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Irinotecan pharmacogenomics

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Abstract

Irinotecan is a camptothecin analog used as an anticancer drug. Severe, potentially life-threatening toxicities can occur from irinotecan treatment. Although multiple genes may play a role in irinotecan activity, the majority of evidence to date suggests that variation in expression of UGT1A1 caused by a common promoter polymorphism (*UGT1A1*28*) is strongly associated with toxicity; however, this link is dose dependent. Variations in other pharmacokinetic genes, particularly the transporter *ABCC2*, also contribute to irinotecan toxicity. In addition, recent studies have shown that pharmacodynamic genes such as *TDP1* and *XRCC1* can also play a role in both toxicity and response.

Keywords

ABCC2; irinotecan; pharmacogenomics; TDP1; toxicity; UGT1A1; XRCC1

Camptothecin, a cytotoxic agent found in *Camptotheca acuminata*, was developed as an anticancer agent in the early 1970s [1–3]. Its mechanism of action is to bind to the DNA/topoisomerase I complex during DNA replication, preventing the resealing of single-strand breaks. Ultimately, the replication machinery collides with the camptothecin/toposiomerase I complex, shattering the DNA [4]. However, camptothecin is insoluble and attempts to address this both reduced the efficacy and increased the toxicity of the drug.

Camptothecin analogs were developed in the 1990s to circumvent the solubility problems. Irinotecan (also known as CPT-11, Camptosar®) is an analog approved for first-line therapy of advanced colorectal cancer in combination with 5-fluorouracil and/or leucovorin. In addition, irinotecan/cisplatin combination therapy is used for other cancers, for example lung and ovarian [5–6]. Recent studies have involved the combination of irinotecan with bevacizumab or cetuximab [1–2,7–8].

Diarrhea and neutropenia are major limiting factors for irinotecan, with up to 36% of patients experiencing severe, potentially life-threatening toxicities [9]. Methods such as pharmacogenomics to prospectively screen patients for DNA variations (Table 1) prior to selecting irinotecan therapy or dose would help improve patient care and reduce healthcare costs [10–12].

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Irinotecan pharmacokinetics

Metabolism

Irinotecan is a prodrug, metabolized into the active form, SN-38, via human carboxylesterases CES1 and CES2. CYP3A4 converts irinotecan into the inactive metabolite, APC. The active SN-38 can be subsequently inactivated through glucuronidation via members of the UDP-glucuronosyltransferase family [12]. UGT1A enzymes are a product of alternative splicing from the *UGT1A* locus located on chromosome 2q37. A total of 13 *UGT1A* genes are encoded at this locus (including four pseudogenes). Each UGT1A enzyme has a unique promoter and a unique exon 1, while the remaining four exons are shared with all members of the UGT1A family [13].

Metabolism pharmacogenomics

Carboxylesterases—Carboxylesterase 2 is the key enzyme responsible for hydrolyzing CPT-11 to the active SN-38 form [14]. CES2 expression is highly variable among individuals [15–16], and *in vitro* studies suggest that increased CES2 expression leads to increased irinotecan metabolism [17]. However, extensive assessment of the *CES2* gene did not identify any functional polymorphisms [18–19], and characterization of a common promoter variant in the 5′-UTR of *CES2* (referred to as 830C>G; located at −171C>G) did not identify any associations with CES2 expression or catalytic activity, or irinotecan toxicity or outcome [20]. *CES2* is, however, controlled by three distinct promoter regions [21], and it is possible that control of promoter choice may explain some of the individual variation in CES2 expression.

CES1 plays a minor role in irinotecan metabolism, and extensive resequencing of *CES1* also did not identify any functional polymorphisms [18]. However, in a Japanese hypertensive patient population, a −816A>C variant in the *CES1* promoter region has been reported to affect *CES1* promoter activity [22], but this remains to be assessed in the context of irinotecan metabolism.

CYP3A4—CYP3A4 inactivates irinotecan through conversion into the metabolite APC [23]. While there is no evidence of variants in the *CYP3A4* gene providing a useful screen for APC conversion, the interindividual variability in CYP3A4 activity can be exploited for irinotecan dosing [24].

UGT1A1—The most comprehensively studied genetic marker linked to toxicity from irinotecan therapy is found in the UDP-glucuronosyltransferase gene, *UGT1A1*. The UGT1A1 enzyme is responsible for hepatic bilirubin glucuronidation, and reduced UGT1A1 expression leads to Gilbert's syndrome [25]. Expression of UGT1A1 is, in part, controlled by a polymorphic dinucleotide repeat within the *UGT1A1* promoter TATA element consisting of between five and eight copies of a TA repeat ($[TA]_nTAA$), with the $(TA)_6TAA$ allele the most common (considered wild-type) and $(TA)_7TAA$ the most frequently recorded variant allele (usually denoted *UGT1A1*28*) [26]. The longer the repeat allele, the lower the corresponding *UGT1A1* gene expression, with patients carrying the $(TA)_7TAA$ and $(TA)_8TAA$ alleles having significantly lower UGT1A1 expression. The frequency of the *UGT1A1*28* allele has been assessed worldwide and ranges from approximately 15% in Asians to 45% in Africans. It is also found in 26–38% of Caucasians, African–Americans and Hispanics [27–29]. As increasing the number of TA repeats decreases UGT1A1 expression, the presence of more than six TA repeats in the *UGT1A1* promoter region leads to reduced glucuronidation, including reduced SN-38G formation. This results in an excess build-up of SN-38, leading to toxicity [12,25,30].

Early studies confirmed the link between *UGT1A1*28* and irinotecan toxicity, specifically diarrhea and neutropenia [27,31], and a retrospective analysis of DNA from 524 metastatic colorectal cancer patients on the N9741 study also associated *UGT1A1*28* with the incidence of toxicities (neutropenia, febrile neutropenia and vomiting) [32]. Furthermore, a prospective study of 66 patients with advanced disease treated with irinotecan found that patients homozygous for *UGT1A1*28* had a significantly greater risk of grade IV neutropenia compared with patients with at least one wild-type allele [33].

UGT1A1 in the clinic—In 2005, the US FDA approved a genetic test for *UGT1A1*28* [34] and altered the irinotecan package insert to include toxicity and dosing warnings relating to the *UGT1A1*28* allele [35]. This marked a significant step towards incorporating pharmacogenomics into clinical practice. However, 5 years on, concerns still remain over the specific irinotecan dose required based on genotype [36–37]. A subsequent study has identified that the relationship between *UGT1A1*28* and irinotecan toxicity is dependent on the irinotecan regimen used, rendering *UGT1A1*28* unsuitable as a marker for toxicity with lower doses (50–180 mg/m^2). For moderate-to-high doses (200–350 mg/m^2), the risk of severe hematological toxicity in patients homozygous for *UGT1A1*28* is 27.8-times higher than for patients with at least one wild-type allele [38]. Furthermore, a European study confirmed that toxicity from low-dose irinotecan was not affected by the *UGT1A1*28* variant [39]. Consequently, it appears necessary to further amend the irinotecan package insert to include dose/genotype guidelines. A recent prospective European study of 59 patients showed that when *UGT1A1*28* homozygous patients are excluded; the standard 180 mg/m^2 dose is significantly lower than the irinotecan dose that can be tolerated [40]. Dosing information from a Japanese Phase I study of 27 patients receiving irinotecan and doxifluridine has suggested a starting dose of 70 mg/m^2 for patients heterozygous for *UGT1A1*28*. No homozygous patients were identified in this study [41].

Other *UGT1A1* polymorphisms—There are other significant polymorphisms in the *UGT1A1* gene. Patients with haplotypes containing both the −3156G>A variant and *UGT1A1*28* experienced significantly higher incidence of severe neutropenia compared with patients with haplotypes not containing −3156G>A [33], and in the N9741 study the UGT1A1 −3156 variant was associated with a significantly increased risk of neutropenia [32]. In Caucasian populations, the **28* and −3156 alleles are in strong linkage disequilibrium [33].

In Asian populations where the frequency of *UGT1A1*28* is low [42], other *UGT1A1* variants can also play a role in irinotecan toxicity [12,43–50]. For example, in Korean patients with non-small-cell lung cancer treated with irinotecan-containing therapy, there were associations between the exon 1 polymorphism *UGT1A1*6* (G71R), irinotecan pharmacokinetics, and toxicity from irinotecan therapy [47]. In a further study of 88 Japanese cancer patients receiving irinotecan, two haplotype groups were associated with reduced area under the curve (AUC) ratios of SN-38G to SN-38, which is predicted to have an effect on irinotecan toxicity. These haplotypes were denoted **28* (containing the *UGT1A1*28* allele) and **6* (containing the exon 1 G71R polymorphism) [44]. Patients with the **6* haplotype alone did not show significant variation in their AUC ratios; however, patients with one **6* haplotype and one **28* haplotype had significantly lower AUC ratios compared with patients with homozygous wild-type *UGT1A1* [44].

Other *UGT1A* genes—Variants in *UGT1A7* and *UGT1A9* are also associated with SN-38 glucuronidation [51] and irinotecan toxicities (particularly diarrhea) [47,52,53], although these studies require further exploration. *UGT1A7*3* has been associated with hematologic toxicity in metastatic colorectal cancer patients treated with irinotecan [54]. Furthermore,

*UGT1A7*2* and **3*, as well as *UGT1A9* -118(dT) alleles, were associated with response to irinotecan [52].

Transport

Irinotecan and SN-38 may be transported out of the cell via members of the ATP-binding cassette transporter family [55], specifically ABCB1 (MDR1; P-glycoprotein), ABCC2 (CMOAT; MRP2) and ABCG2 (BCRP). In addition, glucuronidated SN-38 can be removed from the cell by ABCC2 (Figure 1).

Transport pharmacogenomics

ABCB1—In 65 patients treated with irinotecan, the common *ABCB1* 1236C>T variant caused significantly decreased clearance of irinotecan [56]. *ABCB1* 3435C>T was associated with diarrhea caused by irinotecan-containing therapy in a subset of 87 patients from a Phase III small-cell lung cancer trial [57]. In a further study, a haplotype containing the three most commonly studied *ABCB1* polymorphisms (1236C>T, 2677G>T and 3435C>T) was associated with reduced renal clearance in 49 Asian patients receiving irinotecan [58]. The *ABCB1* haplotype was also associated with response and survival in 140 colorectal cancer patients from the Nordic VI trial [59]. In the same study, *ABCB1* 3435C>T was also predictive of early toxic events [59].

ABCC2—In 64 patients with solid tumors treated with irinotecan, a significant correlation was observed with irinotecan and metabolite clearance, and the 3972T>C polymorphism [43], which was also associated with toxicity [60]. *ABCC2* -24T homozygotes and 3972T homozygotes also experienced significantly better response rates and progression-free survival in non-small-cell lung cancer patients receiving irinotecan and cisplatin [61]. In addition, a haplotype in the multidrug transporter *ABCC2* is associated with toxicity in patients lacking *UGT1A1*28* [46,62–63], suggesting that this haplotype could be a secondary screen for patients who are wild-type for *UGT1A1*, to further reduce the risk of toxicity.

ABCG2—Cell lines overexpressing ABCG2 are resistant to several topoisomerase I inhibitors, including irinotecan [64] and SN-38 [65]. The *ABCG2* variant 421C>A (Q141K) reduced *ABCG2* gene expression and caused irinotecan resistance in cancer cell lines [66] and neutropenia in 55 patients receiving irinotecan monotherapy when assessed as a haplotype with *ABCG2* IVS12 +49G>T [67]. Alone, the *ABCG2* 421C>A variant was not associated with toxicity [49,61]. A further polymorphism, *ABCG2* 34G>A, was significantly associated with diarrhea in 107 cancer patients [60] but was not associated with toxicity or outcome in 107 non-small-cell lung cancer patients [61].

Irinotecan pharmacodynamics

Topoisomerase I is the target for SN-38, and several downstream genes have been associated with camptothecin sensitivity, and are consequently included in the irinotecan pathway (Figure 1) including *XRCC1* [68], *ADPRT* [69], *TDP1* [70], *CDC45L* [71] and *NF-κB1* [72–73].

Pharmacodynamics & pharmacogenomics

A retrospective analysis of 107 colorectal cancer patients identified a significant association with *TDP1* IVS12 +79T>G and grade 3/4 neutropenia, and the *TDP1* variant and an *XRCC1* haplotype and response to irinotecan [74]. Associations with toxicity were not seen in a follow-up study of 85 cancer patients [75], although the dose of irinotecan was higher (300–350 mg/m^2 compared with a median of 180 mg/m^2 in [74]), and no significant association

with *XRCC1* R399Q and toxicity was seen in 18 colorectal cancer patients [76]. However, the variant *XRCC1* R399Q was associated with overall survival in 43 Turkish metastatic colorectal cancer patients [77]. Assessment of irinotecan pharmacodynamics in the context of pharmacogenomics is in its infancy, and subsequent validation experiments are required.

Future perspective

Toxicity is a major dose-limiting, life-threatening side effect from irinotecan chemotherapy. There are comprehensive data to suggest that *UGT1A1*28* may provide a genetic marker that patients can be screened for prior to irinotecan therapy and/or dose selection, and this has the potential to be a cost-effective screening approach [78]. However, a decade on from the initial association with toxicity, there are still questions remaining about how to interpret the genetic information [37]. Moreover, *UGT1A1*28* does not account for all the toxicity seen from irinotecan therapy. Consequently, although screening for this allele can identify patients at risk, the lack of *UGT1A1*28* does not preclude the chances of a patient experiencing severe toxicity.

Alongside variants in other *UGT1A* genes, transporters, and pharmacodynamic genes (Table 1), *in vitro* studies have shown that altered expression of PXR (encoded by the *NR1I2* gene) can affect SN-38 glucuronidation [79]. Consequently, variation in the *NR1I2* gene should be explored in the context of irinotecan therapy. Recent work has also suggested that epigenetic factors, such as methylation, may also play a role in altering UGT1A1 expression [80], and it is possible that screening of the tumor cells as well as germline DNA may also be needed for a comprehensive irinotecan pharmacogenomic profile.

Conclusion

Although *UGT1A1*28* provides a compelling story for irinotecan toxicity, it is not the only answer. Variation in any gene involved in the irinotecan pathway (Figure 1) could play a role in either toxicity or response. As well as polymorphisms, either assessed singly or in the form of a haplotype, other genomic alterations, such as epigenetics, also need to be assessed to build a comprehensive pharmacogenomic profile. This may require assessing DNA from tumor tissue to analyze specific alterations in the tumor genome, alongside the more typical germline DNA screening. Currently, markers for irinotecan response are few, and many remain unvalidated. Further analysis, particularly of the pharmacodynamic genes, will hopefully identify the genetic basis of response to irinotecan.

Executive summary

- Irinotecan is approved, in combination, for the treatment of metastatic colorectal cancer. It is also used for treating other solid tumors such as ovarian and non-small-cell lung cancer.
- Severe toxicity from irinotecan occurs in up to 36% of patients.

Irinotecan pharmacokinetics

- A polymorphic dinucleotide repeat in the *UGT1A1* promoter region (*UGT1A1*28*) is significantly associated with irinotecan toxicity.
- There is now a US FDA-approved test for *UGT1A1*28*, and the irinotecan package insert contains warnings about *UGT1A1*28* and risk of toxicity.
- The *UGT1A1*28* association with irinotecan toxicity is dose dependent.
- Other *UGT1A* polymorphisms may also play a role in irinotecan toxicity, especially in populations with a low incidence of *UGT1A1*28*.

- *ABCB1* polymorphisms have been associated with both toxicity and response.
- An *ABCC2* haplotype may predict irinotecan toxicity in patients who are not carriers of *UGT1A1*28*.

Irinotecan pharmacodynamics

- Initial studies have shown that XRCC1 and TDP1 are associated with toxicity and response.

Future perspective

- Phase I studies aimed at determining *UGT1A1*28*-dependent dosing of irinotecan will help to improve the use of irinotecan pharmacogenomics in clinical practice.
- Other pharmacogenomic studies, including expression panels and epigenetic markers, may prove to be useful indicators of outcome and toxicity to irinotecan.

Conclusion

- Although *UGT1A1*28* is a strong candidate as a pharmacogenomic marker for irinotecan toxicity, a panel of markers will be required in order to be as predictive as possible prior to irinotecan therapy selection or irinotecan dose selection.

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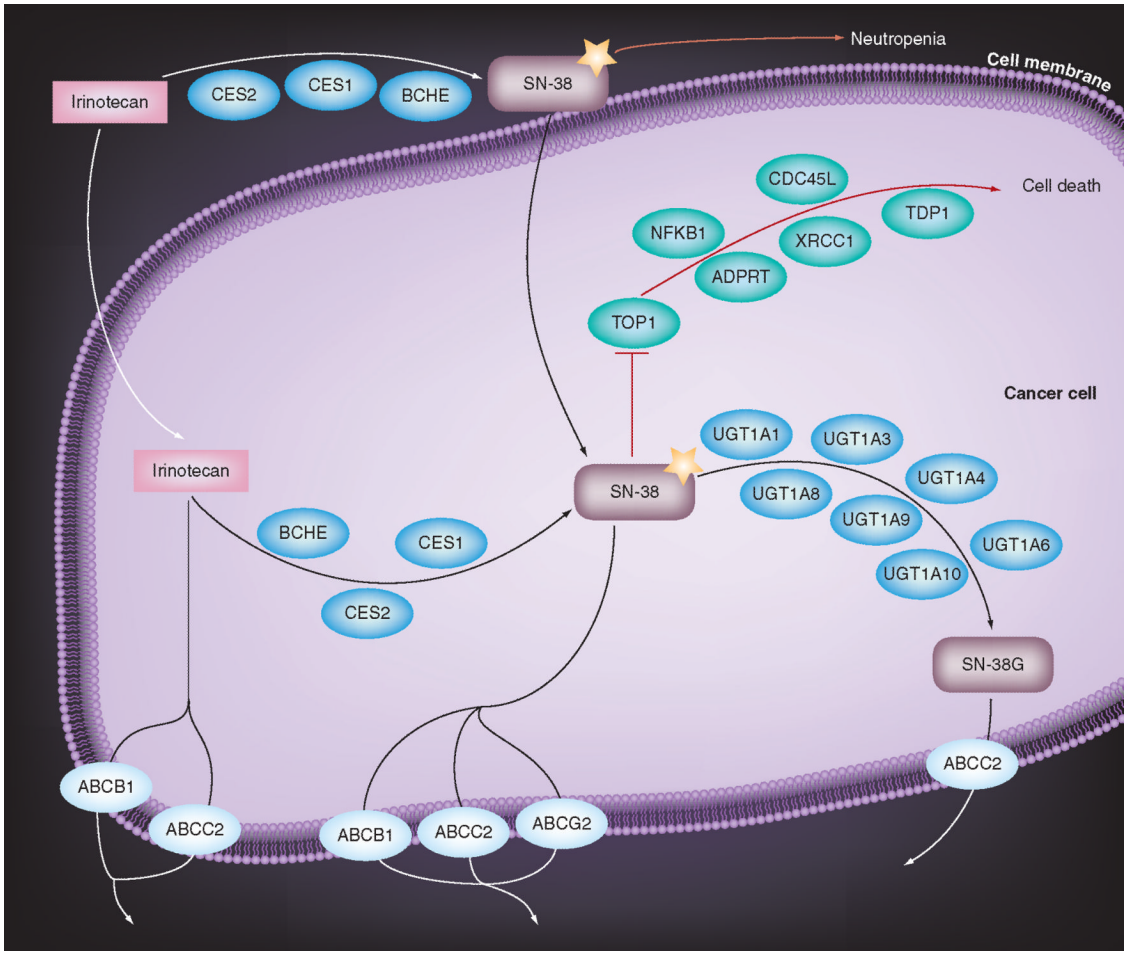

Figure 1. Irinotecan cancer cell pathway
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Table 1

Summary of genes and variants from irinotecan pharmacogenomics studies.

Gene	Variant	dbSNP ID	Effect	Ref.
ABCB1	1236C>T	rs1128503	Decreased irinotecan clearance; risk of toxicity and reduced survival when in haplotype with 2677 and 3435	[56,58,59]
ABCB1	2677G>A/T	rs2032582	Risk of toxicity and reduced survival when in haplotype with 1236 and 3435	[58,59]
ABCB1	3435C>T	rs1045642	Increased toxicity; risk of toxicity and reduced survival when in haplotype with 1236 and 2677	[57–59]
ABCC2	−24C>T	rs717620	Increased response and survival with 3972; toxicity as part of *ABCC2* haplotype in patients without *GT1A1*28*	[46,61–63]
ABCC2	3972T>C	rs3740066	Increased response and survival with −24; toxicity as part of *ABCC2* haplotype in patients without *UGT1A1*28*	[43,46,60–63]
ABCG2	34G>A	rs2231137	Increased toxicity; no association with toxicity and outcome	[60,61]
ABCG2	421C>A; Q141K	rs2231142	Reduced expression; irinotecan resistance; toxicity with IVS12 +49G>T	[49,61,66,67]
ABCG2	IVS12+49G>T	rs3832043	Toxicity with 421C>A	[49,61,66,67]
CES1	−816A>C	Unknown	Altered *CES1* promoter activity	[22]
CES2	830C>G; −171C>G	rs11075646	No association with expression, catalytic activity, toxicity or outcome	[20]
CYP3A4	Activity		Altered irinotecan dosing requirement	[24]
NR1I2	Expression		Altered SN-38 glucuronidation	[79]
TDP1	IVS12+79T>G	rs2401863	Response; no toxicity association at higher doses	[74,75]
UGT1A1	−3156G>A	rs10929302	Increased risk of toxicity	[32,33]
UGT1A1	$(TA)_7$ TAA, **28*	rs8175347	Increased risk of toxicity; dose dependent	[32,33,38–41]
UGT1A1	G71R, **6*	rs4148323	Increased risk of toxicity	[44,47]
UGT1A7	**2* (N129K and R131K)	rs17868323, rs17868324	SN-38 glucuronidation; response	[47,52]
UGT1A7	**3* (N129K, R131K and W208R)	rs17868323, rs17868324, rs11692021	SN-38 glucuronidation; increased risk of toxicity; altered response	[47,52,54]
UGT1A9	−118(dT)	rs3832043	SN-30 glucuronidation; response	[44,47,52,54]
XRCC1	Haplotype (−1149delGGCC, R399Q)	rs321329 rs25487	Response	[74]
XRCC1	R399Q	rs25487	No association with toxicity; association with response	[76,77]

dbSNP: SNP database