies are needed before considering these other genes for personalizing irinotecan prescribing.

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Contributions:

Maisa Nazzal conducted the literature search, compiled the relevant studies, and drafted the manuscript. Dr. Amy Pasternak supervised the project, provided guidance and critically revised the manuscript. Both authors read and approved the final manuscript.

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