Clinical Cancer Research

A CYP3A4 Phenotype–Based Dosing Algorithm for Individualized Treatment of Irinotecan

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Abstract

Purpose: Irinotecan, the prodrug of SN-38, is extensively metabolized by cytochrome P450-3A4 (CYP3A4). A randomized trial was done to assess the utility of an algorithm for individualized irinotecan dose calculation based on a priori CYP3A4 activity measurements by the midazolam clearance test.

Experimental Design: Patients were randomized to receive irinotecan at a conventional dose level of 350 mg/m^2 (group A) or doses based on an equation consisting of midazolam clearance, γ-glutamyl-transferase, and height (group B). Pharmacokinetics and toxicities were obtained during the first treatment course.

Results: Demographics of 40 evaluable cancer patients were balanced between both groups, including *UGT1A1*28* genotype and smoking status. The absolute dose of irinotecan ranged from 480 to 800 mg in group A and 380 to 1,060 mg in group B. The mean absolute dose and area under the curve of irinotecan and SN-38 were not significantly different in either group ($P > 0.18$). In group B, the interindividual variability in the area under the curve of irinotecan and SN-38 was reduced by 19% and 25%, respectively ($P > 0.22$). Compared with group A, the incidence of grades 3 to 4 neutropenia was >4-fold lower in group B (45 versus 10%; $P = 0.013$). The incidence of grades 3 to 4 diarrhea was equal in both groups (10%).

Conclusions: Incorporation of CYP3A4 phenotyping in dose calculation resulted in an improved predictability of the pharmacokinetic and toxicity profile of irinotecan, thereby lowering the incidence of severe neutropenia. In combination with *UGT1A1*28* genotyping, CYP3A4 phenotype determination should be explored further as a strategy for the individualization of irinotecan treatment. *Clin Cancer Res; 16(2); 736–42.* ©2010 AACR.

In 1996, the topoisomerase-I inhibitor irinotecan received accelerated approval in the United States for the second-line treatment of patients with metastatic colorectal carcinoma. Currently, irinotecan is approved as a single agent as well as in combination with other drugs (i.e., fluorouracil, oxaliplatin, and bevacizumab) in different first-line and second-line regimens for the treatment of this disease (1–4).

Several enzymes and drug transporters are involved in the elimination of irinotecan, including members of the cytochrome P450 3A (CYP3A) and uridine-diphosphate glucuronosyltransferase 1A (UGT1A) families, both of which influence exposure to the active metabolite, SN-38 (Fig. 1; ref. 5). Because the expression and function of these proteins could be affected by numerous environmental and genetic factors, the pharmacokinetics of irinotecan and its metabolites vary greatly between patients (5, 6).

Like most other cytotoxic anticancer agents, irinotecan has a narrow therapeutic window. Therefore, the large interindividual pharmacokinetic variability may result in overtreatment with unacceptable side effects in some patients and in undertreatment with diminished therapeutic effects in others. The conventional dose calculation of irinotecan is based on an individual's body surface area (BSA), although this approach does not result in reduced pharmacokinetic variability (Fig. 2A) compared with a flat-fixed dose (7, 8). New dosing strategies that take the pharmacologic profile of irinotecan in the individual patient into account could potentially replace BSA-based dosing, if this would lead to a reduction in the pharmacokinetic variability. Ideally, this should prevent the occurrence of highly unpredictable

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Translational Relevance

Like most other chemotherapeutic agents, irinotecan has a narrow therapeutic window. This leads to under-dosing or unexpected toxicities in individual cases. Adjusting the dose to the patient's body surface area does not lead to a lower interindividual variability in the pharmacokinetics of irinotecan and its active metabolite, SN-38. This urged the need to develop alternative dosing strategies. Strategies solely based on genotype, like excluding patients with two UGT1A1*28 alleles, might lower the number of extreme toxicities. However, this will not exclude all serious side effects, as environmental factors (i.e., smoking and comedication) and other genetic variants may also seriously affect the metabolism and, as a result, the therapeutic outcome of this drug. Here, we propose an alternate dosing strategy for irinotecan therapy that involves a priori assessment of cytochrome P450-3A4 activity and show that this approach is feasible and can improve interindividual pharmacologic variability.

severe toxicities associated with irinotecan administration, such as neutropenia and late-onset diarrhea, and should result in a maximal antitumor response in each patient.

Thus far, new dosing strategies have mainly focused on polymorphisms affecting the expression of enzymes involved in the metabolism of SN-38, such as the UGT1A1*28 polymorphism (9–11). It should be pointed out, however, that the expression of many enzymes and transporters of relevance to irinotecan is also influenced by environmental factors, such as comedication, complementary and alternative medicine, disease status, and lifestyle (12). Therefore, dose-individualization strategies should not solely focus on inherited variables.

From drug-interaction studies involving enzyme-inducing and enzyme-inhibiting compounds, such as St.-John's-wort and ketoconazole, it is known that the CYP3A4 pathway plays a crucial role in the inactivation of irinotecan into a number of inactive, oxidative metabolites (13, 14). Because CYP3A4 activity can be influenced by many factors, and is largely variable between patients (15), it has been proposed that a priori assessment of the functional activity of CYP3A4, for instance by using probe drugs such as midazolam or erythromycin (16), may aid in irinotecan dose calculation. Previously, we found that CYP3A4 activity as determined by midazolam pharmacokinetics was highly correlated with irinotecan clearance (17).

We developed a new dosing equation for irinotecan treatment by using linear regression analysis to identify clinical parameters that could predict irinotecan clearance. Here, we report on a randomized clinical trial in which we compared classic BSA-based dosing with individualized irinotecan dose calculation on the basis of an equation that incorporated an individual's CYP3A4 activity, height, and γ-glutamyltransferase.

Materials and Methods

Patients. Patients were included according to the following inclusion criteria: (*a*) a histologically or cytologically confirmed diagnosis of any form of metastatic cancer which was thought to be sensitive to irinotecan treatment; (*b*) age ≥18 y; (*c*) a WHO performance score of <2; and (*d*) adequate hematologic, renal, and hepatic function as determined within 2 wk before inclusion and repeated 1 d prior to the start of treatment. An additional criterion was used for baseline γ-glutamyltransferase (<200 units/L, which is approximately five times the upper limit of normal) because it was one of the three parameters on which the dosing equation was based, and this was the upper limit that was seen in the earlier study upon which the equation was formulated (17).

During the study period, starting 3 wk before irinotecan administration, patients were not allowed to use grapefruit or grapefruit juice, St.-John's-wort or any other known inhibitor and/or inducer of CYP3A4. Use of temazepam was prohibited as well because this compound was used as the internal standard for the midazolam assay. Other specific exclusion criteria included (*a*) any form of anticancer treatment within 4 wk of the start of irinotecan administration, (*b*) unresolved bowel obstruction or chronic colic disease, and (*c*) any form of illness that would prohibit the process of understanding and giving of informed consent. All patients gave written informed consent and the local institutional review boards
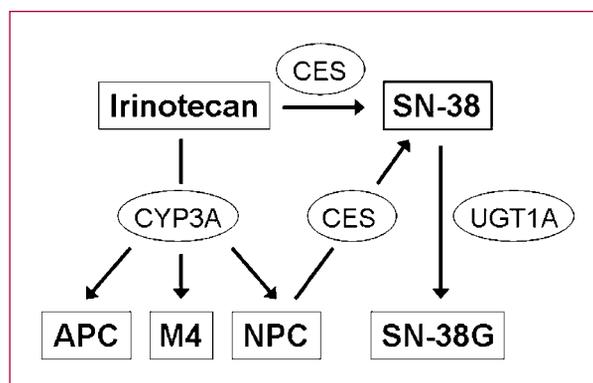
Fig. 1. Metabolism of irinotecan. Irinotecan is converted into its 100 to 1,000 times more active metabolite SN-38 by human carboxylesterases type 1 and 2, which are predominately found in the liver. The affinity for this reaction is low, because only ~3% of irinotecan is converted into SN-38. SN-38 is glucuronidated by UGT1A into the inactive metabolite SN-38G. β-Glucuronidase–producing bacteria can reverse this reaction in the intestines, reactivating SN-38, and causing the dose-limiting toxicity diarrhea. Competing with the formation of SN-38 is the CYP3A-mediated inactivation of irinotecan into the metabolites APC and NPC. APC, 7-ethyl-10-[4-N-(5-aminopentanoic acid)-1-piperidino]-carbonyloxy-camptothecin; CES, carboxylesterases; CYP3A, cytochrome P450 3A isoforms (3A4/3A5); M4, fourth unspecified metabolite of irinotecan; NPC, 7-ethyl-10-(4-amino-1-piperidino)-carbonyl-oxycamptothecin; SN-38, 7-ethyl-10-hydroxy camptothecin; SN-38G, glucuronide form of SN-38; UGT1A, uridine diphosphate glucuronosyltransferase 1A isoforms (1A1/1A7/1A9).
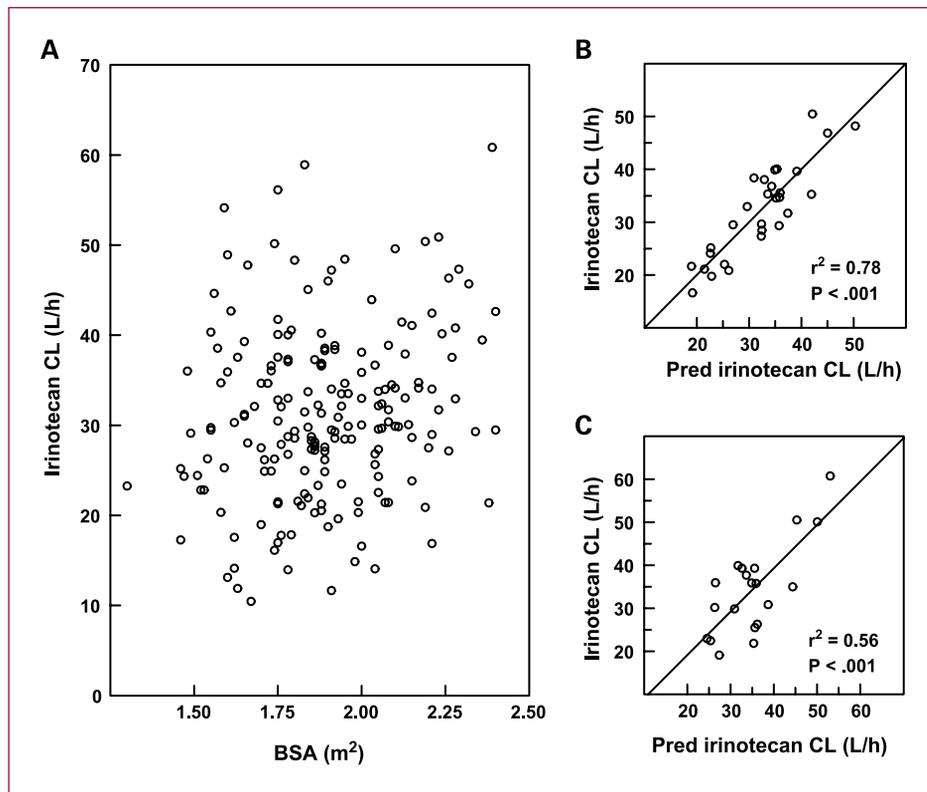
Fig. 2. Development and validation of a new dosing equation for irinotecan. *A*, the relationship between BSA and irinotecan clearance in a cohort of 190 patients (18). Conclusion: BSA-based dosing does not reduce the interindividual pharmacokinetic variability of irinotecan. *B* and *C*, correlation between the equation-based predicted clearance and the measured irinotecan clearance in the former study (*B*, n = 30; ref. 17), and in the current study (*C*, n = 20). CL, clearance; N, number; pred, predicted.

approved the clinical protocol, which was written in accordance with the declaration of Helsinki.

Treatment. Before the start of treatment, baseline toxicities were recorded, a physical examination took place, and bone marrow, renal, and hepatic function were obtained using routine laboratory analyses. Patients were randomized to either receive a BSA-based dose of 350 mg/m² or a dose calculated from an equation that took into account the height, baseline γ-glutamyltransferase, and midazolam clearance of the patient. This equation was derived from data obtained previously in 30 patients (17) using regression analysis in Stata version 8.2 (Stata Corp.). All patient-related factors that could possibly affect irinotecan clearance were taken into account, and included age, height, weight, BSA, baseline blood cell counts, measures of liver and renal function, and genetic variation in genes encoding ATP-binding cassette drug transporters and drug-metabolizing enzymes involved in the elimination pathway of irinotecan.

The final equation for irinotecan clearance was:

$0.0325 \times$ midazolam clearance (mL/min) $- 0.0396 \times \gamma$-glutamyltransferase (units/L) $+ 27.180 \times$ height (m) $- 31.926$.

This equation explained ~80% of the variability in irinotecan clearance (Fig. 2B), whereas BSA explained only ~21% (data not shown). A dose for each patient in the equation group was calculated by multiplying the predicted irinotecan clearance by 22.157 (μg × h/mL), which

was the mean area under the curve of irinotecan observed previously, and this value was arbitrarily defined as the target measure of systemic exposure (17). To eliminate age as a potential confounding variable, patients were stratified and matched according to age (≤55 versus >55 y) within each treatment group and within each participating institution. Application of premedication and treatment of gastrointestinal toxicity were done as described previously (18).

Pharmacologic studies. All patients underwent a midazolam clearance test seven or 8 d prior to the start of irinotecan treatment. A midazolam dose of 0.025 mg/kg was injected i.v. as a bolus, followed by a running infusion of 0.9% saline over a 30-s period. Blood sample collection, analytic measurements of midazolam, irinotecan and SN-38 in plasma, and pharmacokinetic parameter calculations were done as described previously, with minor modification (17). Following separate consent, DNA was obtained from all patients and analyzed for the *UGT1A1*28* variant using a LightCycler method (19), with modifications (17).

Toxicity evaluation. Patients were seen weekly at the outpatient clinic for follow-up, which included a physical examination and routine hematologic, renal, and hepatic laboratory analyses. All side effects, including leukopenia, neutropenia, and late-onset diarrhea were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0.[5]

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[5] http://ctep.cancer.gov/forms/CTCAEv3.pdf

Statistical considerations. Statistical calculations were done using SPSS version 14.0 (SPSS Inc.) and Stata version 8.2 (Stata Corp.). An estimation of the SEM of the interindividual variability was obtained as described (20). Based on an estimated mean interindividual variability in irinotecan area under the curve of 30% with a SD of 22.6 in patients receiving a dose of 350 mg/m^2, a sample size of 20 patients per treatment group was necessary to detect a 50% lower variability with a two-sided $P = 0.05$ and a power of 80%.

Differences in categorical data were analyzed using χ^2 test. Differences in interindividual pharmacokinetics and all other continuous variables in both groups were calculated using a Student's t test. Root mean square error, mean predictive error, and Pearson's correlation coefficient were used to relate two continuous variables (21). All data are presented as means with SD or 95% confidence intervals in parentheses, unless stated otherwise. $P < 0.05$ values were considered significant.

Results

Patient characteristics. Forty-five cancer patients were randomized between September 2005 and August 2007 to receive a BSA-based dose or an equation-based irinotecan dose, and received irinotecan treatment in accordance with the protocol. Of these, five patients were not evaluable for analysis; three due to technical problems with blood sampling, one was lost to follow-up, and one had an elevation of γ-glutamyltransferase induced by alcohol abuse at the start of treatment. The remaining 40 patients (22 males and 18 females) with a mean age of 58 (range, 27–70) were evaluable for analysis. No significant differences were seen in age, gender, smoking status, *UGT1A1*28* genotype, and number of previous chemotherapeutic treatments between both groups (Table 1).

Pharmacokinetics of midazolam. CYP3A4 activity, as determined by midazolam clearance, varied ~6-fold (range, 203-1,257 mL/min), with a mean of 698 mL/min (95%

Table 1. Patient characteristics

Characteristics*	BSA group (n = 20)	Equation group (n = 20)	$P^†$
Sex			
Male	11 (50%)	11 (50%)	
Female	9 (50%)	9 (50%)	
Age (y)‡	57 (27-70)	55 (27-69)	0.60§
Height (m)‡	1.74 (1.52-1.85)	1.75 (1.54-1.87)	0.83§
γ-Glutamyltransferase (units/L)‡	76 (57)	61 (46)	0.34§
Smoking status$^\parallel$			0.63
No	16 (48%)	17 (52%)	
Yes	3 (60%)	2 (40%)	
Previous chemotherapy			0.72
0-1	14 (48%)	15 (52%)	
≥2	6 (55%)	5 (45%)	
Tumor type			0.18
Colorectal	3 (43%)	4 (57%)	
Gastric	2 (40%)	3 (60%)	
Pancreas	2 (50%)	2 (50%)	
Miscellaneous¶	13 (54%)	11 (46%)	
UGT1A1*28 genotype**			0.79
6/6	9 (56%)	7 (44%)	
6/7	8 (44%)	10 (56%)	
7/7	1 (50%)	1 (50%)	

*Data are presented as absolute numbers with percentages in parentheses, unless stated otherwise.

$^†P$ values result from χ^2 test, unless stated otherwise.

‡Data presented as mean with range or SD in parentheses.

$^§P$ values resulting from two-sample t tests.

$^\parallel n$ = 38 (smoking status unknown in two patients).

¶Including sarcoma (4), esophageal carcinoma (3), breast cancer (3), (adeno)carcinoma of unknown primary (2), jejunal carcinoma (2), small cell lung cancer (2), urothelial carcinoma (2), melanoma (2), cholangiocarcinoma (1), ovarian carcinoma (1), medulloblastoma (1), and head and neck cancer (1).
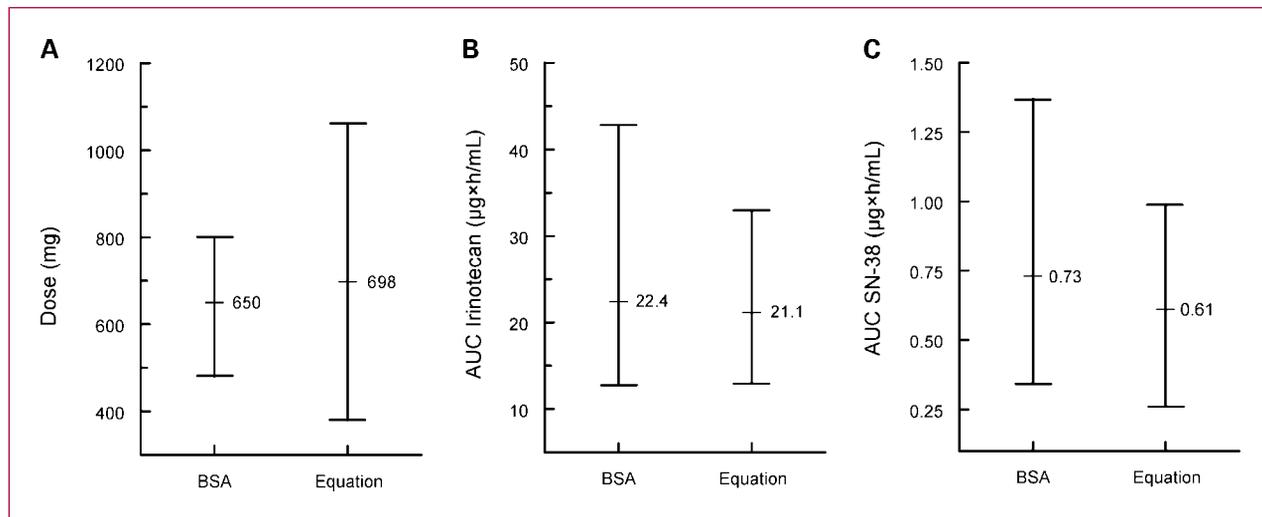
**n = 36 (genotype unknown in four patients).

Fig. 3. Interindividual variability in the dose and pharmacokinetics of irinotecan. Range, means, and interindividual variability of the administered dose (*A*), irinotecan area under the plasma concentration time curve (*B*), and SN-38 area under the plasma concentration time curve (*C*) in the BSA (*left*) and the equation group (*right*).

confidence interval, 609-786 mL/min). These data are consistent with previously reported values (17, 22, 23).

Pharmacokinetics of irinotecan. The mean absolute dose was not significantly different between either group (650 versus 698 mg; $P = 0.28$; Fig. 3A). However, the range of doses was much broader in the group that received the dose calculated by the equation (480-800 versus 380-1,060 mg). If the patients from the equation group would have been dosed on BSA, this would have resulted in a slightly lower mean dose of 675 mg, and a range of 494 to 830 mg for this group.

There were no differences in the mean area under the curve of irinotecan and SN-38 between both groups of patients ($P > 0.18$; Fig. 3B and C). In the group receiving the dose calculated by the equation, the interindividual variability (expressed by SD/mean) in the area under the curve was 19% lower for irinotecan (31% versus 25%; $P = 0.35$) and 25% lower for SN-38 (45% versus 34%; $P = 0.22$), whereas the mean interindividual variability in the administered dose was significantly higher in this group (11% versus 26%; $P = 0.002$).

The predicted clearance of irinotecan calculated by the equation was correlated with the observed clearance in the group receiving the dose calculated by the equation (root mean square error, 21.8%; mean predictive error, 4.08%, $R^2 = 0.56$; $P < 0.001$; Fig. 2C).

Toxicities of irinotecan. The incidence of grades 3 to 4 neutropenia was more than four times lower in the patients receiving the equation-based dose (45% versus 10%; 95% confidence interval, 0.025-0.748; $P = 0.013$; Fig. 4). Similarly, the incidence of grades 3 to 4 leukopenia was three times lower in this group (45% versus 15%; 95% confidence interval, 0.048-0.977; $P = 0.038$). In the group receiving a BSA-based dose, three patients experienced febrile neutropenia (15%), whereas in the other group, none of the pa-

tients experienced this dose-reducing side effect. Although not reaching statistical significance, a lower mean nadir WBC count (66% versus 45%; $P = 0.10$) and nadir absolute neutrophil count (80% versus 55%; $P = 0.10$) were found in the group receiving an irinotecan dose determined by the equation. No differences were seen in the incidence of severe diarrhea (grades 3-4), which was 10% in both groups.

Discussion

We developed a new dosing algorithm for irinotecan treatment, which was based on an individual's CYP3A4 activity, γ-glutamyltransferase, and height, and was
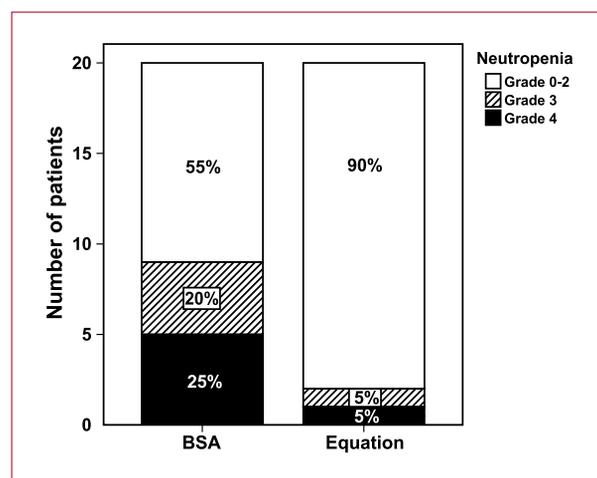

Fig. 4. Toxicities of irinotecan. Bar graph showing that the incidence of severe (grades 3-4) neutropenia (according to the Common Terminology Criteria of Adverse Events) was higher in the BSA group (*left*) when compared with the equation group (*right*; $P = 0.013$).

prospectively compared with BSA-based dosing in a randomized trial. We found that the predicted irinotecan clearance according to the equation was correlated (with little bias and good accuracy) with the measured clearance in the group that received the equation-based dose. As a result, the interindividual pharmacokinetic variability of irinotecan and its active metabolite SN-38 were 19% to 25% lower in the equation-based dosing group, whereas the dose range was substantially broader in this group. In line with the known association between irinotecan pharmacokinetics and drug-related toxicities (5, 8, 18), a >4-fold reduction of severe myelosuppression was observed in the equation-based dosing group as compared with the other group.

In our study, we excluded all patients who were using known CYP3A inducers and/or inhibitors which could not be replaced by other medicines because of the potential hazard or treatment failure when giving these patients a (full) BSA-based dose. However, in clinical practice, patients who are taking this medication would probably benefit even more from dosing on the basis of our CYP3A phenotype–based equation.

It is noteworthy that two patients in the equation-based dosing group were treated with an absolute irinotecan dose of 1,060 mg. This is an extremely high dose because the standard dose for the three-weekly schedule was 350 mg/m^2, suggesting that only patients with a BSA of >3.0 m^2 would have received a similar absolute dose, which is usually only the case for morbidly obese individuals. Even under these circumstances, most physicians would not prescribe such a high dose because doses are typically capped at a BSA of 2.0 m^2 (24). In the current study, both patients received a total of six courses of irinotecan at a dose of 1,060 mg in each course without experiencing any toxicity higher than grade 1. It is of interest to note that one of these patients was even heterozygous for the UGT1A1*28 allele, and may therefore have been genetically predisposed to an increased risk of experiencing severe toxicity after irinotecan treatment (25, 26). This illustrates the feasibility of administering higher doses of irinotecan than the approved BSA-based dose in subgroups of patients that are at low risk for experiencing severe side effects. The selection of such patients might also increase the potential clinical benefit of irinotecan, whereas the administration of lower doses, based on our equation, to patients who cannot tolerate standard doses might decrease the occurrence of potentially life-threatening adverse effects.

One could speculate that the response to treatment might be negatively affected by the use of a dosing algorithm that is associated with a reduced incidence of severe side effects. However, it should be pointed out that the systemic exposure to both irinotecan and SN-38 was equal in both groups, and that overall, the administered doses were even slightly higher in the equation-based dosing group, making this hypothesis unlikely. In addition, if the patients from the equation group were dosed on BSA, this would have resulted in a lower mean absolute dose. Our view is that by predicting irinotecan exposure in the individual patient, those patients who were at risk for severe

toxicities based on their phenotypic profile had received a lower dose, whereas those patients with a more favorable profile had received a higher dose. The average administered dose and exposure to irinotecan in the whole group remained equal, but by administering a tailored dose to each individual, the overall toxicity in the group was reduced. Additional investigation into the influence of equation-based dosing on antitumor activity (response and survival) of irinotecan is required to support this theory.

In addition to its role in irinotecan dosing, CYP3A4 phenotyping may also be valuable in dose calculations of other anticancer drugs with narrow therapeutic windows that are extensively metabolized by CYP3A4, such as docetaxel (27, 28), sunitinib (29), and gefitinib (30). Indeed, Yamamoto et al. have shown the potential clinical effect of applying CYP3A4-phenotyping into the dose calculation of docetaxel (31). The applied equation consisted of urinary concentrations of 6β-hydroxycortisol as a measure of CYP3A4 activity, α1 acid glycoprotein, transaminases and age, and resulted in a reduced interindividual pharmacokinetic variability when compared with BSA-based dosing. However, before these kinds of dose calculations could be clinically implemented, CYP3A4 phenotyping tests should become routinely available in daily clinical practice, and become less time-consuming and less invasive. Further refining of these tests is warranted, for example, by developing strategies for determining midazolam clearance that involve a reduced number of blood samples, and by specifically identifying an optimal CYP3A4 probe for each agent under investigation (32).

The small population that was investigated in our study could have accounted for the fact that the 19% to 25% differences in interindividual pharmacokinetic variability were not statistically significant. Yet, these decreases may have clinical relevance. Importantly, the study showed a significant change in grades 3 to 4 hematologic toxicity in favor of the equation-based dose calculation. However, independent confirmation of our study results is necessary, as well as a demonstration that the antitumor response is equal in both groups or higher when the irinotecan dose is calculated according to the equation. Because irinotecan is often administered in combination regimens; at lower doses, and at a higher frequency than the regimen that was investigated in our study, it is also necessary to investigate the relevance of equation-based dose calculation in other irinotecan schemes before implementing this dosing strategy.

In conclusion, the current study supports the feasibility of using CYP3A4 activity, height, and baseline γ-glutamyltransferase measurements to individualize irinotecan dose calculation. The application of this methodology was associated with a reduced interindividual pharmacokinetic variability, although it was not statistically significant. The incidence of severe myelosuppression was significantly reduced in the equation-based dosing group compared with the BSA-based dosing strategy. In combination with UGT1A1*28 genotyping, CYP3A4 phenotype determination should be explored further as a strategy to identify

patients that are at risk for experiencing severe side effects following irinotecan administration (33).

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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