

Pharmacogenomics of irinotecan

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Although the clinical importance of genetic testing has not been uniformly established for all tumor types, treatment-related genetic variables will certainly become part of survival planning as the field of pharmacogenetics matures. Many practical issues await resolution before genetic screening for clinically relevant polymorphisms becomes a reality. Until then, clinical considerations such as volume status, renal function, and preexisting bowel dysfunction may suggest the need to modify the dosage or mode of administration of irinotecan for patients with metastatic colorectal cancer.

This patient's history of diabetes and preexisting peripheral neuropathy are indications for strong consideration of irinotecan (Camptosar)-based chemotherapy, in light of the potential for additional neurotoxicity with oxaliplatin (Eloxatin).¹ One of the persistent challenges in administering chemotherapy to patients with mCRC is the considerable variation in treatment response. This marked heterogeneity, coupled with the narrow therapeutic index characteristic of cytotoxic medications, means that in most cases, the expected efficacy and potential toxicity of a chosen regimen are somewhat unpredictable and cannot be estimated prospectively apart from a general likelihood drawn from clinical trials enrolling populations with a similar disease stage and histopathology.^{2,3}

Consequently, advances in the field of pharmacogenomics, which suggests a genetic basis for individual differences in treatment response, susceptibility to toxicity, and even survival, are of great interest to contemporary oncologists. Rapidly evolving developments hint at the still-unproved possibility that genetics-based assessment tools may be used in a clinically meaningful way to predict the efficacy and tolerability of chemotherapy, identify prognostic differences, stratify patients, and guide the creation of highly tailored regimens for individual patients.²⁻⁸ It is a daunting task. Approximately 30,000 genes comprise the human genome in a population of

Case history

A 55-year-old frail woman was newly diagnosed with metastatic colorectal cancer (mCRC). She has a small lesion on the liver, and numerous other small lesions throughout the pelvic region are apparent. Liver function is unimpaired, and serum bilirubin levels are within the normal range at the time of assessment. The patient has long-standing type 2 diabetes, mild peripheral neuropathy, and hypertension. Her Eastern Cooperative Oncology Group (ECOG) performance status (PS) is 2. She is willing to undergo chemotherapy, but tolerability is a major concern of her family and primary care physician. Is it appropriate to screen this individual for genetic polymorphisms linked to an elevated risk of irinotecan-associated toxicity?

over 3 billion nucleotides; in these nucleotides, mutations occur with sufficient frequency that any two human subjects will differ by roughly 2.5 million single nucleotide polymorphisms.⁹

Chemotherapy is often administered at a maximally tolerated dose as established in clinical studies. Treatment is initiated with the expectation that

Manuscript received February 26, 2007; accepted March 16, 2007.

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one in three patients will experience unacceptable toxicity.¹⁰ Genetic polymorphisms affecting drug metabolism are an important contributing factor to interindividual variations in drug tolerability, since polymorphic alleles coding for enzymes involved in drug metabolism may yield peptides with absent, degraded, or enhanced activity.⁹ In addition to molecular variations, many other factors can contribute to the development of severe treatment-related toxicity, including poor patient selection, inadequate surveillance, associated organ dysfunction, and interactions with concurrent drug therapy.⁷ Although a number of clinical pharmacogenetic tests are available, little information exists to prove that their rou-

tine use is cost-effective or predictive of outcome. Studies are required to validate a standardized clinical role for pharmacogenetic testing and to establish the best method of interpreting test results so that treatment regimens can be tailored to different patient groups.⁷

Clinical implications of genetic polymorphisms

Subsets of patients who are genetically predisposed to irinotecan toxicity have well-described polymorphisms in the enzyme uridine diphosphate-glucuronosyltransferase (UGT) 1A1. This enzyme, which participates in the conjugation of bilirubin, is also responsible for the inactivation of SN-38, a potent topoisomerase inhibitor

formed by the hydrolysis of irinotecan (Figure 1).

UGT1A1 polymorphisms differ in the number of repeating insertions or deletions in the transcription-orienting TATA box. Variants have been identified with 5, 6, 7, and 8 repeats, of which the 6- and 7-repeat patterns are the most common. Individuals who have the 7-TA allele (*UGT1A1*28*) have the most reduced expression of *UGT1A1* compared with other variants.¹⁰⁻¹⁴

Reduced levels of this enzyme result in impaired degradation of irinotecan, greater bioavailability of SN-38, and thus greater exposure of tissue—both normal and malignant—to the active metabolite. Studies have demonstrated that individuals who are homozygous for *UGT1A1*28* (7/7) are substantially more likely to experience severe grade 3/4 hematologic toxicity and may be at greater risk for severe diarrhea (Table 1).^{13,15-18} The risk for neutropenia is highly associated with the homozygous 7/7 genotype. These patients have a profound deficit in the enzyme activity that is required for metabolism of the toxic irinotecan metabolite.

In a retrospective case-controlled study enrolling mostly patients with lung cancer, individuals who were heterozygous or homozygous for *UGT1A1*28* (6/7 and 7/7, respectively) were at significantly greater risk of developing severe diarrhea or neutropenia during treatment with irinotecan ($P < 0.001$; odds ratio, 7.23; 95% confidence interval [CI], 2.52–22.3). It is worth noting that in this same study, homozygous and heterozygous phenotypes were found in matched controls who did not develop toxicity, although at a much reduced prevalence.¹³

These findings were confirmed prospectively in 66 cancer patients receiving monotherapy with irinotecan (350 mg/m² every 3 weeks). Patients with a range of solid tu-

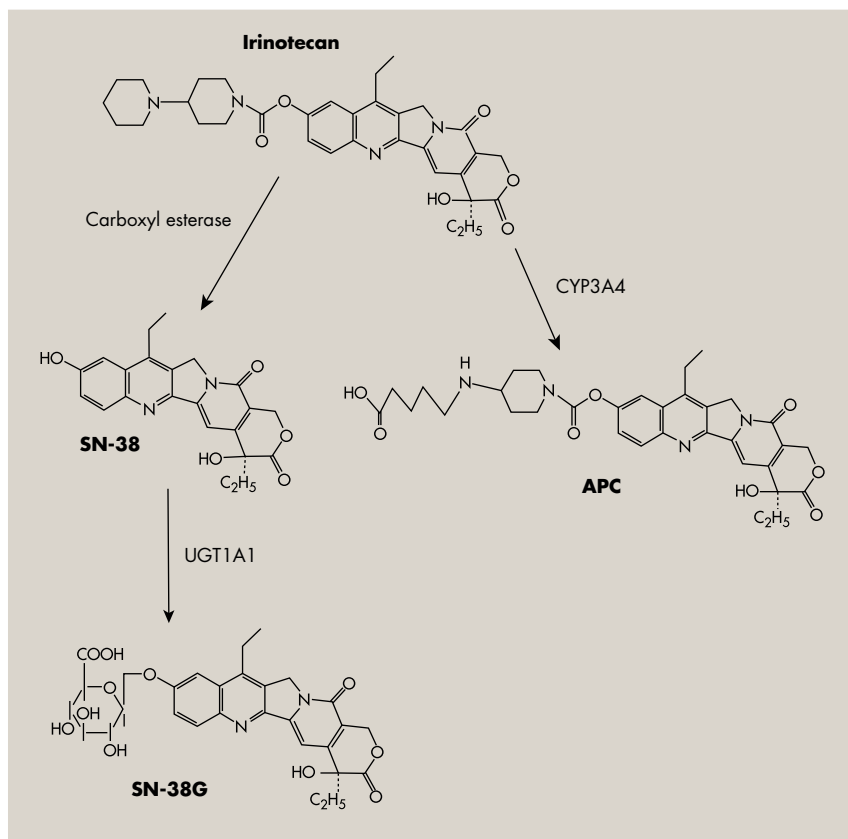


FIGURE 1 Hydrolysis of irinotecan yields the active metabolite SN-38. Glucuronidation of SN-38 to SN-38G is catalyzed by the enzyme UGT1A1, for which numerous polymorphisms exist. These polymorphisms differ according to the number of TA repeats, with UGT1A1 expression inversely related to the number of repeats. Impaired degradation of SN-38 leads to prolonged exposure to and persistence of the active metabolite of irinotecan within the bowel lumen.¹⁰⁻¹²

mors or lymphoma, including lung (n = 19), gastroesophageal (n = 14), colorectal (n = 10), or other (n = 23) cancers, were enrolled in this study; tumors were either of a type known to respond to irinotecan or for which no therapy of proven benefit existed. All patients had advanced refractory disease, with prior exposure to a median of two chemotherapy regimens (range, 0–6). The overall prevalence of grade 4 neutropenia was 9.5%, but it was noted in 3 of 6 patients (50%) who were 7/7 homozygous and in 3 of 24 patients (12.5%) who were 6/7 heterozygous. The relative risk of grade 4 neutropenia was 9.3 (95% CI, 2.4–36.4) for homozygous 7/7 patients in comparison with others.

An additional finding in this study was that pretreatment total bilirubin levels were significantly higher in patients with grade 4 neutropenia (0.83 ± 0.08 mg/dL) compared with those without grade 4 neutropenia (0.47 ± 0.03 mg/dL; $P < 0.001$).¹⁵ These results suggest that pretreatment total bilirubin level is a predictor of severe neutropenia, but they do not clarify whether total bilirubin is a better predictor than genotype in identifying those subjects at greatest risk of hematologic toxicity. Although both elements appeared to have comparable predictive value in this study, it remains unanswered whether total bilirubin level is sufficiently interchangeable with genotyping information so that it may be used in its place when DNA testing is unavailable.¹⁵

In a multivariate model of neutropenia associated with irinotecan in 109 chemotherapy-naïve individuals undergoing initial treatment with irinotecan plus infusional 5-fluorouracil/leucovorin (5-FU/LV; FOLFIRI; n = 35), irinotecan plus oral capecitabine (Xeloda; CapeIRI; n = 33), or modified IFL (mIFL; n = 41), serum bilirubin levels did not appear to offer additional predictive value for hematologic toxicity. In this

TABLE 1

Risk for severe neutropenia during irinotecan chemotherapy in patients with a 7/7 genotype vs 6/6 or 6/7 genotypes

Primary author	Genotype, number (%)		Estimated OR (unadjusted) for severe neutropenia	95% CI
	7/7	6/6 + 6/7*		
Innocenti ¹⁵	3/6 (50%)	3/53 (6%)	16.7	2.3–120.6
Rouits ¹⁶	4/7 (57%)	10/66 (15%)	7.5	1.4–38.5
Marcuello ^{18 †}	4/10 (40%)	18/85 (21%)	2.5	0.6–9.7
Ando ^{13 ‡}	4/7 (57%)	22/111 (20%)	5.4	1.1–25.9

OR = overall response; CI = confidence interval

* Risks are pooled for 6/6 and 6/7 patients

† Grade 3/4 neutropenia

‡ Grade 4 leukopenia and/or grade 3/4 diarrhea^{13,15–18}

population, frequencies of *UGT1A1* genotypes 6/6, 6/7, and 7/7 were 45%, 45%, and 10%, respectively.

In the FOLFIRI group, one patient experienced a first-cycle absolute neutrophil count (ANC) nadir below 1,000 white blood cells/mm³ (grade 3 neutropenia) and two had a first-cycle ANC nadir below 500 white blood cells/mm³ (grade 4), whereas three patients receiving mIFL demonstrated grade 3 and three demonstrated grade 4 neutropenia. In the group treated with CapeIRI, two patients had grade 3 and three patients had grade 4 neutropenia. Three linear regression models adjusting for age and gender were tested, incorporating as variables *UGT1A1* genotype, baseline bilirubin level, or both. Resulting r^2 values were low, suggesting the presence of other, unidentified contributory factors, although the addition of *UGT1A1* genotype increased predictive power by 5%–10% for all groups. In association with age, gender, and genotype, bilirubin levels offered little additional explanatory power for ANC nadir, particularly when FOLFIRI was the underlying regimen.¹⁹

A recent report evaluated the relationship between *UGT1A1* genotype, chemotherapy regimen, toxicity, and outcome in 520 patients in the North Central Cancer Treatment Group N9741 trial.²⁰ Patients were randomly assigned to receive treat-

ment with IFL (n = 114), oxaliplatin plus infusional 5-FU/LV (FOLFOX; n = 299), or irinotecan plus oxaliplatin (IROX; n = 107). Among all patients in the study, the 6/6 genotype was present in 14.8% of patients; the 6/7 genotype, in 18.2% of patients; and the 7/7 genotype, in 36.2% of patients ($P = 0.007$).

An association between the 7/7 genotype and susceptibility to grade 4 neutropenia was observed in all treatment arms, attaining statistical significance with receipt of any chemotherapy ($P = 0.007$) and irinotecan and oxaliplatin specifically ($P = 0.004$).²⁰ The overall frequency of the 7/7 genotype was low, occurring in only 9% of study patients; however, exclusion of these homozygous patients would have made only a slight difference, reducing the rate of grade 4 hematologic toxicity from 18% to 17%, thus emphasizing that toxicity manifests for myriad reasons regardless of genotype.

Is genotyping of practical benefit?

Should the patient in this scenario be screened for *UGT1A1* polymorphisms? There would appear to be little practical benefit in determining her genotype; even if she were to be identified as a 7/7 homozygote, her real risk of treatment-emergent toxicity is unknown. Since our patient was frail at baseline, with a moder-

ately impaired PS, dose modification may be considered based on readily apparent clinical factors without the need for genetic testing. Balanced against treatment toxicity is the fact that irinotecan is a validated standard-of-care component of first- and second-line treatment of mCRC. Overall survival of patients is dramatically improved with exposure to all active drugs—including 5-FU, oxaliplatin, and irinotecan—during the course of therapy.^{21,22} For patients similar to ours, who present after failing to respond to first-line therapy with FOLFOX, it is neither practical nor ethically supportable to exclude them—even in the presence of specific polymorphisms—from receiving potentially effective irinotecan-based therapy.

In this case scenario, a dose reduction should be considered even without knowing the genotype. All chemotherapy drugs have a narrow therapeutic index and a range of adverse effects, including some with potentially great severity. Screening for susceptibility to toxicity during treatment with an irinotecan-containing regimen such as IFL or FOLFIRI would not be predictive, based on currently available data. Even if all 7/7 genotypes were identified, toxicity may still develop spontaneously in the most prevalent, wild-type variant (6/6).

A decade of use has shown that the most salient aspects of irinotecan-related toxicity arise from modifiable factors, such as mode of administration (bolus versus infusion), and specific clinical considerations (volume status, renal function, preexisting bowel dysfunction).¹ A number of clinically apparent variables may suggest the need to modify the dosage of irinotecan before resorting to genetic testing.

Although the clinical importance of genetic testing has not been uniformly established for all tumor types, patient groups, and clinical situations,

the discussion of treatment-related genetic variables will certainly become part of survival planning as the field of pharmacogenetics matures. Many practical issues await resolution before genetic screening for clinically relevant polymorphisms—and truly individualized therapy based on the presence or absence of specific enzyme pathways—becomes a reality.

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Conflicts of interest: Dr. Lenz is a consultant for Pfizer Inc, Genentech, sanofi-aventis Group, ImClone, Bristol-Meyers Squibb, Merck KG, ResponseGenetics, Inc., and Amgen. He has received honoraria from Pfizer, Genentech, sanofi-aventis Group, ImClone, Bristol-Meyers Squibb, Merck KG, and Amgen; and is a stock owner of ResponseGenetics.