UGT1A1 Polymorphism Can Predict Hematologic Toxicity in Patients Treated with Irinotecan

Jean-François Côté,1 Sylvain Kirzin,1 Andrew Kramar,2 Jean-François Mosnier,4 Marie-Danièle Diebold,5 Isabelle Soubeyran,6 Anne-Sophie Thirouard,7 Janick Selves,8 Pierre Laurent-Puig,1 and Marc Ychou3

Abstract

Purpose: Irinotecan (CPT-11) is approved in metastatic colorectal cancer treatment and can cause severe toxicity. The main purpose of our study was to assess the role of different polymorphisms on the occurrence of hematologic toxicities and disease-free survival in high-risk stage III colon cancer patients receiving 5-fluorouracil (5FU) and CPT-11 adjuvant chemotherapy regimen in a prospective randomized trial.

Experimental Design: Four hundred patients were randomized in a phase III trial comparing LV5FU2 to LV5FU2 + CPT-11. DNA from 184 patients was extracted and genotyped to detect nucleotide polymorphism: 3435C>T for ABCB1, 6986A>G for CYP3A5, UGT1A1*28 and -3156G>A for UGT1A1.

Results: Genotype frequencies were similar in both treatment arms. In the test arm, no significant difference was observed in toxicity or disease-free survival for ABCB1 and CYP3A5 polymorphisms. UGT1A1*28 homozygous patients showed more frequent severe hematologic toxicity (50%) than UGT1A1*1 homozygous patients (16.2%), P = 0.06. Moreover, patients homozygous for the mutant allele of -3156G>A UGT1A1 polymorphism showed more frequent severe hematologic toxicity (50%) than patients homozygous for wild-type allele (12.5%), P = 0.01. This toxicity occurred significantly earlier in homozygous mutant than wild-type homozygous patients (P = 0.043). In a Cox model, the hazard ratio for severe hematologic toxicity is significantly higher for patients with the A/A compared with the G/G genotype [hazard ratio, 8.4; 95% confidence interval, 1.9–37.2; P = 0.005].

Conclusions: This study supports the clinical utility of identification of UGT1A1 promoter polymorphisms before LV5FU2 + CPT-11 treatment to predict early hematologic toxicity. The -3156G>A polymorphism seems to be a better predictor than the UGT1A1 (TA)6(TA)>(TA)7(TA)6(TA)7 TAA polymorphism.

Irinotecan (7-ethyl-10-[4-(1-piperidino)-1-piperidino]-carbon- yloxycamptothecin) (CPT-11) is a water-soluble analogue of 20(S)-camptothecin (CPT) and is an inactive prodrug. Its major metabolite, SN-38, is a potent active topoisomerase I inhibitor and is known to be toxic (1).

Due to its efficacy, CPT-11 is currently approved worldwide for use as first-line therapy in metastatic colorectal cancer, in combination with 5-fluorouracil (5FU) and leucovorin (LV; ref. 2). Adjuvant CPT-11 in combination with 5FU has recently been investigated in colorectal cancer. One limitation of CPT-11 is the unpredictable and occasionally fatal gastrointestinal and hematologic toxicity, which varies greatly between individuals. Predictive markers of CPT-11 toxicity may thus be deduced from the CPT-11 metabolic pathway.

CPT-11 is metabolized by carboxylesterase (CES), essentially the isoenzyme CES2, to active SN-38, then is further conjugated and detoxified by UDP-glucuronosyltransferase (UGT) 1A1 enzyme to yield its β-glucuronide, SN-38 G (3, 4). SN-38 G is excreted in the small intestine via the bile, where bacterial glucuronidase breaks down the glucuronide into SN-38 and glucuronic acid (5). Bilirubin undergoes the same glucuronidation by
UGT1A1 and is excreted into the bile (6). More than 50 genetic variants in the promoter and coding regions of the UGT1A1 gene are currently known to affect enzyme activity (7), leading to different forms of unconjugated hyperbilirubinemia known as Crigler-Najjar syndrome types I and II and Gilbert’s syndrome, a mild unconjugated hyperbilirubinemia with no structural liver disease or overt hemolysis (8). One of the most common genotypes in Gilbert’s syndrome in Caucasian populations is the inheritance of a promoter region containing an extra TA dinucleotide in the [A(TA)6TAA] element, leading to 30% to 80% reduction in the expression of UGT1A1 protein (9, 10). Therefore, patients who are homozygous for this variant allele (designated as UGT1A1*28) exhibit a metabolic ratio of SN-38/SN-38G higher than that observed for homozygous wild-type patients with an attenuated expression of UGT1A1 and are predisposed to SN-38 initiated diarrhea (11, 12) and severe hematologic toxicity (11, 13). A more recently investigated promoter polymorphism, -3156G>A UGT1A1, seems to be a better predictor of the UGT1A1 status than UGT1A1*28 (14).

CPT-11 is also catalyzed by the cytochrome P450 (CYP) 3A subfamily, which catalyzes the metabolism of structurally diverse xenobiotics (15) and is the most abundant CYP enzyme in the human liver and small intestine (16). Substantial interindividual differences in CYP3A expression contribute to the variations in the oral bioavailability and systemic clearance of CYP3A substrates (17). In adults, the main CYP3A isoforms are CYP3A4 and CYP3A5. CYP3A5 plays a role in the elimination of CPT-11, forming the APC complex, a metabolite in which antitumor activity is 500 times less compared with SN-38. The polymorphism of CYP3A5 gene 6986A>G has already been described. Those with the CYP3A5*3 allele display sequence variability in intron 3 that creates a cryptic splice site and encodes an aberrantly spliced mRNA with a premature codon stop, leading to the absence of protein expression (18, 19). Because CYP3A5 enzymes play a role in the elimination CPT-11, this polymorphism may partly explain the interindividual variability of CPT-11 toxicity.

In addition, CPT-11 and SN-38 can be transported out of the cell by the P-glycoprotein, a trans-membrane efflux pump (20, 21) that is a member of the ATP-binding cassette family. P-glycoprotein, also called MDR1 (multidrug resistance), is encoded by the human ABCB1 gene (ATP-binding cassette, subfamily B; ref. 22). Significant interindividual variations in the expression and function of P-glycoprotein may be a result of genetic factors. Various single nucleotide polymorphisms (SNP) have been identified within the ABCB1 gene in the past few years (22). The SNP located on exon 26 3435C>T described by Hoffmeyer et al. (21) shows a correlation of this polymorphism with expression levels and function of ABCB1.

The main purpose of our study was to assess the role of different polymorphisms on the occurrence of hematologic toxicities and disease-free survival in high-risk stage III colon cancer patients receiving 5FU and CPT-11 adjuvant chemotherapy combined through the FOLFIRI regimen in a prospective randomized trial. The role of the following polymorphisms were investigated: two polymorphisms in the promoter region of UGT1A1, namely, UGT1A1*28 (rs8175347) and the -3156G>A (rs10929302), the polymorphism 3435C>T for ABCB1 (rs1045642) and 6986A>G for CYP3A5 (rs776746).

**Materials and Methods**

**Study design.** Four hundred patients were randomized between November 1998 and September 2002 in 75 centers in France to the
phase III clinical trial FNCLCC Accord02/FFCD9802 comparing LV5FU2 alone versus LV5FU2 + CPT-11. All the patients signed an informed consent for the pharmacogenetic study.

Patients with high-risk stage III colon cancer were included (i.e., patients with postoperative N2 or N1 but with acute complication occlusion or perforation). They were randomized to either arm A, LV5FU2 (leucovorin 200 mg/m² as a 2-h infusion, 5FU 400 mg/m² bolus and 600 mg/m² 22 h continuous infusion, d1-2); or arm B, LV5FU2 + CPT-11 (irinotecan 180 mg/m² 90 min infusion d1+LV5FU2) every 2 weeks for 12 cycles with no growth factors. Patients were stratified by center, by the delay between surgery and start of chemotherapy (≤28 days; >28 days), and by age (<65 years; ≥65 years).

From this clinical trial, paraffin-embedded samples from normal tissue for the pharmacogenetic study were obtained for 184 of the 400 patients from different centers in France, 91 from arm A (LV5FU2) and 93 from arm B (LV5FU2 + CPT-11).

**Sample preparation and DNA extraction.** Three 20-μm slices were cut from each normal paraffin-embedded block. Slices were deparaffinized twice with 1.2 mL toluene, vortexed and centrifuged, then washed twice with 1.2 mL of 100% ethanol. The samples were resuspended in 180 μL of Qiaamp buffer ALT (Qiagen, Courtaboeuf, France) and 20 μL proteinase K (Roche Diagnostics, Mannheim, Germany). Samples were incubated overnight at 56°C with gentle shaking, and proteinase K was added twice. After 36 h, DNA was extracted from each sample using the QIAamp DNA Mini Kit from Qiagen according to the manufacturer’s instructions. The final concentration of each DNA sample was adjusted to 25 ng/μL containing 4 μL of DNA polymerase, and water) and 2.3 μL of TaqMan Universal PCR Master Mix No AmpEraseUNG, AmpliTaqGold DNA polymerase, and water.

**Determination of UGT1A1, CYP3A5, and ABCB1 gene polymorphism.** The variant sequences of a two-nucleotide insertion (TA) within TATA box resulting in the sequence (TA)₂ (rs10929302), 3435C>T for ABCB1 (rs1045642) and 6986A>G for ABCB1 (rs7776476) were characterized.

**Table 2.** Severe hematologic toxicity according to TA indel (UGT1A1), -3156G>A (UGT1A1), 6986A>G (CYP3A5), and 3435C>T (ABCB1) polymorphisms in the B arm

<table>
<thead>
<tr>
<th>Gene</th>
<th>SNPs</th>
<th>Severe hematologic toxicity</th>
<th>P*</th>
<th>N = 93</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>wt/wt, n (%)</td>
<td>wt/wt, n (%)</td>
<td>m/m, n (%)</td>
<td>wt/wt, n (%)</td>
</tr>
<tr>
<td>UGT1A1</td>
<td>TA indel</td>
<td>31 (46)</td>
<td>33 (48)</td>
<td>4 (6)</td>
</tr>
<tr>
<td></td>
<td>-3156G&gt;A</td>
<td>35 (52)</td>
<td>30 (44)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>CYP3A5</td>
<td>6986A&gt;G</td>
<td>1 (2)</td>
<td>10 (14)</td>
<td>59 (84)</td>
</tr>
<tr>
<td>ABCB1</td>
<td>3435C&gt;T</td>
<td>15 (22)</td>
<td>39 (57)</td>
<td>14 (21)</td>
</tr>
</tbody>
</table>

Abbreviations: wt, wild-type allele; m, mutant allele.

*p for trend test.

The TA indel variation of UGT1A1 was studied by fragment analysis. Briefly, a PCR was done in 15 μL containing 4 μL of DNA (25 ng/μL), 0.5 μmol/L each of forward (5'-SHEX-TIACCCTGGTG-TATCGATTGG-3') and reverse (5'-CTTGCGTCCTGGGACAGGTG-3') primer from Qiagen, 0.8 mmol/L of deoxyribonucleotide triphosphates, 1.5 μL of 10× PCR buffer from Qiagen, 0.3 μL of 5× Solution Q (Qiagen), 0.9 μL of 25 mmol/L MgCl₂ (Qiagen), 0.75 units Taq Hotstar (Qiagen), and 2.3 μL of water and run according to the following cycle profile: 95°C for 10 min, 40 cycles at 94°C for 30 s, 56°C for 30 s, 72°C for 30 s, and a final extension of 10 min at 72°C. The PCR was realized on thermal cycler PTC-100 (MJ Research Inc., Watertown, MA). For molecular analysis of [A(TA)]₂, fluorescence-labeled PCR products were separated by automated capillary electrophoresis on the ABI PRISM 310 Genetic Analyzer (Applied Biosystems, Foster City, CA) and analyzed with GeneScan and Genotyper software (Applied Biosystems). The TA₆ allele corresponds to a 74-bp fragment, TA₇ allele corresponds to a 68-bp fragment, TA₈ allele corresponds to a 62-bp fragment, and TA₉ corresponds to 80-bp fragments. For each run, positive controls were added, including patients with different genotype (i.e., TA₆/TA₇, TA₇/TA₈, TA₈/TA₉, TA₆/TA₉, TA₇/TA₉, and TA₈/TA₉).

**Table 3.** Severe neutropenia according to TA indel (UGT1A1), -3156G>A (UGT1A1), 6986A>G (CYP3A5), and 3435C>T (ABCB1) polymorphisms in the B arm

<table>
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</tr>
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<tbody>
<tr>
<td></td>
<td>wt/wt, n (%)</td>
<td>wt/wt, n (%)</td>
<td>m/m, n (%)</td>
<td>wt/wt, n (%)</td>
</tr>
<tr>
<td>UGT1A1</td>
<td>TA indel</td>
<td>32 (46)</td>
<td>34 (49)</td>
<td>4 (6)</td>
</tr>
<tr>
<td></td>
<td>-3156G&gt;A</td>
<td>36 (51)</td>
<td>31 (44)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>CYP3A5</td>
<td>6986A&gt;G</td>
<td>1 (2)</td>
<td>11 (15)</td>
<td>60 (83)</td>
</tr>
<tr>
<td>ABCB1</td>
<td>3435C&gt;T</td>
<td>15 (21.4)</td>
<td>40 (57.2)</td>
<td>15 (21.4)</td>
</tr>
</tbody>
</table>

Abbreviations: wt, wild-type allele; m, mutant allele.

*p for trend test.
PRISM 7900HT from Applied Biosystems according to the manufacturer’s instructions. Genotypes were determined automatically using ABI Sequence Detection System software (SDS Software 2.1, Applied Biosystems). The ambiguous genotypes were analyzed by two independent observers (J.F. Côté, S. Kirzin), and discordant results were reamplified and reanalyzed.

Statistical analysis. The clinical trial data were managed and analyzed in the biostatistics unit of the Val d’Aurelle Regional Cancer Centre in Montpellier, France. Toxicities were graded according to National Cancer Institute-Common Toxicity Criteria v2. Severe hematologic toxicity consisted of either grade 3 or 4 neutropenia, thrombocytopenia, anemia, or leucopenia. For each genotype, association with hematological and gastrointestinal toxicity in each treatment arm was evaluated using a nonparametric test for trend across equally spaced ordered groups. Toxicity-free survival rates by cycle and disease-free survival rates from randomization were estimated using the Kaplan-Meier method. Univariate comparisons were done with the log rank test. Multivariate analyses, adjusted for important clinical variables, were done using the Cox proportional hazards model.

The deviations from the Hardy-Weinberg equilibrium of allele and genotype frequencies for the various SNPs were assessed by Fisher’s exact test. Pairwise linkage disequilibrium between UGT1A1*28 and UGT1A1 -3156G>A was estimated by a log-linear model, and the extent of disequilibrium was expressed in terms of D’, which is the ratio of the unstandardized coefficient to its maximal/minimal value.

Results

Polymorphism frequencies. The FNCLCC Accord02/FFCD9802 trial included 400 patients. Normal DNA was available for 184 patients. Demographic and clinical data of this subset of patients did not differ significantly from the patients not selected for this analysis.

The frequencies of the variant tested alleles estimated on the entire series of 184 patients were 32.1%, 30.1%, 91.2%, and 50.3% for UGT1A1 TA7, UGT1A1 -3156 A, CYP3A5 6986 G, and ABCB1 3435 T alleles, respectively. These frequencies are in accordance with those observed in Caucasian populations. Table 1 shows the genotype distribution of the different polymorphisms. All of these genotypes were distributed according to the Hardy-Weinberg equilibrium.

Distribution of the different UGT1A1 genotypes according to hematologic toxicity. Figure 1A and B show the distribution of the different UGT1A1 genotypes according to hematologic toxicity grades from patients in arm B. An increased frequency of homozygous variant genotypes was observed with increased hematologic toxicity. The P values were equal to 0.055 and 0.059 for UGT1A1*28 and -3156G>A polymorphisms, respectively (trend test).

Hematologic toxicity and neutropenia. Analysis of severe hematologic toxic events showed more frequent toxicities

Table 5. Cox multivariate analysis of the occurrence of grade 3 to 4 hematologic toxicity in arm B (N = 89)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard ratio</th>
<th>P*</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.07</td>
<td>0.019</td>
<td>1.01-1.13</td>
</tr>
<tr>
<td>Gender (reference group M)</td>
<td>3.7</td>
<td>0.007</td>
<td>1.43-9.47</td>
</tr>
<tr>
<td>-3156 UGT1A1 wt/m</td>
<td>2.8</td>
<td>0.052</td>
<td>0.99-7.88</td>
</tr>
<tr>
<td>-3156 UGT1A1 m/m</td>
<td>8.4</td>
<td>0.005</td>
<td>1.90-37.19</td>
</tr>
</tbody>
</table>

Abbreviations: wt, wild-type allele; m, mutant allele. *P from Wald test.
for the different fourth cycle (Fig. 2).

penia was observed for patients with AA genotype after the
0.024. Neither severe hematologic toxicity nor severe neutro-
toxicity occurs significantly earlier in patients with AA genotype
was considered, a similar result was observed with a
genotypes (Fig. 2, Table 2). When only severe neutropenia was considered, these
results remained in the same range (Table 3).

Regarding the 6986A>G (CYP3A5) and 3435C>T (ABCB1) polymorphisms, no statistically significant difference was found in the frequency of the different genotypes versus occurrence of severe hematologic toxicity or severe neutropenia (Tables 2 and 3).

Concerning the patients in arm A, no statistically significant difference was found in the frequency of the different genotypes versus the occurrence of severe hematologic toxicity according to the four SNP genotypes (Table 4).

Hematologic toxicity-free survival curves. Severe hematologic toxicity occurs significantly earlier in patients with AA genotype for UGT1A1 -3156G>A polymorphism than for the other genotypes (Fig. 2, P = 0.043). When only severe neutropenia was considered, a similar result was observed with a P value of 0.024. Neither severe hematologic toxicity nor severe neutropenia was observed for patients with AA genotype after the fourth cycle (Fig. 2).

Cox multivariate analysis. A Cox multivariate analysis was done to estimate the hazard ratio of severe hematologic toxicity for the different UGT1A1 -3156G>A genotypes. The hazard ratio for development of a grade 3 to 4 hematologic toxicity, after adjustment for age and gender was 8.4; 95% confidence interval, 1.9–37.2 for patients with the AA genotype of SNP -3156G>A UGT1A1 compared with the GG genotype (Table 5, P = 0.005).

Haplotypes and the occurrence of severe hematologic toxicity was observed is provided in Table 6.

Although the test for a difference of haplotype frequencies between the two groups of patients did not reach statistical significance (P = 0.081), the two haplotypes carrying the A allele tended to be at a higher frequency in patients with a severe hematologic toxicity than those without this allele. This is in agreement with the results observed in the univariate analysis.

Gastrointestinal toxicity. No significant statistical difference in the occurrence of severe gastrointestinal toxicity (grade 3 or more diarrhea, nausea, vomiting, or mucositis) was seen in 184 patients from either treatment arm, LV5FU2 alone, or in combination with CPT-11 in relation to SNPs of UGT1A1 promoter TA indel, UGT1A1 -3156G>A, CYP3A5 6986A>G, and ABCB1 3435C>T (Tables 7 and 8).

Dose relation CPT-11 and TA indel (UGT1A1), -3156G>A (UGT1A1) SNPs. No difference in median CPT-11 doses received was observed between the different genotypes.

Survival and polymorphisms. No significant survival difference was observed between patients in arm B according to different polymorphisms. There was a tendency for better disease-free survival for homozygous patients with the variant genotype of UGT1A1*28 SNP with 3-year disease-free survival of 87% versus 52% and 42% for wild-type homozygous and heterozygous patients, respectively (P = 0.06; Fig. 3).

Discussion

This series of colon cancer patients shows the impact of four polymorphisms on irinotecan induced chemotherapy toxicity in an adjuvant chemotherapy situation. An association was found between two polymorphisms of the promoter region of UGT1A1 and the occurrence of severe hematologic toxicity and, more specifically, severe neutropenia. These results confirm

<table>
<thead>
<tr>
<th>Table 6. Frequency of the different haplotypes of UGT1A1 gene according to severe hematologic toxicity</th>
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<tbody>
<tr>
<td><strong>Haplogroup</strong></td>
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<tr>
<td>----------------</td>
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<tr>
<td>-3156G&gt;A TA indel</td>
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<td>G</td>
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<td>G</td>
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<tr>
<td>A</td>
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<table>
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<th>Table 7. Gastrointestinal toxicity according to TA indel (UGT1A1), -3156G&gt;A (UGT1A1), 6986A&gt;G (CYP3A5), and 3435C&gt;T (ABCB1) polymorphisms in the B arm</th>
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<tbody>
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<td><strong>Gene</strong></td>
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</tr>
<tr>
<td>wt/wt, n (%)</td>
</tr>
<tr>
<td>UGT1A1</td>
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<tr>
<td>UGT1A1</td>
</tr>
<tr>
<td>CYP3A5</td>
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<tr>
<td>ABCB1</td>
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</table>

Abbreviations: wt, wild-type allele; m, mutant allele.

*P for trend test.
those of Innocenti et al. (14) observed in 66 patients with advanced disease refractory to chemotherapy.

This toxicity is due to a deficit in glucuronidation as observed in Gilbert’s syndrome. In our series, the frequency of patients homozygous for the UGT1A1*28 allele partially responsible for this syndrome is similar to that observed in other Caucasian populations (7, 10).

The -3156G>A polymorphism is in strong linkage disequilibrium with UGT1A1*28 polymorphism (D’ > 0.94). In addition, -3156G>A polymorphism maybe a better predictor of hematologic toxicity than UGT1A1*28 polymorphism, as suggested by Innocenti (14). The association with toxicity was significant only for the -3156G>A polymorphism. Haplotype analysis showed a higher frequency of severe hematologic toxicity for patients with the A allele of -3156G>A, regardless of the associated UGT1A1 TA6TA6/TA7TA7 polymorphism. More data are necessary to explore the role of the UGT1A1 haplotype in the occurrence of severe side effects and the relative predictive weight of each of the UGT1A1 promoter polymorphisms.

This study showed that most severe hematologic or severe neutropenia toxicities occur in most mutant homozygous patients for -3156G>A polymorphism during the first cycle of chemotherapy and never after the fourth cycle (Fig. 2). Exploration of the -3156G>A UGT1A1 polymorphism, before CPT-11 treatment to predict the early CPT-11 hematologic toxicity, seems interesting in the management of the patient. Specific studies are needed to validate a modification of the mode of administration of CPT-11 in these homozygous mutant patients. In particular, the concomitant administration of granulocyte colony-stimulating agent with CPT-11 should be tested to avoid adverse severe hematologic side effects in this subgroup of patients.

Multivariate analysis showed a strong independent role of gender in the occurrence of severe hematologic toxicity. The association of gender and glucuronidation has already been reported (10, 14). Drugs metabolized by phase II enzymes (glucuronidation, conjugation, glucuronyltransferases, methyltransferases, and dehydrogenases) are usually cleared faster in men than in women (mg/kg basis; ref. 23). The clinical consequences of this interaction have never been shown in patients receiving CPT-11 and need to be further explored.

In our study, CPT-11 – induced gastrointestinal toxicity such as diarrhea showed no statistically significant relationship with the UGT1A1 polymorphisms, in contrast to the series reported by Marcuello et al. (24). In their study of 95 metastatic colorectal cancer patients, the occurrence of severe diarrhea was more frequent in homozygous UGT1A1*28 patients as compared with wild-type patients, possibly related to the higher doses of the CPT-11 regimen. In addition, a recent study by Massacesi et al. (25), showed that UGT1A1 promoter polymorphism (TA indel) predicted the risk of diarrhea, emesis, and fatigue with CPT-11 and raltitrexed treatment. They were unable to evaluate the predictive role of UGT1A1 promoter polymorphism (TA indel) for hematologic toxicity because they used a schedule for CPT-11, which reduced the number of grade 3 or 4 neutropenic events to only a few. CPT-11 was administered at a dose of 80 mg/m2 (as a 30-min infusion) on days 1, 8, 15, 22, 36, 43, 50, and 57.

The absence of a significant association of severe hematologic toxicity or diarrhea with ABCB1 and CYP3A5 polymorphism in agreement with previous published results (26) and suggests a major role of glucuronidation in the detoxification of the SN-38 compound. At least two other genes from the large family of ABC transporters (ABCC2 and ABCG2) could also play a role in irinotecan metabolism, but no significant effects on the severity of adverse effects have been found thus far (27).

In conclusion, this study supports the clinical utility of identification of UGT1A1 promoter polymorphisms before LV5FU2 + CPT-11 treatment to predict early hematologic toxicity. The -3156G>A polymorphism seems to be a better predictor than the UGT1A1 (TA)6TA6>(TA)7TA7 polymorphism.
References

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