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FACTORS INFLUENCING THE PHARMACOKINETICS (PK) OF THE ANTICANCER DRUG IRINOTECAN (CPT-11) AND ITS MAJOR METABOLITES, SN-38 AND SN-38G

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ABSTRACT

Purpose. To evaluate significant covariate effects on the PK of CPT-11 (C), SN-38 (S) and SN-38G (G).

Methods. Data obtained from 2 Phase II and 1 Phase III trials in 581 patients (pts) with colorectal cancer who received infusions of C 100 (99 pts), 125 (481 pts), or 150 mg/m² (1 pt) wkly for 4 wks, followed by a 2-wk rest period. Sparse sampling was performed after the wk 1 and/or 3 dose of Course 1 resulting in 2495, 2493 and 1107 samples for C, S, and G, respectively. Covariate effects were evaluated with a validated 5-compartment model via NONMEM® using p = 0.0001 as inclusion/exclusion criteria.

Results. The table shows the % change in the typical clearances when a covariate is changed in the indicated way.

Clearance Pathway	C→	C→S	S→G	G→	G→S
Typical Value (L/hr)	**26**	**3.54**	**309**	**16.9**	**71.1**
Change in covariate	**Cov. effect (% change from typical value)**				
Hemoglobin (1 g/dL)	7	-10			4
Tot. bili (0.1 mg/dL)	-3	3			
CLcr (10 ml/min)	-5				
Perf. Status = 1 (vs 0)	-14		12		
Perf. Status = 2 (vs 0)	-40	22			-81
Hisp./Asian (vs Cauc.)		-27			
Female (vs Male)		-19			
5-FU/LV (vs No)*			-20	32	
AST (10 U/L)	-3	3	7		

* Some patients received CPT-11 in combination with 5-FU/LV

Conclusions. This comprehensive analysis provides insights into the magnitude of covariate effects. Consideration of such factors may be important for optimal irinotecan dosing.

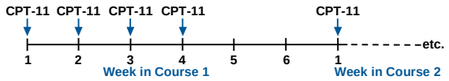
INTRODUCTION

- Irinotecan (CPT-11), a camptothecin-derived inhibitor of topoisomerase-1, is a prodrug that undergoes metabolism to an active metabolite, SN-38. The metabolite is further conjugated to form the secondary metabolite, SN-38G.
- A five-compartment population pharmacokinetic model was previously developed that simultaneously describes the plasma concentration profiles for CPT-11, SN-38, and SN-38G.
- Since diarrhea and myelosuppression associated with irinotecan therapy may relate to prodrug/metabolite exposure, understanding of patient factors that influence the pharmacokinetics of CPT-11 and its metabolites would be of value for more optimal design of dosage regimens.
- Previous studies evaluating the influence of patient covariates on the pharmacokinetics of CPT-11, SN-38, and SN-38G have provided conflicting findings that may in part be the result of use of non-compartmental analysis methods for a drug with complex metabolism.
- This analysis describes the evaluation of significant covariate effects on the pharmacokinetics of CPT-11, SN-38, and SN-38G using a validated 5-compartment model.[1]

METHODS

Study Design and Data

- Data were obtained from 1 Phase III and 2 Phase II trials of CPT-11 in patients with colorectal cancer.
- Dose: 100-150 mg/m² infused over 90 minutes weekly for 4 weeks, followed by 2-week rest (6-week cycle). Dose adjustments were based on predefined criteria.



- PK sampling: week 1 (and week 3 for 1 study) of Course 1 at pre-dose, end of infusion, and at 1, 2, 4, and 24 hours post-infusion in the 2 studies, and only at 2 and 6-8 hours post-infusion in the third study.

Bioanalytical Assay Method

- Total (sum of lactone + hydroxyacid form) CPT-11 and SN-38 concentrations (determined by HPLC)
- Species measured: CPT-11 and SN-38 – all studies; SN-38G in 2 studies
- Mean interassay precision ≤ 6% for all species
- Mean interassay QC sample recovery range: 92-112% for all species

Pharmacostatistical Model

- NONMEM® V using first-order estimation
- Five-compartment PK model
- Exponential error model evaluated for interindividual error
- Constant coefficient of variation and combined additive plus constant coefficient of variation error models evaluated for residual error

Covariate Analysis

- Patient covariates: hemoglobin, total bilirubin (TBIL), creatinine clearance (CLcr), ECOG performance status (PS), race, gender, coadministration of 5-fluorouracil/leucovorin, aspartate aminotransferase (AST), age, body surface area (BSA), dose
- Continuous covariates modeled using linear, exponential, and/or power models
- Dichotomous and categorical covariates modeled using proportional or additive shift models
- Univariate analyses performed followed by stepwise backward elimination to determine significant subject covariates

Statistical Analyses

- Statistical significance assessed for univariate analyses using alpha = 0.001; backward elimination using alpha = 0.0001
- Goodness-of-fit plots of each NONMEM® analysis assessed by examination of:
  - scatterplots of predicted versus measured concentrations and versus weighted residuals
  - %SEM of the parameter estimates
  - changes in the estimates of the interindividual and residual variability
  - physiologic relevance
  - numerical stability

Simulations

- Assessed individual covariate effects on concentration-time profiles and area under the concentration-time profiles (AUC)
- Dose selection: 125 mg/m² for a typical subject with BSA = 1.85 m²
- Data:
  - continuous covariates: values selected as every 10th percentile of the population range
  - categorical covariates: selected as all real values (0,1…)
  - all other covariates – fixed at population median (continuous) or population probabilities (dichotomous)
- Concentrations and AUC's expressed as CPT-11 equivalent in units of ng/mL and ng/mL•hr, respectively, with calibration of molecular weights

RESULTS

Table 1: Covariate Definitions and Distributions (n = 581)

Variable Name	Definition	Mean ± SD; Median (min, max); or % (n/N)
AGEC	Age group: 1 if AGE ≥ 65 and 0 otherwise	40.1% (233/581) and 59.9% (348/581)
AGEN	Age (years)	60.7 ± 11.8; 63.0 (25, 87)
AST	Aspartate aminotransferase (U/L)	37.7 ± 28.0; 28.0 (7.0, 176.0)
BSA	Body surface area (m²)	1.86 ± 0.23; 1.85 (1.36, 2.46)
CLcr	Creatinine clearance (mL/min)²	87.7 ± 30.5; 83.3 (22.4, 225.9)
DOSE	Doses administered (mg/m²)	120.8 ± 9.5; 125 (100, 150)
FU5	Co-medication of 5-Fluorouracil/Leucovorin	26.3% (153/581)
HGB	Hemoglobin (g/dL)	12.6 ± 1.73; 12.6 (8.0, 19.1)
PS	Performance status (PS): 0, 1 (PS1) and 2 (PS2)	49.5% (287/581), 41.1% (239/581), and 9.5% (55/581)
RACE	Race: Whites (RACW), Black (RACB) and Others (RACO)	86.4% (502/581), 6.9% (40/581), and 6.7% (39/581)
SEXF	Gender: 1 for females and 0 for males	42.5% (247/581) and 57.5% (334/581)
TBIL	Total bilirubin (mg/dL)	0.64 ± 0.37; 0.50 (0.1, 2.5)
WTKG	Body weight (kg)	75.8 ± 17.1; 74.5 (42.4, 152.6)

- Covariates with significant influence on CPT-11 PK were: hemoglobin, total bilirubin, creatinine clearance, performance status score of 2, race Others (= Hispanic/Asian), female gender, concurrent 5-FU/leucovorin, and aspartate aminotransferase.
- For detailed PK parameter estimates, refer to the appendix.

Figure 1: Model Structure

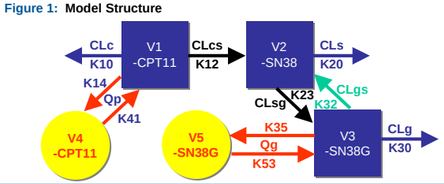


Figure 2: Goodness-of-Fit of the Final Model

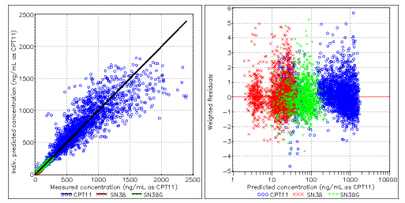


Figure 3: Effect of PS on Predicted Concentration-Time Profiles

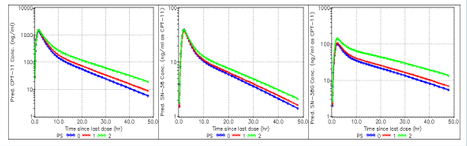


Figure 4: Effect of Total Bilirubin (TBIL, mg/dL) on Predicted Concentration-Time Profiles

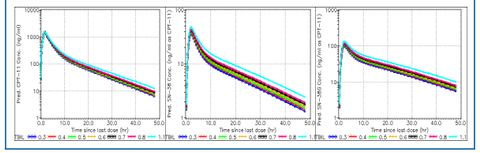
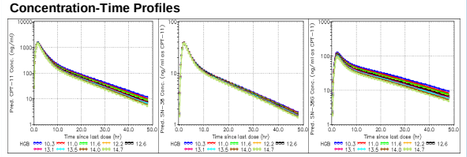


Figure 5: Effect of Hemoglobin (HGB, g/dL) on Predicted Concentration-Time Profiles



CONCLUSIONS

- This analysis provides the first simultaneous compartmental-based quantitative evaluation of the magnitude of covariate effects on PK of CPT-11 and its major metabolites.
- Eight covariates were shown to significantly influence (+/-) the clearances of CPT-11, SN-38, and/or SN-38G.
- Factors associated with the largest % changes (+/-) in clearances across the species were an ECOG performance score of 2 and high total bilirubin.
- Clinical development of other therapeutic agents with complex metabolism may be facilitated through application of this analysis approach.

APPENDIX

Estimates of PK Parameters and Covariate Effects:

CLc = {(26.0±0.612)+(1.85±0.25)*(HGB-12.6)+(-8.88±1.34)*[(TBIL-0.50) *FBL +1.5*(1-FBL)]+(-11.6±1.70)*(PS2-0.0947)+(0.123±0.0149) *(CRCL-83.3)+(-0.0862±0.0233)*[(AST-28.0)*FLG+92*(1-FLG)]+ (-4.18 ± 1.03)*(PS1-0.411)}*exp(N(0, ω_c^2)) (L/hr),
with ω_c^2 = 0.18 ± 0.0174

CLcs = {(3.54±0.0832) +(-0.143±0.0416)*(HGB-12.6)+(1.11±0.243)* [(TBIL-0.50)*FBL+1.5*(1-FBL)]+(1.30±0.324)*(RACO-0.0671)+ (0.769±0.152)*(SEXF-0.425)+(0.0107±0.00377)*[(AST-28.0)*FLG +92* (1-FLG)]+(0.771±0.383)*(PS2-0.0947)}*exp(N(0, ω_{cs}^2))(L/hr),
with ω_{cs}^2 = 0.0785±0.00824

CLs = (44.1±4.26)/[1+(0.230±0.0109)(309±29.8)/(16.9±0.787)] (L/hr)

CLsg = {(309±29.8)+(2.01±0.458)*[(AST-28.0)*FLG+92*(1-FLG)]+ (-66.5±17.2)*(FU5-0.263)+(35.0±16.8)*(PS1-0.411)}* exp(N(0, ω_{sg}^2)) (L/hr), with ω_{sg}^2 = 0.171±0.0199

CLg = {(16.9±0.787)+(4.97±1.64)*(FU5-0.263)}* exp(N(0, ω_g^2)) (L/hr),
with ω_g^2 = 0.257±0.041

CLgs = (309±29.8)*(0.230±0.0109)+(7.38±1.44)*(HGB-12.6)+(-33.3±6.54) * (PS2-0.0947) (L/hr)

$\omega_{sg}\omega_g$ = -0.110 ± 0.0171

V1 = 109 ± 5.16 (L);
V2 = 40.4 ± 6.4 (L);
V3 = 9.12 ± 2.52 (L);
V4 = 109 ± 11.2 (L);
V5 = 188 ± 15.3 (L)

Q_p = 14.0 ± 1.95 (L/hr);
Q_g = 26.7 ± 1.18 (L/hr)

$C_{CPTmeas}$ = $C_{CPTpred}$ *(1+N(0, σ_c^2)) (ng/mL as CPT-11),
with σ_c^2 = 0.0656 ± 0.00416

$C_{SN38meas}$ = $C_{SN38pred}$*(1+N(0, σ_s^2)) (ng/mL as CPT-11),
with σ_s^2 = 0.103 ± 0.00706

$C_{SN38Gmeas}$ = $C_{SN38Gpred}$*(1+N(0, σ_g^2)) (ng/mL as CPT-11),
with σ_g^2 = 0.0326± 0.00316

Where:

FBL = 0 if TBIL > 2 and 1 otherwise;
FLG = 0 if AST > 120 and 1 otherwise; and
N(0, σ^2) = a normal distribution centered at 0 .

REFERENCES

1. A. Xiao, J. Fiedler-Kelly, L. Schaaf, J. McGovren, G. Elfring, S. Sardella, and M. Redman. Simultaneous Population Pharmacokinetic (PPK) Modeling of Irinotecan (CPT-11) and Its Major Metabolites, SN-38 and SN-38G. Poster for ASCPT, Atlanta, GA, Mar 21-24, 2002.
2. Cockcroft DW, Gault MH. Prediction of Creatinine Clearance from Serum Creatinine. Nephron 1976; 16:31-41.