UGT1A1*28 Genotype and Irinotecan-Induced Neutropenia: Dose Matters

Janelle M. Hoskins, Richard M. Goldberg, Pingping Qu, Joseph G. Ibrahim, Howard L. McLeod

The Food and Drug Administration and Pfizer changed the package insert for irinotecan to include a patient’s UGT1A1*28 genotype as a risk factor for severe neutropenia on the basis of the findings of four pharmacogenetic studies, which found that irinotecan-treated patients who were homozygous for the UGT1A1*28 allele had a greater risk of hematologic toxic effects than patients who had one or two copies of the wild-type allele (UGT1A1*1). Findings of subsequent irinotecan pharmacogenetic studies have been inconsistent. In a meta-analysis, we reviewed data presented in nine studies that included a total of 10 sets of patients (for a total of 821 patients) and assessed the association of irinotecan dose with the risk of irinotecan-related hematologic toxicities (grade III–IV) for patients with a UGT1A1*28/*28 genotype. The risk of toxicity was higher among patients with a UGT1A1*28/*28 genotype than among those with a UGT1A1*1/*1 or UGT1A1*1/*28 genotype at both medium (odds ratio [OR] = 3.22, 95% confidence interval [CI] = 1.52 to 6.81; \( P = .008 \)) and high (OR = 27.8, 95% CI = 4.0 to 195; \( P = .005 \)) doses of irinotecan. However, risk was similar at lower doses (OR = 1.80, 95% CI = 0.37 to 8.84; \( P = .41 \)). Low doses of irinotecan (100–125 mg/m²) are in the commonly used therapeutic range. The risk of experiencing irinotecan-induced hematologic toxicity for patients with a UGT1A1*28/*28 genotype thus appears to be a function of the dose of irinotecan administered.


Irinotecan (Camptosar), a topoisomerase I poison, is approved for use in combination with 5-fluorouracil and leucovorin chemotherapy for first-line treatment of metastatic colorectal cancer and as a single agent in second-line salvage therapy of 5-fluorouracil refractory metastatic colorectal cancer disease. It is also commonly used to treat esophageal, non–small-cell lung, and breast cancers and other solid tumors in a second- or third-line setting. Irinotecan can be administered weekly, every 2 weeks, or every 3 weeks at doses ranging from 50 to 350 mg/m². The principal dose-limiting toxicities are delayed diarrhea and neutropenia; these toxicities are reversible, not cumulative, and related to irinotecan dose (1). Irinotecan is metabolized in vivo by carboxylesterases to the active metabolite SN-38, which is 100- to 1000-fold more potent than irinotecan as a topoisomerase I poison. SN-38 is eliminated predominantly by glucuronidation to SN-38 glucuronide. This glucuronidation reaction is mediated primarily by UDP-glucuronosyltransferase 1 family polypeptide A1, which is encoded by the UGT1A1 gene. Systemic exposure to SN-38 (as measured by area under the concentration–time curve) is related to the number of TA base repeats that a patient carries in the promoter region of each UGT1A1 allele (2–5). The wild-type allele (i.e., allele UGT1A1*1) has six TA repeats, and the variant allele (i.e., allele UGT1A1*28) has seven TA repeats. Patients who are homozygous for the UGT1A1*28 allele glucuronidate SN-38 less efficiently than patients who have one or two wild-type alleles; therefore, homozygous patients are exposed to higher plasma concentrations of SN-38 (3).

In November 2004, the US Food and Drug Administration (FDA) Advisory Committee on Pharmaceutical Sciences considered the findings of four pharmacogenetic trials that had assessed the association between UGT1A1*28 genotype and irinotecan-induced toxicities in a total of 30 patients who were homozygous for the UGT1A1*28 allele (4,6–8). In these studies, associations between the UGT1A1*28/*28 genotype and hematologic toxicity and/or diarrhea were observed. As a result of these findings, the FDA advised Pfizer Pharmaceuticals, the manufacturer of irinotecan, to amend the product information for the drug to include the association between the UGT1A1*28 genotype and hematologic toxicity and to recommend that patients with the UGT1A1*28/*28 genotype receive a lower starting dose of irinotecan. These changes took effect in July 2005. A diagnostic test for the UGT1A1*28 genotype (i.e., Invader UGT1A1 Molecular Assay; Third Wave Technologies, Inc, Madison, WI) for irinotecan dosing was approved in August 2005 by the FDA (9).

Subsequent results have begun to clarify the association between UGT1A1*28 and irinotecan-induced toxicities, particularly for dosing schedules that were not reviewed in the initial FDA committee meeting. Some studies (4,7) found that the UGT1A1*28/*28 genotype predicted grade III–IV neutropenia but not diarrhea, and other studies (6,10) found that the genotype predicted grade III–IV diarrhea but not hematologic toxicity. These results contrast with studies in which the UGT1A1*28...
logic toxicity in three (3, 4, 14) of the 10 samples. A UGT1A1*28/*28 genotype was associated with severe hematologic toxicity in a total of 821 patients. Two irinotecan-containing regimens were administered to patients in the N9741 study (14), and in our analyses, we analyzed the patients treated with each regimen as two separate samples. A summary of the 10 pharmacogenetic samples included in our analyses is presented in Table 1. Among the samples, patients received a variety of irinotecan-containing regimens, including commonly used higher doses (200–350 mg/m²) administered every 21 days, an intermediate dose (180 mg/m²) administered every 2 weeks, or lower doses (80–125 mg/m²) administered weekly; irinotecan was given either alone or in combination with other anticancer agents. A UGT1A1*28/*28 genotype was associated with severe hematologic toxicity in three (3, 4, 14) of the 10 samples (P <.05, two-sided Fisher’s exact test; see Table 1 for P values) and tended to be associated with toxicity in two of the samples (6, 13) (P <.1). In the other five samples, the UGT1A1*28/*28 genotype was not associated with toxicity.

Heterogeneity among samples was tested by use of a chi-square test, and the presence of heterogeneity was not detected (P = .25). Publication bias was assessed by a funnel plot of the log odds ratio (OR) of individual samples against the standard error of the log odds ratios. The plot (Fig. 1) appeared to be symmetrical about the horizontal line (weighted average log OR = 1.35), with the diameter of the funnel decreasing with decreasing standard error (i.e., increasing sample size), indicating no evidence of publication bias. The observation suggests that studies demonstrating non–statistically significant associations between UGT1A1*28/*28 genotype and irinotecan-related hematologic toxicity were ascertained and included in the meta-analytic study.

To assess whether irinotecan dose modulates the association between UGT1A1*28 genotype and the risk of hematologic toxicity, we used a generalized linear mixed model (available in the SAS PROC GLIMMIX program, SAS Institute, Cary, NC) and considered dose as both a continuous and categorical variable. By using a unified regression model, we could account for the sample size of each genotype and of each sample. We first considered dose as a continuous variable and compared the rate of severe hematologic toxicity induced by irinotecan between patients with a UGT1A1*28/*28 genotype and patients with one or two wild-type alleles (UGT1A1*1/1 or UGT1A1*1/*28 genotype). The results showed that the risk of hematologic toxicity between patients with a UGT1A1*28 and those with a UGT1A1*1/*1 or UGT1A1*1/*28 increased statistically significantly as irinotecan dose increased (slope = 0.012; P = .028). At a low dose level the risk was relatively low, but at a medium to high dose level the risk was higher. For example, at an irinotecan dose of 100 mg/m², the odds of hematologic toxicity for UGT1A1*28/*28 patients was 1.28 times higher than for UGT1A1*1/*1 or UGT1A1*1/*28 patients (OR = 1.28, 95% confidence interval [CI] = 0.42 to 3.91; P = .63), and, at a dose of 250 mg/m², it was 3.23 times higher (OR = 8.07, 95% CI = 3.23 to 20.2; P <.001).

In a further analysis, we assessed the association between UGT1A1*28 genotype and hematologic toxicity and their interaction with irinotecan dose as a categorical variable. Irinotecan dose levels were pooled into the following three groups: low (<150 mg/m²), medium (150–250 mg/m²), and high (>250 mg/m²) doses on the basis of the three most commonly used dosage regimens. At medium doses, the risk of toxicity was higher among patients with a UGT1A1*28/*28 genotype than those with a UGT1A1*1/*1 or UGT1A1*1/*28 genotype (OR = 3.22, 95% CI = 1.52 to 6.81; P = .008); similarly, at high doses, the risk was higher among patients with a UGT1A1*28/*28 genotype than among

**CONTEXT AND CAVEATS**

**Prior knowledge**

In four previous studies, a UGT1A1*28 genotype among irinotecan-treated patients was associated with an increased risk of severe neutropenia.

**Study design**

A meta-analysis of nine studies that included 10 sets of patients (for a total of 821 patients) assessed the association between irinotecan dose and the risk of grade III and IV hematologic toxic effects by UGT1A1*1* or UGT1A1*28 genotype.

**Contribution**

The risk of hematologic toxic effects at high and medium irinotecan doses was higher among patients with a UGT1A1*28/*28 genotype than among those with a UGT1A1*1/*28 or UGT1A1*1/*1 genotype. However, at lower doses, risk was similar for patients with all genotypes. Low doses of irinotecan (100–125 mg/m²) are in the commonly used therapeutic range.

**Implications**

At low doses of irinotecan, decisions about treating individual patients can be made according to standard clinical practice because genotype was not associated with risk. At higher doses, genotype-based decisions are advisable because of the association between the UGT1A1*28/*28 genotype and increased risk of irinotecan-induced toxic effects.

**Limitations**

There were many sources of heterogeneity among the studies analyzed. Some sources of heterogeneity could have influenced patient participation in a trial and, therefore, the dose of irinotecan that was received. Others could have been related to the dose of irinotecan administered by trials. These factors may also have directly modulated the association observed. Because of limited power or the unavailability of individual data, the relationship between these factors and the association could not be assessed.
Table 1. Summary of 10 samples included in our analyses that assessed the diagnostic value of the homozygous UGT1A1*28 genotype to predict irinotecan-induced grade III–IV hematologic toxicity†

<table>
<thead>
<tr>
<th>Irinotecan dose, mg/m² (%) patients</th>
<th>Schedule</th>
<th>Concomitant chemotherapy</th>
<th>Trial type</th>
<th>Patient type</th>
<th>Toxicity (grade III–IV)</th>
<th>Toxicity criteria</th>
<th>No. of patients</th>
<th>Overall incidence of toxicity§</th>
<th>No. of UGT1A1*28/*28 patients (frequency, %)</th>
<th>UGT1A1*28/*28</th>
<th>UGT1A1*1/*1 or *1/*28</th>
<th>Two-sided Fisher’s exact P</th>
<th>First author</th>
<th>Sample ref.</th>
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<tr>
<td>350 Every 3 wk</td>
<td>None</td>
<td>Phase I, prospective</td>
<td>Solid tumors, lymphoma</td>
<td>Neutropenia</td>
<td>NCI 61 18 (11/61) 6 (10)</td>
<td>83 (5/6) 11 (6/55)</td>
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<tr>
<td>300 Every 3 wk</td>
<td>None</td>
<td>Phase I, prospective</td>
<td>Solid tumors, lymphoma</td>
<td>Neutropenia</td>
<td>NCI 20 10 (2/20) 4 (20)</td>
<td>50 (2/4) 0 (0/16)</td>
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<td>200 Every 3 wk OXA</td>
<td>Prospective</td>
<td>Advanced colorectal</td>
<td>Neutropenia (IV only)</td>
<td>NCI 103 17 (17/103) 11 (11)</td>
<td>55 (5/11) 12 (11/92)</td>
<td>.002 McLeod (14)</td>
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<td>180 Biweekly 5FU</td>
<td>Prospective</td>
<td>Metastatic colorectal</td>
<td>Neutropenia WHO</td>
<td>WHO 56 25 (14/56) 5 (9)</td>
<td>60 (3/5) 22 (1/51)</td>
<td>.09 Marcuello (6)</td>
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<td>180 Biweekly 5FU</td>
<td>Prospective</td>
<td>Metastatic colorectal</td>
<td>Neutropenia WHO</td>
<td>WHO 58 28 (16/58) 7 (12)</td>
<td>57 (4/7) 24 (1/51)</td>
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<td>180 Biweekly 5FU Retrospective</td>
<td>Advanced colorectal</td>
<td>Neutropenia WHO</td>
<td>WHO 46 33 (15/47) 5 (11)</td>
<td>60 (3/5) 29 (1/24)</td>
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<tr>
<td>100 Weekly 5FU</td>
<td>Prospective</td>
<td>Advanced colorectal</td>
<td>Neutropenia (IV only)</td>
<td>NCI 109 10 (11/109) 11 (10)</td>
<td>18 (2/11) 9 (9/96)</td>
<td>.31 McLeod (14)</td>
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<td>14 (1/7) 6 (3/49)</td>
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<tr>
<td>100 (22) Weekly CAP</td>
<td>CAP</td>
<td>Phase II, prospective</td>
<td>Metastatic colorectal</td>
<td>Neutropenia WHO</td>
<td>NCI 64† 5 (3/64) 6 (9)</td>
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<tr>
<td>125 (78) Weekly CAP</td>
<td>CAP</td>
<td>Phase II, prospective</td>
<td>Metastatic colorectal</td>
<td>Neutropenia WHO</td>
<td>NCI 64† 5 (3/64) 6 (9)</td>
<td>0 (0/6) 5 (3/58)</td>
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† ref. = reference; NCI = National Cancer Institute common toxicity criteria; OXA = oxaliplatin; 5FU = 5-fluorouracil; WHO = World Health Organization; RAL = raltitrexed; CAP = capecitabine.
‡ NCI and WHO systems grade an absolute neutrophil count of less than 1000 × 10⁶ cells per L of blood as grade III–IV neutropenia (http://safetyprofiler-ctep.nci.nih.gov/CTC/CTC.aspx, http://www.who.int/en/).
§ The toxicity incidence (overall or by genotype group) is reported as a percentage. Values in parentheses are number of patients overall or in each genotype group with hematologic toxicity/number of total patients in that group.
|| More than one irinotecan-containing regimen was administered in these studies. Only results from patients who received irinotecan at 180 mg/m² biweekly with 5-fluorouracil were considered in these analyses.
†† Patients with TA₅ and TA₈ alleles are included in these results.
those with a UGT1A1*1/*1 or UGT1A1*1/*28 genotype (OR = 27.8, 95% CI = 4.00 to 195; \( P = .005 \)). In contrast, at low irinotecan doses, the risk of toxicity was not statistically significantly different between patients with a UGT1A1*28/*28 genotype and those with a wild-type allele (OR = 1.80, 95% CI = 0.37 to 8.84; \( P = .41 \)). Results from the categorical-dose and the continuous-dose analyses were similar; i.e., a statistically significant association was found between genotype and toxicity at medium or high doses of irinotecan but not at low doses.

We also assessed whether irinotecan dose modulates the association between UGT1A1*28 genotype and irinotecan-induced diarrhea (grade III–IV). We identified nine studies (3,4,6,7,10,11,13–15) that assessed the relationship between UGT1A1*28 genotype and toxicity. As noted above, the N9741 study (14) administered two irinotecan-containing regimens to patients, and we treated the patient who was administered the different regimens as two separate samples. In addition, only grade IV diarrhea data were available for the study (14). Of the 10 samples, UGT1A1*28/*28 genotype was associated with severe diarrhea in only one sample (relative risk = 3.40, 95% CI = 1.76 to 6.59; \( P = .02 \), two-sided Fisher’s exact test), indicating that UGT1A1*28 genotype was not associated with diarrhea (6). We next assessed the relationships between irinotecan dose and the incidence of irinotecan-induced diarrhea (grade III–IV) by genotype. The incidence of severe diarrhea in patients with a UGT1A1*28/*28 genotype was not related to irinotecan dose \((r^2 = 0.8; P = .1; n = 10 \text{ samples})\) (data not shown); however, the rate of diarrhea among patients with one or two wild-type alleles was inversely associated with dose \((r^2 = .43; P = .04; n = 10 \text{ samples})\) (data not shown). Thus, the risk of diarrhea among patients with a UGT1A1*28/*28 genotype was not associated with irinotecan dose, and so we did not examine this relationship further.

We observed that, at higher irinotecan doses (>150 mg/m²), the risk of hematologic toxicity was strongly associated with the UGT1A1*28 polymorphism. In contrast, at lower doses (<150 mg/m²), the risk of hematologic toxicity among patients with a UGT1A1*28/*28 genotype was not statistically significantly different from that among patients with one or two wild-type alleles (i.e., UGT1A1*1/*28 or UGT1A1*1/*1, respectively). This observation is consistent with a classic gene–environment interaction, in which the association between genotype and outcome depends on the level of exposure to an environmental factor—in this case, the dose of irinotecan (16). To our knowledge, this is the first demonstration of a gene–environment interaction in the context of pharmacogenetics. In contrast, among patients with the UGT1A1*28/*28 genotype, irinotecan dose was not associated with diarrhea. Heterogeneity of irinotecan administration, diarrhea management with loperamide, coadministered chemotherapeutic agents among trials, and difficulty in scoring this toxicity might contribute to the incidence of this adverse event and explain some of the interstudy variation in the incidence of diarrhea among patients with a UGT1A1*28/*28 genotype. The utility of UGT1A1*28 genotype to predict irinotecan-induced diarrhea, therefore, remains unclear and requires further investigation.

We propose two potential strategies for irinotecan dosing to accommodate the modulatory effect of irinotecan dose on the risk of hematologic toxicities among patients with a UGT1A1*28/*28 genotype. The first is based on a prior selection of the most convenient and appropriate regimen for the individual patient. When regimens with a low dose of irinotecan (<150 mg/m²) given weekly are being considered, decisions concerning the best irinotecan dose for individual patients could be made on the basis of standard clinical practice rather than genotype because genotype was not associated with an increased risk of toxicity. Low doses of irinotecan (100–125 mg/m²) are in the commonly used therapeutic range (17). For patients receiving a more convenient high-dose regimen (>250 mg/m²), however, genotype-based decisions are advisable because UGT1A1*28 genotype was associated with toxicity at higher doses of irinotecan (>150 mg/m²). For patients with a UGT1A1*28/*28 genotype, a starting irinotecan dose reduction of one level is recommended in the package insert from the manufacturer (18), whereas, for patients with one or two wild-type alleles a standard irinotecan dose can be used. Patients with a UGT1A1*28/*28 genotype had a heightened risk of toxicity at intermediate doses (150–250 mg/m²) that were given biweekly or every 3 weeks. However, the odds of toxicity at intermediate doses are likely to be within a range acceptable to many patients who do not have other risk factors for neutropenia (e.g., they are not elderly or have not had prior myelotoxic therapy). We suggest that patients and physicians should strongly consider UGT1A1*28 testing for patients with other predictors of irinotecan-induced neutropenia. Alternatively, all patients could initiate therapy at a dose reduction of one level, with doses being increased if toxicity is modest. This approach apparently does not adversely influence outcomes of patients treated with low doses of irinotecan, but clear survival data are not available for high-dose irinotecan regimens (19).

The second potential strategy is to select an irinotecan-containing regimen with a level of toxicity risk that is acceptable to the patient and physician by use of Fig. 2, A, and results of the random effects model for irinotecan as a categorical variable. For irinotecan doses of up to 150 mg/m², the absolute risk of severe neutropenia among patients with a UGT1A1*28/*28 genotype is similar to the overall risk for all patients (i.e., ~15%). The absolute
The two different irinotecan-containing regimens in the N9741 trial, which included only grade IV toxicity, were treated as two separate samples in our analyses (14).

Although this test, which assesses the relationship between the probabilities of experiencing hematologic toxicity under the generalized linear mixed model at any dose level in the original dose range; dotted lines = 95% confidence intervals. For trials in which more than one irinotecan regimen was administered, we considered only the results from patients who received irinotecan at 180 mg/m² biweekly with 5-fluorouracil (6,7).

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Confounding by genotype error, clinical phenotype, or other variables may also be sources of bias. UGT1A1*28 genotyping was conducted in different laboratories that used different methodologies; however, none of the samples in our study departed from the Hardy–Weinberg equilibrium (P>0.05; chi-square test). Although this test, which assesses the relationship between the frequency of the UGT1A1*28 allele and UGT1A1*28 genotypes in a population, is not the most sensitive measure of assay reliability, it suggests that genotype error was not a large source of bias. Additionally, the genotyping assays for UGT1A1*28 are not especially prone to errors, suggesting that genotype error is an unlikely source of bias among the studies. In our analysis, grade III–IV neutropenia data (absolute neutrophil count nadir of <1000 × 10⁶ cells per L) were available for seven samples (3,4,6,7,10,11,13), whereas only grade IV neutropenia information (14) and grade III–IV hematologic toxicity data (12) could be extracted from the literature for other samples. We treated these clinical events as equivalent, which may have introduced bias into our analysis. Data were extracted from publications for some samples (6,7,10) and obtained via correspondence with authors for other samples (3,4,11–14). Possible data errors reported in publications and others introduced by extracting data from publications could be other sources of bias that were not addressed by our methodology.

A diagnostic test that identifies patients at high risk of dose-limiting toxicities to irinotecan would be clinically useful. Although initial studies (4,6–8) found UGT1A1*28 genotype to be strongly associated with risk of toxicity, results of subsequent studies (10–14) were inconsistent. In our meta-analysis, we found that risk of toxicity within a genotype group is also an opportunity for the patient’s threshold for risk to help dictate the drug schedule or even specific regimen.

This study has several limitations. We used a meta-analytic approach to combine information from independent trials that had addressed the question whether patients homozygous for the UGT1A1*28 allele have an elevated risk of hematologic toxicity to assess whether the interaction between genotype and toxicity was associated with the administered dose of irinotecan. There were many sources of heterogeneity among the studies, including patient characteristics (e.g., age, ethnicity, sex, performance status, and number of previous chemotherapies), patient eligibility criteria (e.g., type of tumor, stage of disease, and number of previous chemotherapies), treatment schedules (e.g., dose of irinotecan and time between courses and coadministered chemotherapies), and study design (e.g., phase I, phase II, prospective, and retrospective trial). Some sources of heterogeneity (including the stage of tumor, type of tumor, and line of chemotherapy) could have influenced patient participation in a trial and therefore the dose of irinotecan that was received, and other factors (including time between irinotecan doses and coadministered chemotherapies) could have been related to the dose of irinotecan administered by trials. These factors may have directly modulated the association between UGT1A1*28 genotype and irinotecan-related toxicity. Unfortunately, we were unable to assess whether these factors influenced the association between genotype and toxicity among the samples either because of limited power due to the small sample size or because the individual data were not available.

Confounding by genotype error, clinical phenotype, or other variables may also be sources of bias. UGT1A1*28 genotyping was conducted in different laboratories that used different methodologies; however, none of the samples in our study departed from the Hardy–Weinberg equilibrium (P>0.05; chi-square test). Although this test, which assesses the relationship between the frequency of the UGT1A1*28 allele and UGT1A1*28 genotypes in a population, is not the most sensitive measure of assay reliability, it suggests that genotype error was not a large source of bias. Additionally, the genotyping assays for UGT1A1*28 are not especially prone to errors, suggesting that genotype error is an unlikely source of bias among the studies. In our analysis, grade III–IV neutropenia data (absolute neutrophil count nadir of <1000 × 10⁶ cells per L) were available for seven samples (3,4,6,7,10,11,13), whereas only grade IV neutropenia information (14) and grade III–IV hematologic toxicity data (12) could be extracted from the literature for other samples. We treated these clinical events as equivalent, which may have introduced bias into our analysis. Data were extracted from publications for some samples (6,7,10) and obtained via correspondence with authors for other samples (3,4,11–14). Possible data errors reported in publications and others introduced by extracting data from publications could be other sources of bias that were not addressed by our methodology.

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the irinotecan dose delivered modulated the association between UGT1A1*28 genotype and irinotecan-induced hematologic toxicity and that the interaction was clinically important only at higher irinotecan doses. At lower irinotecan doses, factors other than UGT1A1*28 genotype, either genetic or nongenetic, are likely to determine a patient’s risk of hematologic toxicity, whereas at higher drug doses, UGT1A1*28 genotype appears to be an important determinant. We recommend that the product information for irinotecan be amended to describe the association between irinotecan dose and risk of hematologic toxicity among patients with a UGT1A1*28/*28 genotype. We also favor the development of consensus guidelines by national and regional bodies (e.g., the National Cancer Institute, American Society of Clinical Oncologists, European Society of Medical Oncology, or National Comprehensive Cancer Network) for optimal use of UGT1A1*28 genotype information to prescribe irinotecan doses. Finally, we caution that decisions that are based on only a few events may prove to be misleading. Determining the amount of evidence needed to justify the inclusion of black box warnings on product inserts to safeguard patients is a controversial issue that is worthy of further study.

References


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