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

We read with interest the paper from Hoskins et al. (1) on the meta-analysis of the studies that assessed the association of irinotecan dose with the risk of irinotecan-related toxic effects for patients with the UGT1A1*28/*28 genotype. They indicated that the risk of hematologic toxicity was strongly associated with UGT1A1*28 genotype at higher irinotecan doses (>150 mg/m²), not at lower doses (≤150 mg/m²).

We congratulate the authors for their excellent work. We would like to present support for their work from the ongoing study to establish the appropriate dose-adaptation strategy for irinotecan among Japanese patients who are heterozygous for both UGT1A1*28 and UGT1A1*6 or homozygous for each variant. UGT1A1*6, which contributes to the hepatic metabolism of SN-38 (the active metabolite of irinotecan), is more prevalent than UGT1A1*28 in Asian populations (2,3). In the Japanese population, the metabolic ratio of the area under the curve (AUC) for SN-38/AUC for SN-38 glucuronide was statistically significantly higher in patients who were heterozygous for both UGT1A1*28 and UGT1A1*6 or homozygous for UGT1A1*6 than in those with other genotypes (P = .004, Mann-Whitney U test) (4).

In the study, the dose of irinotecan was escalated from 25 to 150 mg/m² because the Japanese package insert information limits the dose for irinotecan to 150 mg/m² in each biweekly regimen when patients do not experience dose-limiting toxicity, which was defined as grade 4 neutropenia or grade 3 or 4 nonhematologic toxic effects according to the Common Toxicity Criteria, version 3.0, of the National Cancer Institute. Genotyping and pharmacokinetic analyses were performed simultaneously as previously reported (4). All patients gave written informed consent approved by the Institutional Review Board of Saitama Medical University.

In plots of metabolic ratios at the administered dose of irinotecan for individual patients, gradual changes in the metabolic ratio of patients were observed according to the dose escalation, with one exception that of patient A (Fig. 1). Patients A, B, and C were homozygous for UGT1A1*6, and patient D was heterozygous for both UGT1A1*28 and UGT1A1*6. Patient A with a primary cancer whose site was unknown had no dose-limiting toxicity but refused to continue irinotecan treatment. During dose escalation, patient B with ovarian cancer experienced grade 4 neutropenia at an irinotecan dose of 100 mg/m², and patient C with lung cancer experienced grade 3 diarrhea with grade 3 neutropenia at a dose of 75 mg/m². Patient D with colon cancer experienced grade 4 neutropenia at an irinotecan dose of 150 mg/m².

Although the dosage of irinotecan in our study was lower than that in Hoskins

![Fig. 1. The metabolic ratio of the area under the curve (AUC) for SN-38/AUC for SN-38 glucuronide (SN-38G) vs the dose of irinotecan. Patients A, B, and C were homozygous for UGT1A1*6. Patient D was heterozygous for both UGT1A1*28 and UGT1A1*6. Squares = patient A; triangles = patient B; open circles = patient C; solid circles = patient D.](https://academic.oup.com/jnci/article-abstract/100/3/224/2519119)
et al. (1), the intrapatient variability in metabolic ratio according to the administered irinotecan dose might explain, in part, the association between irinotecan dose and the risk of irinotecan-related hematologic toxic effects in patients who were expected to have low UGT1A1 activity. In addition, the intrapatient heterogeneity of metabolic ratio among patients with a mutated UGT1A1 genotype may likely be due to factors other than UGT1A1 genotype, either genetic or non-genetic, as discussed by Hoskins et al. (1).

Further studies on the pharmacokinetics, pharmacodynamics, and pharmacogenetics of irinotecan are needed to clarify these issues.

**Notes**
The authors take full responsibility for the design of the study, the collection of the data, the analysis and interpretation of the data, the decision to submit the manuscript for publication, and the writing of the manuscript.

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**References**


**Response**

We thank Dr Ichikawa and colleagues for their kind comments. Their preliminary irinotecan pharmacokinetic data from Japanese cancer patients with low-activity UGT1A1 genotypes who participated in an irinotecan dose escalation study provide some additional support for the findings of our study (1). The ratios of the areas under the concentration time curves of SN–38 to SN–38G for three of the four patients appear to increase with increasing dose of irinotecan. This observation, although based on few patients, indicates that the extent of SN-38 glucuronidation decreased with increasing irinotecan dose. We look forward to seeing the results on completion of their study.

On the basis of the findings of a few initial studies, the US Food and Drug Administration (FDA) made the recommendation that patients with the UGT1A1*28/*28 genotype should receive a lower starting dose of irinotecan, and the package insert of the drug was amended accordingly (1,2) in the interest of patient safety. Our findings indicate that, for UGT1A1*28/*28 patients, UGT1A1*28 genotype–based dosing of irinotecan is likely to improve patient safety if they are being treated with high doses of irinotecan (>250 mg/m²) but not if they are being treated with low doses (<150 mg/m²). Therefore, genotype-based dosing may not be necessary for all patients (1). Our findings also indicate that the current recommendations for irinotecan dosing may be too broad and so the irinotecan package label should be fine tuned to acknowledge the effect of irinotecan dose on the association between UGT1A1*28 genotype and hematologic toxicity. Many media outlets reported our findings with bold titles that implied an FDA error. Rather, we view FDA pharmacogenetic label updates as an iterative process in which refinement of the prescribing information is performed at intervals dictated by the robustness of the new data.

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