Flat-Fixed Dosing of Irinotecan: Influence on Pharmacokinetic and Pharmacodynamic Variability

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ABSTRACT

Purpose: **In a previous analysis, it was shown that body-surface area (BSA) is not a predictor of irinotecan pharmacokinetic parameters. Here, we prospectively evaluated the effects of administering a flat-fixed irinotecan dose to cancer patients, regardless of BSA.**

Experimental Design: **Twenty-six cancer patients (12 females) received a fixed irinotecan dose of 600 mg, given as a 90-min i.v. infusion. Plasma concentrations of irinotecan and its metabolites SN-38 (7-ethyl-10-hydroxycamptothecin) and SN-38G (SN-38 glucuronide) were measured during the first cycle and analyzed using nonlinear mixed-effect modeling. Data were compared with those obtained in 47 cancer patients (19 females) who received irinotecan at a BSA-normalized dose of 350 mg/m^2.**

Results: **The interindividual variability in irinotecan clearance (25.9% *versus* 25.1%; $P = 0.93$), in relative extent of conversion to SN-38 (47.8% *versus* 42.7%; $P = 0.24$), and in relative extent of SN-38 glucuronidation (71.2% *versus* 72.4%; $P = 0.95$) were not significantly different between the two dose groups. Variance differences in irinotecan-mediated hematological side effects were also similar between the 600 mg and 350 mg/m^2 groups ($P > 0.14$).**

Conclusions: **These findings suggest that flat-fixed dosing of irinotecan does not result in increased pharmacokinetic/pharmacodynamic variability and could be safely used to supplant current dosing strategies based on BSA.**

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INTRODUCTION

Irinotecan, registered for the first- and second-line treatment of nonresectable colorectal cancer, is a prodrug of the topoisomerase I inhibitor SN-38 (7-ethyl-10-hydroxycamptothecin), which is formed through a carboxylesterase-mediated cleavage of the parent drug (1, 2). The interindividual variability in irinotecan pharmacokinetic parameters is large and has been associated with variation in its clinical outcome and toxicity profiles (3). This variability is related in part to multiple polymorphic pathways involved in the biotransformation of irinotecan, notably a cytochrome P450 3A4-mediated route for the parent drug (4), and inactivation of SN-38 by members of UGT1A, leading to the formation of SN-38G (SN-38 glucuronide; Ref. 5).

The traditional method of individualizing irinotecan dosage is by using body-surface area (BSA), using a formula derived from weight and height alone. The usefulness of normalizing irinotecan doses to BSA in adults has been questioned recently because irinotecan pharmacokinetic parameters appear to be unrelated to BSA (6, 7). This suggests that the use of BSA-based dosing of irinotecan results in the administration of a standard dose multiplied by a random number, *i.e.*, the ratio of the patient's BSA to an average BSA. In the current study, we evaluated the effects of administering a fixed irinotecan dose to cancer patients, regardless of body size, and compared the interindividual variability in irinotecan pharmacokinetics with data obtained in patients receiving a BSA-normalized dose.

PATIENTS AND METHODS

Treatment of Patients. Patients diagnosed with a histologically confirmed malignant solid tumor for whom irinotecan was assumed to be the best treatment option were eligible for treatment with a flat-fixed irinotecan dose of 600 mg, administered as a 90-min i.v. infusion. The inclusion and exclusion criteria, premedication schedules, and protocols for treatment of drug-induced side effects were identical to those documented previously (8). The drug was given once every 3 weeks until progression of disease or appearance of dose-limiting toxicities. In case of unacceptable toxicities, the following course was postponed for 1 week or a dose reduction of 25% (to 450 mg) was performed, at the discretion of the treating clinician. This group of patients was treated between January 2002 and April 2003 at the Erasmus MC–Daniel den Hoed Cancer Center (Rotterdam, the Netherlands). A separate cohort of patients was treated off protocol with irinotecan given at a BSA-normalized dose of 350 mg/m^2. Pharmacokinetic data from this reference group were published previously (9). None of the patients received any other concurrent chemotherapy or other drugs, food supplements, and/or herbal preparations known to interfere with the pharmacokinetics of irinotecan. The clinical protocols, including blood sampling for the purpose of pharmacological

analyses, were approved by the Erasmus MC Ethics Board, and all patients provided written informed consent.

Pharmacological Evaluation. Blood samples of about 5 ml each were collected in EDTA-containing tubes during the first course of treatment at the following time points: (*a*) immediately before infusion; (*b*) at 30 min after the start of infusion; (*c*) 5 min before the end of infusion; and (*d*) at 10, 20, and 30 min and 1, 1.5, 2, 4, 5, 8.5, 24, 32, 48, and 56 h after the end of infusion. Blood samples were centrifuged to obtain plasma, and concentrations of irinotecan, SN-38, and SN-38G were determined as described previously (10). Previously developed population models were used to predict the pharmacokinetic parameters of the lactone and carboxylate forms of both irinotecan and SN-38 and of total SN-38G (11). The area under the plasma-concentration time curve (AUC) was simulated for irinotecan and its metabolites in all patients from time 0 to 100 h after start of infusion using nonlinear mixed-effect modeling version VI (S. L. Beal and L. B. Sheiner, San Francisco, CA). The following metabolic ratios were calculated on the basis of the predicted AUC values for each individual patient: (*a*) the relative extent of conversion (*i.e.*, the AUC ratio of SN-38 to irinotecan, expressed as a percentage); (*b*) the relative extent of glucuronidation (*i.e.*, the AUC ratio of SN-38G to SN-38); and (*c*) the biliary index (*i.e.*, the ratio of irinotecan AUC to the relative extent of glucuronidation).

Toxicity was evaluated and graded according to the National Cancer Institute Common Toxicity Criteria version 2.0. Hematological pharmacodynamics were assessed by analysis of the absolute nadir values of blood cell counts and by the relative hematological toxicity, *i.e.*, the percentage decrease in blood cell count, which was defined as follows: percentage decrease = [(pretherapy value − nadir value)/(pretherapy value)] × 100%.

Statistical Considerations. Group sample sizes of 25 (fixed dose) and 50 (BSA-normalized dose) were calculated to achieve approximately 60% power to detect a ratio of 2.00 between the parameter variances in the respective groups, using a two-sided F test with a significance level (α) of 0.05. All pharmacokinetic data are presented as mean values with the coefficient of variation in parentheses, unless stated otherwise. The coefficient of variation was defined as the ratio of SD and the observed mean. A modified Levene test was used to test for equality of variances between the fixed dose and BSA-normalized dose groups. Statistical calculations were performed using Number Cruncher Statistical Systems 2001 and Power Analysis and Sample Size 2001 (NCSS, Kaysville, UT).

RESULTS

A total of 26 cancer patients with a median age of 57 years (range, 38–73 years) and a median BSA of 1.85 m^2 (range, 1.45–2.31 m^2) received at least one course of irinotecan at a dose of 600 mg (Table 1). In the reference group, 47 cancer patients with a median age of 53 years (range, 37–71 years) and a median BSA of 1.87 m^2 (range, 1.40–2.36 m^2) received a BSA-corrected dose of 350 mg/m^2. Patient demographic characteristics were similar between the groups, although the tumor type distribution was different (Table 1). However, it was considered unlikely that this would affect the subsequent pharmacological analysis, and hence data from all patients in both groups were taken into consideration.

Table 1 Patient demographics

Values represent the median value, with range in parentheses (unless stated otherwise).

Variable	600 mg group	350 mg/m^2 group
Total no. of patients entered	26	47
Males	14	28
Females	12	19
Age (yr)	57 (38–73)	53 (37–71)
Length (m)	1.72 (1.55–1.86)	1.73 (1.55–1.92)
Weight (kg)	71 (48–109)	73 (45–108)
Body-surface area (m^2)	1.85 (1.45–2.31)	1.87 (1.40–2.36)
Performance score	1 (0–1)	1 (0–1)
Tumor types [*N* (%)]		
SCLC[a]/NSCLC	13 (50)	2 (4)
Gastrointestinal	8 (31)	32 (68)
Miscellaneous	5 (19)	13 (28)
Infusion duration (h)	1.50 (1.47–1.78)	1.50 (0.75–2.25)

[a] SCLC, small cell lung cancer; NSCLC, non-small cell lung cancer.

Plasma concentration-time curves of irinotecan, SN-38, and SN-38G were well predicted by previously defined nonlinear mixed-effect modeling models (11), without any substantial bias (data not shown). The interindividual variability in irinotecan pharmacokinetics was not significantly different in patients receiving 600 mg or 350 mg/m^2 (Table 2). The mean absolute dose in the latter group was 8.7% higher than that in the fixed-dose group, which contributed to a minor increase in overall systemic exposure to irinotecan, SN-38, and SN-38G. However, variability in the extent of conversion of irinotecan to SN-38 and in the extent of SN-38 glucuronidation was identical in both groups ($P \geq 0.24$; Table 2). Likewise, the interindividual variability in irinotecan-mediated hematological side effects between the 600 mg and 350 mg/m^2 groups was not significantly different ($P \geq 0.14$; Table 2). The incidence of grade 3 or 4 diarrhea was slightly higher in the fixed-dose group but was within the range reported previously for a larger cohort of patients treated at a single-agent irinotecan dose of 350 mg/m^2 (1).

DISCUSSION

In the current exploratory study, we demonstrated that fixed dosing of irinotecan, regardless of body size, can be safely used in adult cancer patients as an alternative to the conventional BSA-corrected dosing strategy. Indeed, the interindividual variability in pharmacokinetic and pharmacodynamic parameters, expressed as the percentage coefficient of variation, did not change significantly in the fixed-dose group as compared with the BSA-based dose regimen. Observations similar to those described here for irinotecan have been published previously for the anthracycline epirubicin (12) and, more recently, for paclitaxel (13).

It can be anticipated that implementation of the flat-fixed dosing concept in routine clinical practice would have significant economic implications (14). The ability to manufacture a unit dose has obvious benefits for the pharmaceutical company involved. Similarly, reconstituting a fixed dose

Table 2 Summary of pharmacokinetic and pharmacodynamic parameters

Values represent the mean, with coefficient of variation in parentheses (unless stated otherwise).

Variable	600 mg group	350 mg/m^2 group	P^a
Dose [mg (range)]	600	652 (490–875)	
CL[b] irinotecan lactone (liters/h)	74.4 (25.9)	74.7 (25.1)	0.93
CL irinotecan carboxylate (liters/h)	11.2 (14.4)	11.9 (18.0)	0.28
AUC irinotecan total (μg·h/ml)	18.3 (28.5)	20.0 (30.4)	0.62
REC (%)	3.11 (47.8)	2.82 (42.7)	0.24
REG	7.09 (71.2)	7.89 (72.4)	0.95
BI	4.051 (86.7)	3.540 (61.9)	0.30
WBC nadir ($\times 10^9$/liter)	3.99 (50.2)	3.30 (54.3)	0.84
Decrease in WBC (%)	49.7 (45.9)	58.3 (41.3)	0.67
ANC nadir ($\times 10^9$/liter)	2.44 (71.5)	1.62 (68.8)	0.14
Decrease in ANC (%)	58.1 (39.7)	68.6 (34.4)	0.97
Grade 3/4 diarrhea [*N* (%)]	5 (19)	4 (9)	N/A

[a] Modified Levene test for differences in variance.

[b] CL, plasma clearance; AUC, area under the plasma-concentration time curve; REC, relative extent of conversion (AUC ratio of SN-38 to irinotecan); REG, relative extent of glucuronidation (AUC ratio of SN-38 to SN-38G); BI, biliary index (ratio of irinotecan AUC and REG); ANC, absolute neutrophil count; N/A, not available.

without subsequent individualization for different patients is more efficient and cost-effective than preparing individualized doses and would eliminate a significant source of error in attempting to obtain precise dosing (15). In addition, drug preparation and administration errors are very common for i.v. drugs (16), and are usually the result of systematic error (inaccuracy of the calculation algorithms) and inevitable convergence error, including use of inaccurate height and weight for BSA calculation (17).

The 600-mg dose used in the fixed-dose group was selected on the basis of the assumption of an average BSA for cancer patients of 1.73 m^2, which was the mean value in a European Organization for Research and Treatment of Cancer database that included 3000 patients, both males and females, treated for sarcomas, lymphomas, and rectal cancers during the period 1990–1998.[1] The actual mean BSA value in the present patient cohorts was 1.86 m^2, and this led to a mean absolute dose in the BSA-normalized dose group of slightly more than 600 mg. It is therefore proposed that future clinical trials should evaluate the administration of fixed doses of irinotecan calculated on the basis of an average BSA in any given adult population, *i.e.*, fixed dose (in mg) = conventional dose (in mg/m^2) $\times$ mean BSA (in m^2). Because the pharmacokinetic behavior of irinotecan is dose and time independent (3), the *modus operandi* can also be applied to irinotecan administered as a 30-min infusion and/or at the reduced doses commonly given in weekly regimens.

One limitation of this trial is the relatively small sample size in both arms. However, the pharmacokinetic and pharmacodynamic parameters were almost identical between the cohorts, and it is doubtful that even a very large trial would detect a clinically relevant alteration in the variances. Likewise, although the study was not designed to examine response and survival data, differences in antitumor activity between the dose groups are not expected. We suggest implementation of a fixed dosing strategy for irinotecan, independent of BSA, until better dosing methods become available, which might, for example, be based on factors known to impact on irinotecan elimination pathways (*e.g.*, measures of hepatic dysfunction and UGT1A genotype; Refs. 18–20).

[1] J. Verweij, unpublished data.

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