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Complex Disease—, Gene—, and Drug–Drug Interactions: Impacts of Renal Function, CYP2D6 Phenotype, and OCT2 Activity on Veliparib Pharmacokinetics

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Abstract

Purpose—Veliparib, a poly (ADP-ribose) polymerase (PARP) inhibitor, undergoes renal excretion and liver metabolism. This study quantitatively assessed the interactions of veliparib with metabolizing enzyme (CYP2D6) and transporter (OCT2) in disease settings (renal impairment).

Experimental Design—Veliparib *in vitro* metabolism was examined in human liver microsomes and recombinant enzymes carrying wild-type *CYP2D6* or functional defect variants (*CYP2D6**10 and *4). Plasma pharmacokinetics were evaluated in 27 patients with cancer. A parent–metabolite joint population model was developed to characterize veliparib and metabolite (M8) pharmacokinetics and to identify patient factors influencing veliparib disposition. A physiologically based pharmacokinetic model integrated with a mechanistic kidney module was developed to quantitatively predict the individual and combined effects of renal function, CYP2D6 phenotype, and OCT2 activity on veliparib pharmacokinetics.

Results—*In vitro* intrinsic clearance of CYP2D6.1 and CYP2D6.10 for veliparib metabolism were 0.055 and 0.017 $\mu\text{L}/\text{min}/\text{pmol}$ CYP, respectively. Population mean values for veliparib oral clearance and M8 clearance were 13.3 and 8.6 L/h, respectively. Creatinine clearance was identified as the significant covariate on veliparib oral clearance. Moderate renal impairment, CYP2D6 poor metabolizer, and co-administration of OCT2 inhibitor (cimetidine) increased veliparib steady-state exposure by 80%, 20%, and 30%, respectively. These factors collectively led to >2-fold increase in veliparib exposure.

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Conclusions—Renal function (creatinine clearance) is a significant predictor for veliparib exposure in patients with cancer. Although a single factor (i.e., renal impairment, CYP2D6 deficiency, and reduced OCT2 activity) shows a moderate impact, they collectively could result in a significant and potentially clinically relevant increase in veliparib exposure.

Introduction

Veliparib (or ABT-888) is an orally bioavailable, small molecule inhibitor of poly (ADP-ribose) polymerase-1 (PARP-1) and PARP-2. Functioning as DNA damage sensors for both single- and double-stranded DNA breaks, PARP-1 and PARP-2 are essential in single-stranded DNA break repair by base excision repair pathway (1). Enhanced expression or activity of PARP in tumor cells can lead to radioresistance and chemoresistance (2, 3) and thus, PARP inhibitors hold promise as chemotherapy and radiation sensitizers. Veliparib, a PARP inhibitor capable of sensitizing tumor cells to cytotoxic chemo or radiation therapy, is currently under intensive clinical investigation in combination with DNA-damaging agents or radiation therapy for the treatment of a variety of malignancies (<http://www.clinicaltrials.gov>).

The plasma pharmacokinetics of veliparib have been described previously in patients with cancer enrolled in phase 0 and phase I studies (4–7). Veliparib exhibits a good oral bioavailability and extensive tissue distribution. Renal excretion seems the major route of elimination for veliparib, with average 70% (range, 31%–115%) of oral dose being recovered in the urine as the unchanged drug in patients with cancer receiving a single dose of 50 mg (4). Besides the glomerular filtration, active tubular secretion plays an important role in the renal clearance of veliparib (8). Renal secretion of organic cations or anions is a process that involves an entry step at the basolateral membrane and an exit step at the apical membrane of renal tubule cells. Multiple transporters could be involved in this process (9). For example, organic cation transporters (OCT) or organic anion transporters (OAT) mediate drug uptake from the blood into proximal tubule epithelia across the basolateral membrane and subsequently, ATP-binding cassette (ABC) transporters or multidrug and toxin extrusion (MATE) transporters mediate drug efflux into the urine across the apical membrane (9). Veliparib is a good substrate of OCT2 and a weak substrate of ABCB1 (8, 10). *In vivo*, the renal clearance of veliparib was reduced by 1.8-fold and its plasma exposure was increased by 1.5-fold in OCT1/2 double-knockout mice, in comparison with the OCT1/2 wild-type mice (8), suggesting OCT2 is an important transporter involved in the renal secretion of veliparib. In addition to renal clearance, veliparib undergoes liver metabolism predominantly mediated by cytochrome P450 (CYP) 2D6 (10). A lactam metabolite (named M8) is the major metabolite identified *in vitro* and *in vivo* (10), which shows ~5- and 13-fold lower PARP inhibition activity than veliparib as determined from *in vitro* PARP enzyme assay and cellular PARP assay, respectively (11).

In light of multiple pathways involved in the disposition of veliparib, complex disease-, gene-, and drug-drug interactions could occur when several clinical factors exist concomitantly, such as renal or liver dysfunction and changes in metabolism or transport activities caused by genetic polymorphisms or interactions with coadministered drugs. These factors individually may not have a significant impact on the drug pharmacokinetics, but

they collectively can be additive or synergistic leading to clinical relevant changes in the drug exposure. The pharmacokinetic–pharmacodynamic relationship for veliparib has been demonstrated in a preclinical syngeneic melanoma model treated with a combination of veliparib and temozolomide, in which the PARP inhibition in tumor tissues and *in vivo* antitumor activity are correlated with veliparib plasma/tumor concentrations (12). Although relationships between veliparib exposure and clinical efficacy or toxicity have not been evaluated comprehensively in patients with cancer, substantial changes in the drug exposure because of complex drug interactions are likely to affect clinical outcome (efficacy or toxicity).

Early identification of these interactions and quantitative prediction of their impacts on drug pharmacokinetics are of great importance to the rational development and optimal use of anticancer drugs such as veliparib, a potential chemosensitizer intended to use in combination with other cytotoxic agents in complicated disease settings. However, identification and quantitative assessment of complex drug interactions in early-phase clinical trials are challenging because of the multifaceted nature of interactions but limited sample size and insufficient statistical power in clinical trials. Recently, the population-based physiologically based pharmacokinetic (PBPK) modeling and simulation approach, which allows *in vitro*–*in vivo* extrapolation and enables simultaneous incorporation of multiple pathophysiological factors, has emerged as a valuable tool for quantitative assessment and prediction of complex drug interactions (13, 14).

In this study, a parent–metabolite population pharmacokinetic model was developed to simultaneously characterize the plasma pharmacokinetics of veliparib and its main metabolite (M8) in patients with cancer and to identify patient factors influencing veliparib disposition. In addition, a PBPK model integrated with a mechanistic kidney module was developed to quantitatively assess the interactions of veliparib with the metabolizing enzyme (CYP2D6) and transporter (OCT2) in disease settings associated with renal impairment.

Materials and Methods

Materials

Veliparib and M8 (A-925088.3) were provided by Abbott Laboratories (Abbott Park, IL). Recombinant human CYP Supersomes (including CYP1A1, CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, and CYP3A5), insect cell control Supersomes, Human CYP2D6.10 Allelic Variant Kit (including CYP2D6.1 and CYP2D6.10 Supersomes), single donor human liver microsomes from individuals carrying *CYP2D6**1/*1 (wild-type) and homozygous *CYP2D6**4/*4, as well as NADPH-regenerating system solutions A and B were purchased from BD Biosciences.

In vitro metabolism study

To determine the major human CYP enzyme(s) contributing to the metabolism of veliparib, the drug (100 µmol/L) was incubated with varying concentrations (20–160 pmol/mL) of CYP1A1, 1A2, 2C9, 2C19, 2D6, 3A4, and 3A5 Supersomes. The reaction mixture (total volume 0.2 mL) containing veliparib (100 µmol/L), 1.3 mmol/L NADP⁺, 3.3 mmol/L

glucose-6-phosphate, 0.4 units/mL glucose-6-phosphate dehydrogenase, 3.3 mmol/L magnesium chloride, and CYP enzyme in 100 mmol/L potassium phosphate buffer solution (PBS; pH 7.4) were incubated at 37°C for 30 minutes. Incubations with insect cell control Supersomes were done simultaneously.

To assess the impact of *CYP2D6* polymorphisms on veliparib metabolism, veliparib (0.5–250 µmol/L) was incubated with CYP2D6.1 or CYP2D6.10 Supersomes (100 pmol/mL) at 37°C for 30 minutes. In addition, veliparib (100 µmol/L) was incubated with single donor human liver microsomes (at protein concentrations of 0.2, 0.6, and 1.8 mg/mL) with wild-type *CYP2D6**1/*1 or functional defect *CYP2D6**4/*4, at 37°C for 30 minutes.

At the end of incubation, the reactions were terminated by adding 50 µL of 1 mol/L NaOH and 1.0 mL of ethyl acetate. The mixture was vortex-mixed for 30 minutes, and centrifuged at $12,000 \times g$ at 4°C for 10 minutes. The organic layer was collected, dried down, and reconstituted in 150 µL of methanol–acetonitrile–0.45% formic acid (2:1:97, v/v), and subjected to high-performance liquid chromatography (HPLC) analysis. Veliparib and metabolites were separated and quantitated by a validated HPLC method using Waters 2690 HPLC system coupled with a photodiode array detector. The samples were separated on a Waters Xterra RP18 column (5 mm, 150×3.9 mm) with a mobile phase consisting of methanol–acetonitrile–0.45% formic acid (2:1:97) running at a flow rate of 1 mL/min. Veliparib and M8 were monitored at the wavelength of 270 nm. Linear calibration curves for veliparib and M8 were constructed in PBS over concentration ranges of 0.02 to 100 µmol/L and 0.8 to 40 µmol/L, respectively. Intra- and interday precisions and accuracies for quality control samples were <15%.

Enzyme kinetic analysis

Substrate disappearance velocity (v) was calculated as $[(C_{s,0} - C_{s,t})/t/\text{CYP concentration}]$, where $C_{s,0}$ and $C_{s,t}$ are the substrate concentration at time 0 and at the end of incubation, respectively, and t is the incubation time. Metabolite formation velocity (v) is calculated as $(C_{m,t}/t/\text{CYP concentration})$, where $C_{m,t}$ is the metabolite concentration at the end of incubation and t is the incubation time. Because velocity (v) versus initial substrate concentration ($C_{s,0}$) plots as well as corresponding Eadie–Hoftee ($v/C_{s,0}$ vs. $C_{s,0}$) and Lineweaver–Burk ($1/v$ vs. $1/C_{s,0}$) plots indicated sigmoidal kinetics, the kinetic profiles of substrate disappearance and metabolite formation were fitted to Hill equation (Equation 1). Fittings were performed with nonlinear regression using the Sigma Plot 12.0 (Systat Software, Inc.). The *in vitro* intrinsic clearance (CL_{int}), calculated from Equation 2 (15), provides an estimate of the highest clearance attained as substrate concentration increases before any saturation of the enzyme sites.

$$v = \frac{V_{\max} \times S^n}{S_{50}^n + S^n} \quad (1)$$

$$CL_{\text{int}} = \frac{V_{\max}}{S_{50}} \times \frac{(n - 1)}{n \times (n - 1)^{1/n}} \quad (2)$$

where $V_{\max}$ is maximum metabolic velocity, S_{50} is the substrate concentration at which 50% of $V_{\max}$ is obtained, and n is the Hill coefficient.

Clinical pharmacokinetic study

Plasma pharmacokinetics of veliparib and M8 were assessed in patients with cancer as part of a phase I clinical trial evaluating the combination therapy of veliparib and irinotecan. Patients with metastatic and refractory solid malignancies and with adequate hematologic, renal, and liver functions were enrolled in the study. The protocol was approved by the Institutional Review Board of the participated institutions (including Wayne State University and University of Maryland), and written informed consent was obtained from each patient.

Veliparib was provided by Abbott Laboratories as 10 and 50 mg immediate release capsules. Cohorts of 3 to 6 patients each were treated with oral veliparib at escalating doses of 10, 20, 40, and 50 mg twice daily in combination with weekly irinotecan (100 or 125 mg/m²). One treatment cycle consisted 21 days. In cycle 1, irinotecan was administered by 1.5-hour intravenous infusion on days 1 and 8; veliparib was administered orally twice daily from day 3 to day 14. In cycle 2, a single dose of veliparib was administered 1 day before irinotecan treatment (day -1) to allow for single-agent veliparib pharmacokinetic sampling, and subsequent doses were given twice daily from days 1 to 14; irinotecan was administered by 1.5-hour intravenous infusion on days 1 and 8.

Pharmacokinetic samples for veliparib, given alone and in combination with irinotecan, were obtained from 27 patients. Series blood samples were collected at predosing, 0.5, 1, 1.5, 3.5, 5.5, 8.5, 10, and 28 hour after oral administration of veliparib on cycle 2 day -1 (i.e., given alone) and on cycle 2 day 8 (i.e., in combined with irinotecan). Blood samples were collected in EDTA tubes, placed on ice, and processed within 1 hour of collection. Plasma was separated by centrifugation at $1,500 \times g$ at 4°C for 10 minutes, and stored at -80°C until analysis. The plasma concentrations of veliparib and M8 were determined using a validated liquid chromatography with tandem mass spectrometry (LC/MS-MS) method (16).

Population pharmacokinetic analysis

A parent-metabolite joint population pharmacokinetic model (Fig. 1A) was developed to describe the plasma concentration-time profiles of veliparib and M8 simultaneously and to identify patient factors influencing veliparib pharmacokinetics. The model was developed in 2 stages: structural model development followed by covariate model development.

The structural model was developed by simultaneously fitting veliparib and M8 plasma concentrations to the parent-metabolite model (Fig. 1A), where veliparib is absorbed into the parent compartment (with an apparent volume of distribution V_p/F) at an absorption rate constant of K_a , and eliminated from the system by both an apparent metabolic clearance CL_{pm}/F (conversion to M8) and additional clearance CL_p/F (via renal excretion and other minor liver metabolism); M8 is eliminated from the metabolite compartment (with a volume of distribution V_m/F) by a clearance CL_m . The following assumptions were made: (i) the

absorption and elimination processes are linear (first-order) at the tested dose levels; (ii) there is no back-transformation of M8 to veliparib; and (iii) there is no presystemic formation of M8. Veliparib and M8 concentration data were log-transformed in the data file. Concentrations below the lower limit of quantitation were treated as missing data. Mean population pharmacokinetic parameters, interindividual variability, and residual error (intraindividual variability) were assessed in the model. Interindividual variability of a pharmacokinetic parameter was expressed as an exponential function. Residual error was modeled with a combination method including an additive and a proportional part, each of which could be excluded if it was estimated to be negligible. The population pharmacokinetic parameters were estimated with the first-order conditional estimation (FOCE) with interaction algorithm implemented in the NONMEM software (version VI; University of California, San Francisco, CA). The pharmacokinetic parameters for individual patients were obtained by POSTHOC Bayesian estimation.

A screen for potential statistically significant covariates was performed with a generalized additive model (GAM) using Xpose 4.0/R 2.6.2 software (Uppsala University, Uppsala, Sweden; ref. 17). The following covariates (shown as the median and range from 27 patients) were screened on all Bayesian estimated pharmacokinetic parameters from the structural model: age (54, 31–73 years), weight (71.2, 45.9–107.2 kg), height (167.0, 153.6–187.5 m), body surface area (1.79, 1.45–2.30 m²), liver function [as indicated by levels of total bilirubin (0.4, 0.1–0.9 mg/dL), aspartate aminotransferase (22, 12–76 IU/L), and alanine aminotransferase (19, 7–49 IU/L)], renal function [as indicated by creatinine clearance (5.9, 3.4–12.5 L/h) estimated based on serum creatinine concentration using Cockcroft–Gault equation]. Potentially statistically significant covariates selected from the GAM analysis were introduced into the covariate model as linear, exponential, or power functions according to the following discrimination criteria: (i) a decrease in the objective function value of greater than 3.875 ($P < 0.05$) during the forward covariate model building; (ii) an increase in the objective function value of greater than 10.828 ($P < 0.001$) during the stepwise backward model reduction; (iii) reduction of relative standard error of estimation; and (iv) reduction of interindividual variability of parameters.

A nonparametric bootstrap resampling was used to determine the confidence intervals of the parameter estimates (18). In bootstrapping, the datasets were generated by randomly sampling the patient data with replacement from the original dataset, and the base model and final covariate models were repeatedly fitted to each of these 1,000 bootstrap replicates of the dataset. The final covariate model was further assessed using a visual predictive check (19). A parametric bootstrap resampling was used to simulate 1,000 replicates of the observed dataset where each parameter was set to the final estimates. Bootstrap analyses were performed using Perl-Speaks-NONMEM (Uppsala University).

PBPK modeling and simulation

Using the population-based PBPK software Simcyp Simulator (version 13.1; Simcyp Ltd.), a whole-body PBPK model integrated with a mechanistic kidney module (Fig. 1B) was developed to simulate veliparib plasma concentration–time profiles in an existing virtual Caucasian population with normal renal function (i.e., “NEurCaucasian” population).

Details on the input drug-dependent parameters for veliparib PBPK model are presented in Table 1. The system-dependent parameters used in the model were based on the existing population data within the Simcyp Simulator, unless stated otherwise. Simulations of 10 trials of 10 subjects each were performed with oral administration of veliparib 40 mg either as a single dose or chronic treatment with twice daily for 15 days. The PBPK model was evaluated by comparisons of the predicted veliparib pharmacokinetic profiles with the observed data in patients with cancer.

The developed PBPK model was used to quantitatively predict the individual and combined effects of renal function, CYP2D6 status, and OCT2 activity on veliparib pharmacokinetics. Simulations of 10 virtual trials with 10 subjects each were performed with oral administration of veliparib 40 mg either as a single dose or twice daily for 14 days in 3 virtual populations, including the population with normal renal function (i.e., “NEurCaucasian”), moderate renal impairment (i.e., “RenalGFR_30–60”), and severe renal impairment (i.e., “RenalGFR_less_30”). Simulations were performed in each virtual population at the following scenarios: (i) CYP2D6 extensive metabolizer (EM); (ii) CYP2D6 poor metabolizer (PM); (iii) CYP2D6 ultrarapid metabolizer (UM); (iv) CYP2D6 EM and coadministration of quinidine (a competitive CYP2D6 inhibitor with an *in vitro* Ki of 0.017 $\mu\text{mol/L}$); (v) CYP2D6 PM and co-administration of quinidine; (vi) CYP2D6 UM and co-administration of quinidine; (vii) CYP2D6 EM and coadministration of cimetidine (a competitive OCT2 inhibitor with an *in vitro* Ki of 0.25 $\mu\text{mol/L}$); (viii) CYP2D6 PM and co-administration of cimetidine; and (ix) CYP2D6 UM and co-administration of cimetidine. Details on the PBPK simulations were described below.

Renal function is assessed by glomerular filtration rate (GFR), which is estimated based on serum creatinine concentration, age, weight, and sex using Cockcroft–Gault equation within the Simcyp. The impact of renal function was assessed by simulating veliparib plasma concentration–time profiles in 3 virtual populations with normal renal function (GFR, >60 mL/min), moderate renal impairment (GFR 30–60 mL/min), and severe renal impairment (GFR, <30 mL/min). The Simcyp system-dependent parameters for the existing virtual populations (i.e., “NEurCaucasian,” “RenalGFR_30–60,” and “RenalGFR_less_30”) were used in the model.

In these existing virtual populations, the frequencies for CYP2D6 EM, PM, and UM phenotypes are 0.865, 0.082, and 0.053, respectively. When simulating veliparib pharmacokinetic profiles in a population with a particular CYP2D6 phenotype, the frequency for that phenotype was set to 1. Within the Simcyp, the whole organ liver intrinsic clearance mediated by a particular enzyme (e.g., CYP2D6) can be calculated from recombinant CYP *in vitro* kinetic data using Equation 3.

$$\text{CL}_{\text{int}} = \text{ISEF} \times \text{CL}_{\text{int, in vitro}} \times \text{CYP abundance} \times \text{MPPGL} \times \text{liver weight} \quad (3)$$

where CL_{int} (L/h) is liver intrinsic clearance mediated by a particular enzyme (e.g., CYP2D6), $\text{CL}_{\text{int, in vitro}}$ ($\mu\text{L/min/pmol CYP}$) is the *in vitro* intrinsic clearance of a recombinant CYP, CYP abundance has a unit of pmol CYP per milligram microsome protein, MPPGL has a unit of milligrams of microsomal protein per gram of liver, and ISEF

is intersystem extrapolation factor for scaling of recombinant CYP *in vitro* kinetic data. The *in vitro* CL_{int} of 0.055 and 0.017 $\mu\text{L}/\text{min}/\text{pmol}$ CYP, which was estimated from recombinant CYP2D6.1 and CYP2D6.10 enzyme kinetics, was used in the model to represent the enzyme catalytic efficiency for CYP2D6 EM and PM, respectively. CYP2D6 enzyme abundance in the liver was assumed to be the same for EM and PM (mean, 8 pmol/mg micosome protein). For CYP2D6 UM, the enzyme catalytic efficiency was assumed to be the same as the EM (CL_{int} , 0.055 $\mu\text{L}/\text{min}/\text{pmol}$ CYP), whereas the enzyme abundance in the liver was doubled (mean, 16 pmol/mg micosome protein). The Simcyp system-dependent parameters of MPPGL (mean, 39.8 mg/g) and liver weight (mean, 1,718.3 g) were used.

To quantitatively assess the impact of OCT2 activity in the renal clearance of veliparib, the whole-body PBPK model was integrated with a mechanistic kidney module, in which OCT2 was assumed to be the sole basal uptake transporter responsible for the uptake of veliparib from the blood to proximal tubular cells and ABCB1 was assumed to be the sole apical efflux transporters responsible for extruding the drug from the proximal tubular cells to urine. *In vitro* in OCT2-transfected HEK-293 cells, OCT2 transported veliparib into cells with an intrinsic uptake clearance of 8.6 pmol/min/mg protein (8). Thus, the *in vitro* intrinsic uptake clearance of 8.6 pmol/min/million cells was used in the PBPK model, assuming OCT2 uptake activity in 1 million kidney proximal tubule cells equals to its activity in 1 mg protein of the OCT2-transfected HEK cells. Veliparib was a weak substrate for ABCB1. The *in vitro* intrinsic efflux clearance of 2 pmol/min/million cells was selected based on the sensitivity analysis. The passive diffusion from the blood to proximal tubular cells or from the cells to urine were assumed to be negligible because over 99% of veliparib is ionized at the physiological pH (7.4) in the blood or cells.

The effects of CYP2D6 inhibitor (quinidine) or OCT2 inhibitor (cimetidine) on veliparib pharmacokinetics were simulated in a dynamic fashion by linking the inhibitor PBPK model (i.e., minimum PBPK model for quinidine or whole-body model for cimetidine) to veliparib PBPK model (Fig. 1B). The PBPK models and trial designs for the inhibitors were based on the existing data within the Simcyp Simulator. The inhibition of CYP2D6 or OCT2 was assumed to be competitive and reversible. Quinidine was given orally 200 mg either as a single dose or once daily for 14 days. Cimetidine was given orally 400 mg either as a single dose or twice daily for 14 days.

Results

In vitro metabolism of veliparib

In vitro metabolism experiments using recombinant human CYP enzymes indicated that the overall metabolism of veliparib and formation of M8 were mediated predominantly by CYP2D6, to a less extent by CYP1A1, and to a negligible extent by CYP1A2, CYP2C9, CYP2C19, CYP3A, and CYP3A5 (Supplementary Fig. S1).

The functional influence of CYP2D6 polymorphisms on veliparib metabolism was examined by comparing the enzyme kinetics of recombinant CYP2D6.1 (wild type) and CYP2D6.10 (a common functional defect variant). The kinetic profiles of the substrate disappearance and metabolite formation were well fitted by Hill equation (Fig. 2A and B). For the overall

metabolism of veliparib, the estimated $V_{\max}$, S_{50} , and CL_{int} for CYP2D6.1 and CYP2D6.10 were 5.2 pmol/min/pmol CYP versus 1.2 pmol/min/pmol CYP, 55.2 $\mu\text{mol/L}$ versus 45.7 $\mu\text{mol/L}$, and 0.055 $\mu\text{L/min/pmol CYP}$ versus 0.017 $\mu\text{L/min/pmol CYP}$, respectively. For the formation of M8, the estimated $V_{\max}$, S_{50} , and CL_{int} for CYP2D6.1 and CYP2D6.10 were 6.9 pmol/min/pmol CYP versus 0.7 pmol/min/pmol CYP, 93.2 $\mu\text{mol/L}$ versus 142.8 $\mu\text{mol/L}$, and 0.038 $\mu\text{L/min/pmol CYP}$ versus 0.002 $\mu\text{L/min/pmol CYP}$, respectively. Thus, the functional defect recombinant CYP2D6.10 enzyme remained ~30% and 5% of catalytic efficiency (CL_{int}) for veliparib overall metabolism and M8 formation, respectively, compared with the wild-type enzyme.

The functional influence of *CYP2D6* polymorphisms on veliparib metabolism was further examined in 2 single donor human liver microsomes with homozygous *CYP2D6**1/*1 (wild type) or *CYP2D6**4/*4 (a common no function allele). The observed $V_{\max}$ for veliparib overall metabolism and M8 formation in *CYP2D6**4/*4 microsomes was 28% and 33% of those from *CYP2D6**1/*1, respectively (Fig. 2C and D). As *CYP2D6**4/*4 is generally believed to have no CYP2D6 activity, these data suggested that CYP2D6 attributed to ~72% of veliparib overall metabolism, whereas other liver enzymes collectively accounted for the rest 28%.

Pharmacokinetics of veliparib in patients with cancer

Plasma pharmacokinetics of veliparib were evaluated in 27 patients with cancer receiving veliparib alone and in combination with irinotecan. No pharmacokinetic interactions were identified between veliparib and irinotecan (data not shown here). The multiple-dose plasma concentration–time profiles of veliparib and M8 following oral administration of veliparib 10 to 50 mg twice daily were adequately described by a parent–metabolite joint population pharmacokinetic model (Fig. 1A). Serum creatinine clearance was identified as the only statistically significant covariate retained in the final model. Inclusion of creatinine clearance in the final model as a power function resulted in a decrease of the objective function value by 11.35 (from 107.41 to 96.06; $P < 0.01$) and a decrease of the unexplained interindividual variability on veliparib CL_p/F from 30% (structure model) to 20% (final model; Table 2).

The goodness-of-fit plots for the final model are shown in Supplementary Fig. S1. The population pharmacokinetic parameter estimates for veliparib and M8 from the base and final covariate models are presented in Table 2. The population value for veliparib oral clearance (CL/F) in a typical individual with serum creatinine clearance of 6 L/h (or 100 mL/min) was 13.3 L/h, which was the sum of CL_{pm}/F (1.7 L/h) and CL_p/F (11.6 L/h), suggesting that the metabolism to M8 contributed to 13% of veliparib total clearance, whereas renal excretion and additional minor liver metabolism attributed to 87%. Serum creatinine clearance was strongly correlated with the POSTHOC Bayesian estimated veliparib CL_p/F ($r = 0.642$, $P < 0.001$) and CL/F ($r = 0.634$, $P < 0.001$; Fig. 3A and B), but not with CL_{pm}/F ($r = -0.064$, $P = 0.751$).

M8 exhibited a limited distribution with a volume of distribution of 8 L and a rapid elimination with an elimination rate constant of 1.1 h^{-1} (calculated as CL_m/V_m). Interestingly, the rate constant for conversion of veliparib to M8 (calculated as CL_{pm}/V_p)

was 0.013 h^{-1} , which was in line with the terminal disposition rate constant (0.016 h^{-1}) estimated from the slope of log-linear terminal portion of M8 plasma concentration–time curves, indicating that metabolic conversion of veliparib to M8 is a rate-limiting process for the disposition of M8.

The bootstrap visual predictive checks for parent and metabolite concentrations are given in Fig. 3C and D. These visual validations of the final model suggested that ~90% and 94% of the observed veliparib and M8 concentrations were within 95% confidence interval (CI) for quantiles, respectively.

PBPK modeling and simulation

The developed PBPK model integrated with a mechanistic kidney module could adequately describe the observed veliparib pharmacokinetic profiles in patients with cancer. As shown in Fig. 4A and B, the PBPK model-predicted plasma concentration–time profiles in a virtual Caucasian population with normal renal function (i.e., “NEurCaucasian” population) well recovered the observed concentration data obtained from 8 patients with Caucasian cancer receiving veliparib orally 40 mg twice daily, with ~95% of observed data falling within 90% confident interval of the mean simulated concentration–time profile from 100 individuals. The PBPK model-predicted pharmacokinetic parameters, including $C_{\max}$ (mean, 311 ng/mL), $T_{\max}$ (mean, 1.6 hours), AUC (mean, 3,481 ng/mL·h), and CL/F (13.4 L/h) were consistent with the observed values and those estimated from the population pharmacokinetic model. In addition, the PBPK model predicted that renal excretion, CYP2D6 metabolism, and additional liver metabolism contributed to average 72%, 18%, and 10% of veliparib total clearance, respectively, which were in agreement with the observation in patients with cancer that average 70% (range, 31%–115%) of veliparib dose was excreted in the urine as the unchanged drug (4).

The individual and combined effects of renal function, CYP2D6 status, and OCT2 activity on veliparib pharmacokinetics were assessed by simulating veliparib pharmacokinetic profiles following a single-dose or chronic treatment under various scenarios. Supplementary Table S1 summarizes the PBPK model-predicted mean plasma pharmacokinetic parameters and mechanistic kidney model parameters under these scenarios. The magnitude of impact or interaction was expressed as the ratio of the mean value of a parameter (e.g., AUC) under a particular scenario relative to that obtained from the control, which was a virtual population with normal renal function ($\text{GFR} > 60 \text{ mL/min}$) and CYP2D6 EM phenotype and receiving no inhibitors. Fig. 4C presents the AUC ratios under various scenarios.

Compared with normal renal function ($\text{GFR} > 60 \text{ mL/min}$), moderate ($\text{GFR}, 30\text{--}60 \text{ mL/min}$) and severe ($\text{GFR} < 30 \text{ mL/min}$) renal impairment led to ~70% and 1.1-fold increase in veliparib single-dose exposure (AUC), respectively (Fig. 4C). They had greater impacts on the steady-state drug exposure, resulting in 80% and 1.3-fold increase in the AUC_{τ} , respectively (Fig. 4C), because of delayed veliparib renal clearance and thus greater drug accumulation following chronic treatment. The mean renal clearance of veliparib was 54% and 40% in the subjects with moderate and severe renal impairment, respectively, compared with that in those with normal renal function (Supplementary Table S1).

The mean renal clearance of veliparib in subjects with normal renal function was 7.9 L/h. Given an unbound fraction in plasma of 0.49, the mean unbound renal clearance of veliparib (calculated as $7.9/0.49 = 16.1$ L/h; ref. 20) was 2.68-fold of the mean normal glomerular filtration rate (6.0 L/h or 100 mL/min), suggesting active tubular secretion contributes to ~63% of veliparib renal clearance. The mechanistic kidney model was used to assess the impact of OCT2 activity on veliparib renal clearance and accumulation in kidney cells. Sensitivity analyses suggested that when OCT2 activity (indicated by *in vitro* intrinsic uptake clearance) decreasing from 20 to 0.1 $\mu\text{L}/\text{min}/10^6$ cells, veliparib C_{max} and AUC was increased 1.2- and 2.5-fold, respectively, whereas the maximum drug accumulation in the proximal tubule cells, excretion in urine, renal clearance, and total oral clearance was decreased 150-, 1.8-, 4.6-, and 2.5-fold, respectively (Fig. 4D). Interestingly, although the change in the activity of the apical efflux transporter (ABCB1) influenced the maximum drug accumulation in the proximal tubule cells, it had negligible impact on veliparib plasma pharmacokinetic parameters (Supplementary Fig. S3), further supporting the notion that the activity of basolateral uptake transporter OCT2 is rate determining for the renal secretion and clearance of veliparib. In addition, the impact of OCT2 activity was assessed by simulating veliparib pharmacokinetic profiles in subjects receiving co-administration of cimetidine (a competitive OCT2 inhibitor with an *in vitro* K_i of 0.25 $\mu\text{mol}/\text{L}$). It was predicted that co-administration of cimetidine orally 400 mg twice daily led to ~30% increase in veliparib steady-state exposure (Fig. 4C), while resulting in ~30% and 54% decrease in the renal clearance and maximum drug accumulation in kidney cells, respectively.

CYP2D6 activity had a minor impact on veliparib pharmacokinetics. Compared with CYP2D6 EM, the PM had ~20% higher exposure and the UM exhibited ~20% lower exposure to veliparib (Fig. 4C). Co-administration of quinidine (a competitive CYP2D6 inhibitor with an *in vitro* K_i value of 0.017 $\mu\text{mol}/\text{L}$) orally 200 mg once daily had negligible influence on veliparib pharmacokinetics (Fig. 4C). The lack of impact of co-administration of quinidine on veliparib exposure could be explained by the plausibility that partial inhibition of CYP2D6 activity by quinidine under the tested treatment schedule (orally 200 mg once daily) was inadequate to alter veliparib total clearance, given the minor role of CYP2D6 metabolism in the elimination of veliparib.

Although a single factor showed a modest impact on veliparib exposure, their combined effects were significant and potentially clinical relevant (i.e., AUC ratio >2-fold; Fig. 4C). The most significant increase in veliparib exposure was seen in subjects with severe renal impairment and CYP2D6 deficiency (PM) and receiving co-administration of OCT2 inhibitor, in which the single-dose and steady-state exposures were increased by 1.8- and 3.2-fold, respectively, compared with those in subjects with normal renal function and normal CYP2D6/OCT2 activities (Fig. 4C).

Discussion

Veliparib, a potential chemo- and radiosensitizer, is under clinical development in combination with DNA damaging agents or radiation therapy. Substantial changes in the drug exposure because of complex disease-, gene-, and drug-drug interactions involving

renal excretion and liver metabolism are likely to impact clinical outcomes. In this study, using the population pharmacokinetic and PBPK modeling approaches, supported by observed *in vitro* and *in vivo* data, we identified patient factors significantly influencing veliparib disposition, and also quantitatively assessed the individual and combined impacts of renal function, CYP2D6 status, and OCT2 activity on veliparib pharmacokinetics. Our study complements previous knowledge on the disposition of veliparib in patients with cancer, and provides further mechanistic and quantitative insights into the complex interactions of veliparib with metabolizing enzymes and transporters in disease settings. The obtained quantitative information is useful not only in aiding decision-making about whether further clinical studies are needed to assess the interactions and risks, and also in guiding dose optimization in response to complex drug interaction scenarios.

To successfully predict complex drug interactions that involve multiple disposition processes, the quantitative contribution of each disposition pathway and impacts of patient factors on the pathway need to be defined *a priori*. The population pharmacokinetic and PBPK modeling approaches, supported by observed *in vitro* and *in vivo* data, allows for quantitation of the contribution of each disposition pathway to the total drug clearance. The parent–metabolite population pharmacokinetic analysis suggests that ~13% of veliparib oral clearance is attributable to its metabolism to M8, whereas 87% is contributed by renal excretion and additional minor liver metabolism (Table 2). The estimated contribution of the metabolism to M8 to veliparib oral clearance in patients with cancer is supported by *in vivo* observations in rats and dogs showing that M8 is the most significant metabolite accounting for 15% to 24% of the dose (10). Consistently, the PBPK simulations suggest that CYP2D6 metabolism, additional liver metabolism, and renal excretion contribute to ~18%, 10%, and 72% to veliparib oral clearance, respectively. It is thus estimated that CYP2D6 mediates ~64% (calculated as 0.18/0.28) of veliparib metabolism in humans, which is in line with our *in vitro* human liver microsome metabolism data showing that CYP2D6 accounts for ~72% of veliparib overall metabolism. In addition, the mechanistic kidney model predicts that veliparib mean renal clearance is 7.9 L/h (range, 2.4–21.3 L/h) and average 60% (range, 26%–88%) of the dose is recovered in urine as the unchanged drug in a virtual Caucasian population with normal renal function. These predictions are consistent with the observation in patients with cancer that average 70% (range, 31%–115%) of veliparib dose was recovered in the urine as the unchanged drug (4). Furthermore, it is estimated that active renal secretion attributes to ~63% of veliparib renal clearance, which is supported by *in vivo* studies in OCT1/2 double-knockout mice demonstrating that OCT1/2-mediated renal secretion accounts for ~64% of veliparib renal clearance (8). Collectively, these results indicate that CYP2D6 metabolism, additional liver metabolism, kidney glomerular filtration, and active tubular secretion contribute to ~18%, 10%, 27%, and 45% of veliparib total clearance, respectively.

Given the predominant role of renal excretion in the elimination of veliparib, it is not surprising that renal function (measured by creatinine clearance) was identified as the only significant covariate in the parent–metabolite population pharmacokinetic model, which explained ~33% of the interindividual variability on veliparib oral clearance in 27 patients with cancer (Table 2 and Fig. 3A and B). A similar finding has been recently reported from

a population pharmacokinetic analysis of a larger dataset involving 325 patients with cancer, in which creatinine clearance is identified as the significant predictor for veliparib oral clearance (7). The key role of renal function in veliparib pharmacokinetics is further supported by the PBPK simulations showing that veliparib renal clearance is decreased by 46% and 60% in subjects with moderate and severe renal impairment, respectively, and consequently the steady-state drug exposure is increased by ~80% and 1.3-fold, respectively, compared with those in subjects with normal renal function (Fig. 4C). It should be noted that creatinine is freely filtered by the glomerulus, and also actively secreted by the proximal tubules in small amounts such that creatinine clearance overestimates actual glomerular filtration rate by 10% to 20% (21). Recent studies have shown that OCT2 is a dominant transporter involved in the renal secretion of creatinine. Therefore, creatinine clearance is commonly used as a measure of glomerular filtration rate, but it also may indicate, in a small part, the OCT2-mediated active renal secretion.

Active renal secretion accounts for ~63% of the renal clearance and ~45% of the total clearance of veliparib. OCT2, predominantly expressed on the basolateral membrane of kidney proximal tubules, mediates the first step (i. e., basolateral uptake into proximal tubules cells) in the renal secretion of many small organic cation drugs such as metformin and cisplatin. *In vitro*, OCT2 transported veliparib into cells with an intrinsic uptake clearance of 8.6 pmol/min/mg protein, similar to that for metformin (14.8 pmol/mg/min; refs. 8 and 22). *In vivo*, OCT1/2 double-knockout mice exhibited 1.8-fold lower veliparib renal clearance than the wild-type mice (8). Sensitivity analysis using the PBPK model with a mechanistic kidney module suggest that OCT2 activity is rate determining for the renal secretion of veliparib (Fig. 4D and Supplementary Fig. S3). It is well known that OCT2 activity can be modified by genetic polymorphisms or interaction with co-administered drugs.

At least 28 single nucleotide polymorphisms (SNP) have been identified in the OCT2 (SLC22A2) gene (23). Four polymorphic nonsynonymous variants, M165I, A270S, R400C, and K432Q have been found to have altered transporter activity when assayed in *Xenopus laevis* oocytes (23). Of these, the most common nonsynonymous SNP (with an allele frequency of ~10% in different ethnic populations) is the change in nucleotide 808 (G/T), which causes the amino acid change from alanine to serine at position 270 (A270S). It has been shown that the renal clearance and net secretion of metformin are significantly different in the individuals carrying heterozygous 808G/T allele from those with homozygous 808G/G allele (22). In light of similar *in vitro* intrinsic uptake clearance of OCT2 for veliparib and metformin as well as the decisive role of OCT2 in the renal secretion of veliparib, it is plausible that genetic polymorphisms of OCT2 could also influence the renal clearance of veliparib. Further studies are needed to determine the functional and clinical relevance of OCT2 genetic polymorphisms to the pharmacokinetics of veliparib.

In addition to genetic polymorphisms, co-administration of cationic drugs that are substrates of OCT2 may interfere OCT2 function and consequently, could alter the renal secretion and systemic exposure of veliparib. The PBPK simulations demonstrate that co-administration of cimetidine (a competitive OCT2 inhibitor) orally 400 mg twice daily increases veliparib

steady-state exposure by ~30%. Veliparib is currently being evaluated in combination with cisplatin or oxaliplatin in several phase I/II clinical trials. These platinum analogues are good substrates of OCT2. It is evident that OCT2 is a key transporter involved in the renal secretion of cisplatin (24). *Ex vivo* studies have demonstrated that cisplatin competitively inhibits the active uptake of the cation tetraethylammonium by mouse kidney slices and by rat renal basolateral membrane vesicles, and inhibits the renal clearance of organic ions from a basolateral site in the isolated-perfused rat kidney (25–27). These inhibition effects are principally ascribable to the interaction of cisplatin with OCT2. In addition, recent *in vivo* studies suggest that cisplatin competitively inhibits OCT2-mediated renal secretion of creatinine (28). It is thus possible that interference with OCT2 function by chemotherapeutic agents such as cisplatin may alter the renal clearance and exposure of veliparib, or *vice versa*. Further investigations of potential pharmacokinetic interactions at the level of renal transporters between veliparib and cisplatin or oxaliplatin are warranted.

CYP2D6 metabolism contributes to ~18% of veliparib oral clearance. The *CYP2D6* gene is highly polymorphic with more than 63 functional variants identified to date (<http://www.cypalleles.ki.se>). These alleles result in abolished, decreased, normal, or ultrarapid CYP2D6 enzyme activity. The most important null alleles are *CYP2D6**4 (splicing defect) and *CYP2D6**5 (gene deletion); the common alleles with severely reduced enzyme activity are represented by *CYP2D6**10, *17, and *41; duplication or multiduplications of active *CYP2D6* genes [e.g., *CYP2D6**1 × N (N ≥ 2)] result in ultrarapid enzyme activity. The distributions of *CYP2D6* alleles exhibit notable interethnic differences. CYP2D6 PM, mainly resulted from null allele *CYP2D6**4, has a high frequency in Caucasians (5%–14%) compared with Africans (0%–5%) and Asians (0%–1%). By contrary, CYP2D6 UM, resulted from gene duplication or multiduplications, have a high frequency in Saudi Arabians (20%) and black Ethiopians (29%) compared with Caucasians (1%–10%; ref. 29). The interethnic difference in CYP2D6 phenotypes may contribute to the interethnic variations in the disposition and response of drugs that are mainly metabolized by CYP2D6. Nevertheless, in light of the minor role of CYP2D6 metabolism in the elimination of veliparib, changes in CYP2D6 metabolizing activity caused by polymorphisms or interactions with co-administered drug are expected to have insignificant impact on veliparib pharmacokinetics. As demonstrated by the PBPK simulations, although 2 most commonly occurring *CYP2D6* variants (i.e., *CYP2D6**4 and *CYP2D6**10) exhibits significantly lower catalytic capability for veliparib metabolism *in vitro* (Fig. 2), CYP2D6 phenotype (PM or UM) has a minor impact on veliparib pharmacokinetics (i.e., <20% change of AUC in CYP2D6 PM and UM compared with the EM; Fig. 4C); in addition, co-administration of quinidine (a competitive CYP2D6 inhibitor) orally 200 mg once daily has no impact on veliparib exposure (Fig. 4C). These results illustrate the complications associated with translating *in vitro* pharmacological findings to *in vivo* and demonstrate the importance of defining the quantitative contribution of each *in vivo* disposition pathway for accurate *in vitro*–*in vivo* extrapolation.

Although a single factor (i.e., renal impairment, CYP2D6 deficiency, and reduced OCT2 activity) shows a moderate impact, they collectively could lead to significant and potentially clinical relevant changes in veliparib exposure. The PBPK simulations predict that veliparib

steady-state exposure after chronic treatment is increased by >2-fold in subjects with CYP2D6 PM and varying renal impairment, compared with those with the EM phenotype and normal renal function (Fig. 4C). The impact of combined CYP2D6 deficiency and renal impairment becomes more substantial when an OCT2 inhibitor is used concurrently with veliparib. The most significant change in veliparib steady-state exposure (i.e., AUC ratio = 4.2) occurs in subjects with CYP2D6 PM and severe renal impairment and also receiving concomitant OCT2 inhibitor cimetidine (Fig. 4C). The most common severe toxicities associated with veliparib treatment include thrombocytopenia, neutropenia, and leucopenia. The substantial increase in the drug exposure is likely to increase the likelihood that patients experience severe toxicities. Therefore, it should be cautious to administer veliparib to patients with both CYP2D6 deficiency and renal impairment, in particularly when veliparib is combined with other chemotherapeutic agents that may interfere OCT2 function. These results illustrate the importance of evaluating complex drug interactions involving multiple disposition pathways in disease settings. The quantitative information (e.g., AUC ratio) obtained from the PBPK simulations has the potential to guide dose optimization in response to these complex drug interaction scenarios.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Translational Relevance

Early identification of complex disease-, gene-, and drug-drug interactions and quantitative prediction of their impacts are of great importance to the rational development and optimal use of anticancer drugs such as veliparib, a potential chemosensitizer intended to combine with other cytotoxic agents in complicated disease settings. However, identification and quantitation of complex drug interactions in early-phase trials are challenging because of the multifaceted nature of interactions but limited sample size and insufficient statistical power in clinical trials. This study illustrated the utility of in vitro-in vivo extrapolation and physiologically based pharmacokinetic modeling to quantitatively predict individual and combined effects of renal function, CYP2D6 phenotype, and OCT2 activity on veliparib pharmacokinetics. Although a single factor shows a moderate impact, they collectively could result in significant and potentially clinically relevant changes in veliparib exposure. This study complements previous knowledge on veliparib disposition in patients with cancer, and provides further quantitative insights into the interactions of veliparib with metabolizing enzymes and transporters in disease settings. The obtained quantitative information is useful not only in aiding decision-making about whether further clinical studies are needed to assess the interactions and risks, and also in guiding dose optimization in response to complex drug interaction scenarios.

Figure 1.

Schemes of model structures. A, parent–metabolite joint pharmacokinetic model. K_a , first-order absorption rate constant; V_p/F , apparent volume of distribution for the parent drug; CL_{pm}/F , apparent clearance for conversion of the parent drug to metabolite; CL_p/F , apparent clearance of the parent drug via renal excretion and additional liver metabolism; V_m , volume of distribution for the metabolite; CL_m , clearance of the metabolite. B, whole-body PBPK model integrated with a mechanistic kidney module for prediction of veliparib pharmacokinetic profiles. The mechanistic kidney module illustrates the major processes governing drug transfer from blood to the urine: passive diffusion (passive diffusion clearance, CL_{pd}), basolateral transporters-mediated uptake from the blood into proximal tubule cells (uptake transporter intrinsic clearance, $CL_{int,T,up}$), and apical transporters-mediated efflux from the tubule cells into urine (efflux transporter intrinsic clearance, $CL_{int,T,eff}$). The effects of the inhibitor (i.e., quinidine or cimetidine) on the CYP2D6 metabolism or OCT2 uptake activity was simulated in a dynamic fashion by linking the inhibitor model (i.e., limited PBPK model for quinidine or whole-body PBPK model for cimetidine) to veliparib PBPK model.

Figure 2.

Functional influence of *CYP2D6* genetic polymorphisms on *in vitro* metabolism of veliparib. A and B, enzyme kinetics of recombinant human CYP2D6.1 (wild type) and CYP2D6.10 variant for the overall metabolism of veliparib and formation of M8. Veliparib (0.5–250 μmol/L) was incubated with the enzyme (100 pmol/mL) at 37°C for 30 minutes. The symbols represent observed data, and the lines represent the enzyme kinetic curves fitted by Hill equation. C and D, measured reaction rates for the overall metabolism of veliparib and formation of M8 in the single donor human liver microsomes from individuals carrying wild-type *CYP2D6**1*1 and homozygous *CYP2D6**4*4. Veliparib (100 μmol/L) was incubated with the microsomes at the protein concentrations of 0.2, 0.6, and 1.8 mg/mL for 30 minutes. Results are expressed as mean ± standard deviation from three independent experiments. *, paired *t* test, significantly different from *CYP2D6**1*1, *P* < 0.05.

Figure 3.

Parent-metabolite population pharmacokinetic analysis. A and B, association between creatinine clearance (CL_{cr}) and veliparib renal clearance (CL_p/F) and total oral clearance (CL/F), which were estimated from the base model. C and D, visual predictive check for the final model. The symbols represent the observed veliparib and M8 concentrations; the solid and 2 dotted lines represent median and 95% CIs for quantiles based on 1,000 bootstrap replicates; and the shaded areas represent 95% CIs of median, lower, and upper bounds.

Figure 4.

Physiologically based pharmacokinetic modeling and simulation. A and B, observed and predicted single-dose and steady-state plasma concentration–time profiles of veliparib. Simulations of 10 virtual trials with 10 subjects in each were performed in Caucasian population with normal renal function, following oral administration of veliparib as either a single dose of 40 mg or twice daily 40 mg for 15 days. Observed data were obtained from 8 patients with Caucasian cancer with normal renal function receiving a single dose of 40 mg or twice daily dosing. The thick black line represents overall mean predicted concentration–time profile for the virtual population ($n = 100$); dotted and dash line represent the 95th and 5th percentile, respectively; and the symbols represented the observed veliparib concentrations. C, AUC ratios of veliparib under various scenarios. D, sensitivity analysis showing the impact of OCT2 activity (intrinsic uptake clearance) on veliparib plasma pharmacokinetic parameters ($C_{\max}$, maximum plasma concentration; $T_{\max}$, time to reach $C_{\max}$; AUC, area under the concentration–time curve; CL/F , oral clearance) and mechanistic kidney model parameters (CL_r , renal clearance; A_e , accumulated amount of unchanged drug excreted in the urine; $A_{\text{ex-max}}$, maximum amount of drug accumulated in the kidney proximal tubule cells). Sensitivity analysis was performed with OCT2 intrinsic uptake

clearance varying from 0.1 to 20 $\mu\text{L}/\text{min}/10^6$ cells whereas ABCB1 intrinsic efflux clearance fixing at 2 $\mu\text{L}/\text{min}/10^6$ cells.

Table 1
Drug-dependent parameters used in veliparib PBPK model with a mechanistic kidney module

Parameter	Value	Reference/comments
Physicochemical		
Molecular weight (g/mol)	244.29	Chembase.cn (http://en.chembase.cn/molecule-4883.html)
Log <i>P</i>	0.18	Chembase.cn (http://en.chembase.cn/molecule-4883.html)
Compound type	Diprotic base	
PKa ₁	9.22	Experimental; Investigator Brochure (IB)
PKa ₂	12.78	Experimental; IB
B/P	1.35	Experimental; IB
f _u	0.48	Experimental; IB
Absorption: First order		
f _a	1	Based on the relative bioavailability of tablet formulation is ~100% with reference to solution (IB)
K _a (1/h)	0.90	Obtained from the population pharmacokinetic modeling of observed data in patients with cancer
Lag time (h)	0	
f _{u,gut}	1	Assigned
Distribution: Full PBPK		
V _{ss} (L/kg)	1.25	Predicted by Rodgers and Roland method (Method 2) in Simcyp using a <i>K_p</i> scalar of 0.12
Elimination: Enzyme kinetics		
CL _{int} (μL/min/pmol CYP) for CYP2D6 EM and UM	0.055	Estimated from recombinant human CYP2D6.1 enzyme kinetics
CL _{int} (μL/min/pmol CYP) for CYP2D6 PM	0.017	Estimated from recombinant human CYP2D6.10 enzyme kinetics
f _{u,mic}	1	Assigned based on sensitivity analysis
ISEF	3.5	Optimized based on comparisons of observed and simulated plasma concentration–time profiles and percent contribution of CYP2D6 to overall metabolism
Additional CL _{int} from HLM (μL/min/mg protein)	0.7	Optimized based on comparisons of observed and simulated plasma concentration–time profiles and percent contribution of metabolism to total clearance
Active uptake into hepatocyte	1	Assuming no transporter-mediated active uptake into liver
Biliary clearance	0	Negligible biliary excretion (10)
Mechanistic kidney module		
CL _{int,T,up} (μL/min/10 ⁶ cells) for basal uptake by OCT2	8.59	Obtained from ref. 8, assuming OCT2 uptake activity in 1 million kidney proximal tubule cells equals to its activity in 1 mg protein of the OCT2-transfected HEK cells
CL _{int,T,eff} (μL/min/10 ⁶ cells) for apical efflux by ABCB1	2	Optimized based on sensitivity analysis and comparisons of simulated and observed amount of the drug excreted in urine
CL _{PD,basal} (Blood→Cell)	0	Negligible passive diffusion because >99% of veliparib is ionized at physiological pH (pH 7.4) in blood
CL _{PD,apical} (Cell→Tubule)	0	Negligible passive diffusion because >99% of veliparib is ionized at physiological pH (pH 7.4) in cells
f _{u,Kidney cell}	1	Assigned based on sensitivity analysis
f _{u,Urine}	1	Assigned based on sensitivity analysis

Parameter	Value	Reference/comments
GFR	Default	Using predicted GFR based on creatinine clearance for a particular existing population within Simcyp

Abbreviations: $\log P$, logarithm of the neutral species octanol-to-buffer partition ratio; PK_a , acid dissociation constant; B/P, blood-to-plasma partition ratio; f_u , fraction of unbound drug in plasma; f_a , fraction available from dosage form; K_a , first-order absorption rate constant; f_{gut} , fraction of unbound drug in enterocytes; V_{ss} , volume of distribution at steady-state using tissue volumes for a population representative of healthy volunteers population; CL_{int} , *in vitro* intrinsic clearance; f_{mic} , fraction of unbound drug in *in vitro* microsomal incubation; ISEF: Inter System Extrapolation Factor for scaling of recombinant CYP *in vitro* kinetic data; HLM, human liver microsomes; $CL_{int,T,up}$, uptake transporter intrinsic clearance; $CL_{int,T,eff}$, efflux transporter intrinsic clearance; CL_{PD} , passive diffusion clearance; $f_{uKidney\ cell}$, fraction of unbound drug in kidney cells; f_{uUrine} , fraction of unbound drug in urine; GFR, glomerular filtration rate.

Table 2
Population pharmacokinetic parameters^a for veliparib and M8 in patients with cancer, estimated from the base and final covariate models

Parameter	Base model		Final model	
	Population estimate	95% CI ^b	Population estimate	95% CI ^b
OFV	107.41		96.06	
CL _p /F (L/h)	10.80 (0.80)	(4.63,14.40)	11.62 ^c (0.76)	(4.60,14.60)
CL _{pm} /F (L/h)	2.23 (2.86)	(0.02,7.43)	1.68 (3.23)	(0.02,7.61)
CL _m (L/h)	11.70 (2.91)	(0.12,42.01)	8.64 (3.35)	(0.10,42.90)
V _p /F (L)	123.00 (0.26)	(102.00,141.00)	126.00 (0.26)	(104.00,143.03)
V _m (L)	10.90 (3.01)	(0.10,41.21)	8.05 (3.45)	(0.08,41.61)
K _a (h ⁻¹)	0.90 (1.15)	(0.49,1.89)	0.90 (1.18)	(0.50,1.92)
THETA(9)	—	—	0.60 (0.18)	(0.31,1.25)
IIV of CL _p /F (CV%)	30.03 (3.38)	(11.08,57.40)	19.92 (4.37)	(0.20,44.61)
IIV of CL _{pm} /F (CV%)	29.95 (1.92)	(6.26,45.93)	28.86 (1.91)	(0.29,42.32)
IIV of V _p /F (CV%)	22.05 (2.42)	(0.22,33.62)	25.36 (2.13)	(0.25,36.33)
IIV of K _a (CV%)	122.07 (1.06)	(86.48,166.75)	122.47 (1.07)	(87.44,168.23)
THETA(7) ^d	0.69 (0.41)	(0.45,0.74)	0.59 (0.41)	(0.45,0.74)
THETA(9) ^e	0.01 (7.24)	(0.00,1.08)	0.01 (7.07)	(0.00,1.14)

Abbreviations: OFV, objective function value (−2 times log transformed likelihood); CL_p/F, apparent clearance for the parent drug; CL_{pm}/F, apparent clearance for metabolism to M8; CL_m, clearance for M8; V_p/F, apparent volume of distribution for the parent drug; V_m, volume of distribution for M8; K_a, first-order absorption rate constant; IIV, interindividual variability.

^aData are expressed as the estimates (with % relative standard error based on 1,000 bootstrap replicates).

^b95% CI based on 1,000 bootstrap replicates.

^cTypical value for individuals with serum creatinine clearance (CL_{cr}) of 6.0 L/h (or 100 mL/min), calculated from CL_p = THETA(1) × (CL_{cr}/5.9)^{THETA(9)}.

^dAdditive component in the residue error model.

^eProportional component in the residue error model.