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ORIGINAL ARTICLE

Population pharmacokinetics and exposure–response assessment of veliparib co-administered with temozolomide in patients with myeloid leukemias

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Abstract

Purpose Veliparib is an oral inhibitor of poly(ADP-ribose) polymerase enzyme. Combination of veliparib and temozolomide was well-tolerated and demonstrated clinical activity in older patients with relapsed or refractory acute myeloid leukemia (AML) or AML arising from pre-existing myeloid malignancies. We aimed to perform quantitative assessments of pharmacokinetics, efficacy, and safety of veliparib in this patient population to inform future trial design.

Methods Population pharmacokinetic analysis was performed using Phoenix® NLME with pharmacokinetic data obtained from 37 subjects after oral administration of veliparib in a Phase I study with and without temozolomide. Effect of covariates (age, sex, BMI, creatinine clearance (CL_{CR}), and co-administration of temozolomide) on the pharmacokinetics of veliparib were evaluated, as well as impact of veliparib exposure on mucositis (dose-limiting toxicity), objective response rate (ORR), and overall survival.

Results A two-compartment model with first-order elimination and a first-order absorption with lag-time adequately described veliparib pharmacokinetics. CL_{CR} and body weight were clinically significant covariates for veliparib disposition. The proportion of subjects with all grade mucositis increased with veliparib exposure (AUC). However, no trend in ORR and overall survival was observed with increasing exposure.

Conclusions Veliparib with temozolomide presents a promising combination for older patients with myeloid leukemias. An exposure–safety relationship was established for this combination. Further clinical investigations aimed at elucidating the veliparib exposure–efficacy/safety relationship and optimizing dosing recommendations for maximizing benefit–risk in patients with advanced myeloid malignancies should study veliparib doses ranging up to 120 mg in combination with temozolomide.

Keywords Veliparib · Pharmacometrics · Exposure-response · Temozolomide

Introduction

DNA-damaging agents have been successfully used to treat cancer for decades [1]. However, resistance to these agents occurs relatively often and strongly affects the rate and duration of the clinical response in cancer patients. Therefore,

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different approaches have been developed to abrogate resistance or to increase the efficacy of DNA-damaging agents, including combination with inhibitors of DNA repair, chemotherapeutic drugs with different mechanisms of action or radiotherapy, anti-angiogenic agents, and other biological modulators [2]. One such approach is using a poly(ADP-ribose) polymerase (PARP) inhibitor to potentiate the activity of DNA-damaging agents.

PARP enzymes are a subgroup of the ADP-ribosyltransferases involved in a wide range of cellular functions including DNA transcription, DNA damage response, cell cycle regulation, genomic stability maintenance, and cell death [3]. PARP-1, the most abundant protein, plays an integral role in the repair of single-strand DNA breaks (SSBs) via the base excision repair (BER) pathway. Effective inhibition of PARP-1 leads to the accumulation of single-strand breaks, which ultimately results in double-strand breaks. In addition to these mechanisms of action, PARP inhibitors may also poison DNA by stabilizing PARP-1 and 2 at sites of DNA damage, generating complexes that may be even more toxic than the unrepaired single-strand breaks, which result from PARP inhibition [4].

Veliparib (also known as ABT-888) is a potent, orally bioavailable PARP inhibitor that is currently in development in combination with cytotoxic drugs for the treatment of non-hematologic and hematologic malignancies [5–8]. Temozolomide is an oral anticancer agent approved for the treatment of newly diagnosed glioblastoma and for refractory anaplastic astrocytoma and is under clinical investigation with and without additional agents for other malignancies [9]. Preliminary preclinical studies have demonstrated that veliparib potentiates temozolomide action [10–13]. These laboratory findings formed the basis for the Phase I clinical study in patients with relapsed or refractory acute myeloid leukemia (AML) or AML arising from aggressive myeloid malignancies, where veliparib was co-administered with temozolomide [14]. The combination was well-tolerated in this predominantly elderly patient population and demonstrated clinical activity with an overall response rate (ORR) of 33% (16/48) including a complete response (CR) rate of 17% (8/48). To further understand the quantitative aspects of the data generated from this clinical study, the current analysis focused on developing a population pharmacokinetic (PK) model, evaluating the effect of covariates, quantitating exposure–response relationships for efficacy and safety for veliparib when co-administered with temozolomide, which may ultimately guide more accurate dose selection for future phase II clinical studies.

Methods

Patient population

Adults (median age 69 years, range 20–88) with relapsed or refractory AML, newly diagnosed AML arising from pre-existing myeloid malignancy, therapy-related, or associated with poor-risk karyotype in patients who are ≥ 60 years and not candidates for induction chemotherapy and aggressive or transformed chronic myelomonocytic leukemia-2 (CMML-2) were eligible for the Phase 1 trial (ClinicalTrials.gov Identifier: NCT01139970) [14]. In brief, an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2; multi-lineage bone marrow failure, total bilirubin ≤ 2 mg/dL, aspartate aminotransferase and/or alanine aminotransferase $< 5 \times$ upper limit of normal, and creatinine < 2 mg/dL were allowed. The study was conducted in accordance with the Declaration of Helsinki after approval by the Institutional Review Boards of each participating center. Written informed consent was obtained from each subject prior to enrollment.

Trial design

To evaluate the PK of veliparib alone and the impact of temozolomide on veliparib exposure, a single dose of veliparib was administered on day 1 of cycle 1 to examine the pharmacokinetics of veliparib alone. Subsequently, veliparib was administered orally twice daily (BID) on days 4–12, with temozolomide administered once daily on days 3–9. In subsequent cycles (cycle 2 and beyond), veliparib was administered twice daily on days 1–8, with temozolomide administered days 1–5. Veliparib was administered without regard to food. Each treatment cycle lasted for 28 days, except for cycle 1.

The starting dose of temozolomide selected for this study was 150 mg/m^2 QD for 7 days in combination with veliparib 20 mg BID. Because dose-limiting toxicity (DLT) was not observed at dose level 1, the temozolomide dose was escalated and fixed at 200 mg/m^2. For subsequent dose levels, veliparib dose was escalated using a 3 + 3 scheme. Details of the trial design have been published earlier [14].

Population pharmacokinetic analysis

A total of 48 patients were enrolled in the trial. PK data were available from 37 patients, of whom 35 patients had both assessments of clinical response and PK data collected.

Data

The analysis dataset included 580 veliparib concentration values from 37 patients who were administered an oral dose of veliparib with/without temozolomide co-administration.

For PK, blood samples were collected at 0, 0.25, 0.5, 1, 1.5, 2, 4, 6, 8 and 24 h after dosing on day 1 (veliparib alone) and day 8 (veliparib in the presence of temozolomide). Bioanalytical analysis was performed using a validated liquid chromatography–mass spectrometry method, as previously described [15]. The lower limit of quantitation (LLOQ) for the assay was 10 ng/mL.

Base model selection

Non-linear Mixed Effects (NLME) modeling was utilized for developing the population PK model for veliparib with and without temozolomide. All analyses were performed using Phoenix 64 Build 6.4.0.768-NLME 1.4 software (Certara USA, Inc, Princeton, NJ, USA) and the First-Order Conditional Estimation (FOCE) Extended Least Squares method. R (Rstudio 0.98.1102 with R 3.0.3) was utilized for graphing purposes.

Based on exploratory graphical analysis, different compartment models were tested to develop the base PK model. Additive, proportional (multiplicative) and mixed residual error models were assessed. Exponential error model was used for between subject variability (BSV). Assessment criteria for the selection of models included precision of the fixed effects parameter estimates, goodness-of-fit plots and likelihood ratio test [defined by a decrease in 3.84 units ($\alpha = 0.05$, $df = 1$)].

Covariate model selection

Body-surface area (BSA), age, body weight, lean body mass (LBM), height, sex, creatinine clearance (CL_{CR}) and dose were evaluated as covariates using an exponential model.

CL_{CR}, LBM and BSA were calculated using Cockcroft–Gault, Boer, and Mosteller formulas, respectively [16–18]. Co-administration with temozolomide was evaluated as a covariate on CL/F (apparent clearance from central compartment). Since CL_{CR} is a surrogate for glomerular filtration and total clearance is the sum of the independent clearances for the different pathways of elimination, an additive model (CL/F = CLrenal + CLother) was used to best reflect the physiology of the elimination processes for veliparib. The estimated CL_{CR} values were capped at 120 mL/min for 5 out of 37 subjects to reflect normal physiology. The impact of capping CL_{CR} to 120 mL/min was evaluated and found to be minimal (data not shown).

Trends between empiric Bayesian pharmacokinetic parameter estimates vs covariate plots as well as changes in the estimates of pharmacokinetic parameter variability and likelihood ratio test were assessed to choose covariates. The − 2 log likelihood (− 2LL) was used as the criterion for assessment of whether the addition of a covariate statistically improved the model during the forward [objective function value (OFV) drop of > 3.84 ($\alpha = 0.05$, $df = 1$)] followed by backwards elimination [OFV increase of 6.64 ($\alpha = 0.01$, $df = 1$)] steps, respectively. Once the final covariates were selected, the impact of between occasion variability was explored on various parameters.

Model validation and qualification

Model fit was assessed by plots of the population and individual predicted concentration vs observation concentration and the lack of trends in standard goodness-of-fit plots. A non-parametric bootstrap method (500 bootstrap samples) was implemented to assess precision of estimated parameters. A visual predictive check (VPC) was used to evaluate model performance. The 5th, 50th, and 95th percentiles were generated from the final model parameter estimates using 200 replicates and were then plotted against the original observations. Finally, a quantitative predictive check (QPC) [19] was also performed to evaluate model performance. The 25th, 50th, and 75th percentile for AUC_{inf} and C_{max} for single dose (day 1) and AUC_{tau} and C_{max} for steady state (day 8) were calculated using simulated data (200 replicates) from the final model. Relevant statistics of observed concentrations were compared with the corresponding statistics calculated from simulated data using the final model. Prediction error was calculated using (predicted –observed)/(observed) × 100.

Exposure–response assessment

Response was categorized as complete remission (CR), CR with incomplete recovery (CRi), partial response (PR), hematological improvement (HI), or no response (NR) according to the International Working Group criteria [20] and as described previously [14]. CR, CRi, PR and HI were grouped as objective response (OR) for quantitative analysis. Final population pharmacokinetic model and individual post hoc parameter estimates were used to simulate the exposure metric for each individual. Based on previously published understanding of veliparib exposure metrics like C_{max} and AUC, the exposure metric of predicted steady-state AUC_{tau} was utilized for analysis [21]. Predicted steady-state AUC_{tau} data were arranged in ascending order and divided into quartiles (4 bins) and plotted against objective response rate (ORR) to explore the relationships between veliparib PK and efficacy [22]. In addition, overall survival (OS) trends with exposure quartiles (predicted steady-state AUC_{tau}) were assessed by Kaplan Meier analysis. OS was defined as the survival from first day of the treatment to death or censored at the last follow-up date.

Exposure–safety assessment

Toxicity was described and graded using NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. For exposure–safety analysis, data was pooled from the study. Exposures (predicted steady-state AUC_{tau}) were divided into quartiles as explained above and the proportions of patients experiencing relevant adverse events (all grade) were plotted against exposure quartiles to explore if there was a trend of increasing adverse events with increasing exposures.

Results

Pharmacokinetic analysis

A summary of patient demographics is presented in Table 1. Non-compartmental analysis revealed a linear dose-exposure trend for veliparib [14]. Approximately a 1.3-fold accumulation was observed in AUC at steady state as expected with a reported half-life of approximately 6 h for the BID dosing regimen.

A two-compartment model with first-order absorption and elimination adequately described veliparib pharmacokinetics. The model was parameterized as absorption rate constant (k_a), lag time (t_{lag}), apparent clearance from central compartment (CL/F), apparent central compartment volume of distribution (V_c/F), apparent intercompartmental clearance (Q/F), and apparent peripheral compartment volume of distribution (V_p/F) (Online resource 1). A proportional error model was used to quantitate residual variability and an exponential model was used for BSV. Covariance parameters were incorporated in the final model to account for correlation in the random effects between CL/F and V_c/F. The between subject variability on Q/F and V_p/F and their correlation were not estimated due to high shrinkage. Equations for final covariate model are shown in Eqs. 1 and 2:

$$\frac{CL}{F} = 4.2 + 13.3 \cdot \left(\frac{CL_{CR}\ (mL/min)}{90} \right) \quad (1)$$

$$\frac{V_c}{F} = 144.2 \cdot \left(\frac{WGT\ (kg)}{80.6} \right) . \quad (2)$$

The exponent for body weight and CL_{CR} were set to unity after initial exploration, because estimation of the exponent did not lead to a statistically significant reduction in OFV when compared to fixing it at a value of 1. The parameter estimates from the final model and the associated 95% confidence intervals are provided in Table 2. The population value for veliparib apparent clearance (CL/F) in a typical individual with serum creatinine clearance of 90 mL/min, 60 mL/min and 30 mL/min were 17.5 L/h, 13.1 L/h and 8.6 L/h, respectively, based on Eq. 1. The estimated mean Vc/F was 144 L for a typical subject with weight of 81 kg. The Vc/F for a patient with 60 kg will be 25% lower and that of 120 kg will be 50% higher than 144 L.

Diagnostic plots for goodness of fit for the final model are shown in Fig. 1. Observed vs population predicted or individual predicted concentrations show good agreement (Fig. 1). The absence of any trend in the conditional weighted residual vs time after dose plot shows the appropriateness of the 2-compartment model. The lack of any trend in the conditional weighted residual vs population predicted concentration plot suggests adequacy of the residual error model used (Fig. 1). Individual concentration–time fitted profiles for representative subjects are shown in Fig. 2. The visual predictive check plots in Fig. 3 indicate that the model adequately described the veliparib concentration–time profiles as visual inspection shows that > 90% of observed plasma concentrations fall within the 90% prediction interval. The population pharmacokinetic parameter estimates generated from the final model using 500 replicate data sets in the bootstrap analyses were comparable with those generated using the original data set (Table 2), indicating accuracy and stability of the model parameters.

Further validation of the population pharmacokinetic model and assessment of the degree of prediction error was conducted by QPC. The results of QPC for the 150 mg dose (dose with the highest number of subjects) are depicted in histograms in Online resource 3. The predicted median of the 50th percentile of veliparib C_{max} shows some underprediction (approx. 25%). The prediction error for the 50th percentile for day 1 was < ± 25% for AUC_{inf} [except for 40 mg (35%), where the number of patients was 3] and

Table 1 Summary of patient demographics at baseline

Variable (unit), $N = 37$	Mean ± SD (range)
Age (years)	66.3 ± 10.5 (31– 88)
Body weight (kg)	80.6 ± 22.6 (39.2–132.8)
LBM (kg)	54.3 ± 10.8 (32.3–79.3)
Height (cm)	167 ± 9 (150–184)
BSA (m^2)	1.94 ± 0.36 (1.28–2.69)
CL_{CR} (mL/min)	74.6 ± 27.5 (35.7–120)
Ethnicity, *n* (%)	
Non-Hispanic	36 (97%)
Unknown	1 (3%)
Race, *n* (%)	
White	26 (70%)
Black	10 (27%)
Other	1 (3%)
Sex, male, *n* (%)	18 (49%)

Table 2 Estimates of population pharmacokinetic parameters obtained after fitting the final model to the original dataset and to 500 bootstrap samples

Parameter	Estimate (%RSE)	BSV (% CV)	Bootstrap estimate (median (95% CI))	Bootstrap BSV (% CV)
CL/F_{other} (L/h)	4.20 (53.4)	33.1	4.23 (0.04, 9.81)	36.2
$CL/F_{renal\ filtration}$ (L/h)	13.3 (19.6)		13.2 (7.32, 18.07)	
V_c/F (L)	144 (5.8)	29.4	144 (124.7, 162.6)	29.3
Q/F (L/h)	8.31 (27.7)	NE	8.29 (6.34, 17.13)	NE
V_p/F (L)	81.9 (22.0)	NE	81.9 (52.6, 130.2)	NE
K_a (h^{-1})	2.01 (16.9)	79.0	1.99 (1.39, 2.79)	79.1
t_{lag} (h)	0.23 (2.6)	5.2	0.23 (0.21, 0.24)	11.9
Between occasion variability on K_a	67.6			68.8
Correlation between random effects for CL/*F* and V/F	0.45		0.45	
Correlation between random effects for t_{lag} and K_a	− 0.80		− 0.80	
Proportional error (%)	31% (4.7)		32% (27%, 36%)	

$C_{max} \leq \pm 35\%$ [except 200 mg (47%), where the number of patients was 4]. Predicted error was $< \pm 25\%$ for day 8 for both AUC_{tau} and C_{max}. Overall this confirmed that the final model performed adequately in describing the data.

Previous studies have shown that the clearance of veliparib does not change in the presence of temozolomide administration [8, 14]. Likewise, inclusion of temozolomide, as a categorical covariate, did not have any impact on CL/*F* of veliparib. The addition of the covariates into the population pharmacokinetic models substantially reduced the inter-individual variability in CL/*F* and V_c/F. CL_{CR} and body weight were found to be significant covariates explaining 8% and 11% variability for veliparib CL/*F* and V_c/F, respectively. Between occasion variability had a significant effect on k_a and decreased the BSV on k_a by 32%. Body weight and LBM were explored as covariates on V_c/F and LBM was not found to result in a significant drop in OFV when compared to body weight (Online resource 2).

Exposure–response analysis

There was no clear dose–ORR relationship. The proportion of responders ranged between 25–56% across different doses with an average of 42% (Online resource 4). Quartile plots between model predicted steady-state AUC_{tau} against ORR depicted a reasonably flat relationship (Fig. 4a), similar to the dose–ORR relationship (Online resource 4). Predicted AUC at steady state at different doses are shown in Online Resource 6. An analysis of the patient demographics like weight, age, sex and CL_{CR} revealed that the quartiles were well balanced for these patient characteristics except for slightly lower weight and CL_{CR} for the 4th quartile (Online Resource 7) and these patient characteristics did not seem to be the cause of the observed trend in response.

Exposure–overall survival relationship assessed using Kaplan–Meier curves showed similar survival across the four AUC quartiles (Online resource 5). As reported previously, there was a trend of longer survival as ORR increased (Fig. 4c) [14].

Exposure–safety analysis

The predominant DLT of the veliparib–temozolomide combination was mucositis [14]. The proportion of patients with grades 1–4 (all grade) mucositis increased from 13% at 150 mg of veliparib to 75% at 200 mg (Online resource 4). Dose-limiting grade ≥ 3 mucositis was observed in only 2/35 patients (both at 200 mg dose), and, therefore, not used for assessment in this publication. When all grade mucositis incidence was analyzed against exposure, an increase in proportion of patients experiencing toxicity from 11 to 33% was observed as steady-state mean AUC_{tau} increased from 11,009 (equivalent to approximately 120 mg dose) to 15,493 ug.hr/L (Fig. 4b).

Discussion

The pharmacokinetics of veliparib alone and in combination with cytotoxic DNA-damaging agents has been described in patients with various malignancies [8, 23]. While early studies described veliparib PK using a one-compartment model [8, 23], a two-compartment model described their data better than a one-compartment model in recently published studies [24, 25]. Analysis of data from this trial agrees with the findings of Mehrotra et al. and Niu et al. showing that a two-compartment model appropriately describes veliparib pharmacokinetics [24, 25].

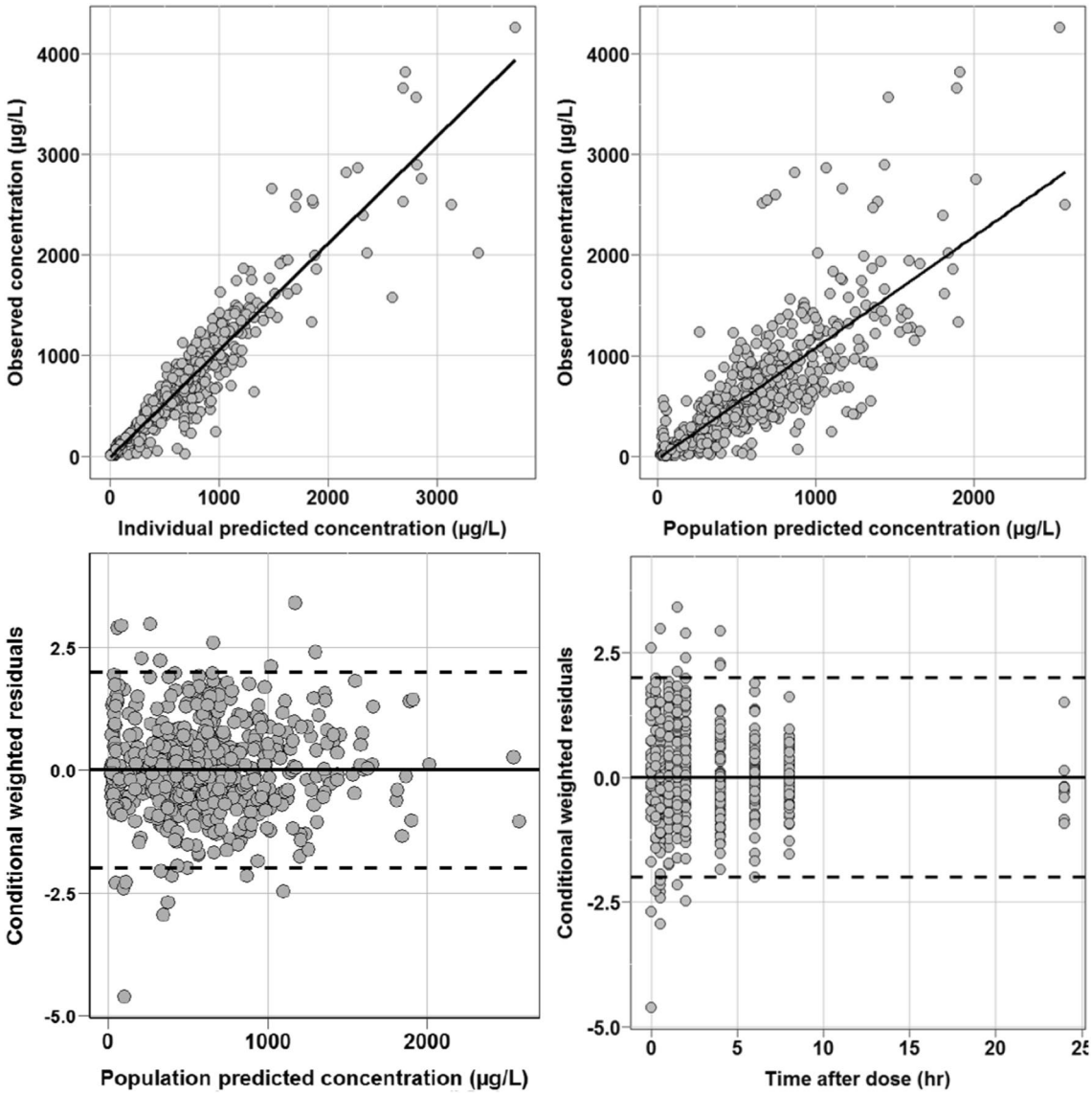

Fig. 1 Goodness-of-fit plots for the final population pharmacokinetic model

Renal excretion is the major route of elimination for veliparib, with 70% of oral dose being recovered in the urine as unchanged drug [5]. In addition to glomerular filtration, active tubular secretion plays an important role in the renal clearance of veliparib [8, 23]. Veliparib also undergoes hepatic metabolism predominantly mediated by cytochrome P450 (CYP) 2D6 [23, 26, 27]. The lactam metabolite M8 is the major metabolite identified in vitro and in vivo, 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 [23]. Our results are in agreement with the previously reported values and show that renal clearance comprises approximately 75% of the total apparent clearance. The apparent central compartment volume of distribution is similar to previous studies. Published bioavailability of approximately 73% and high volume of distribution are consistent with the notion that veliparib is highly permeable and distributes well into the tissues [8, 28].

In patients with non-hematologic malignancies, Salem et al. identified LBM and CL_{CR} as the main covariates explaining the variability in V_c/F and CL/F, respectively [8]. Li et al. used PBPK modeling and population PK modeling to demonstrate that renal function (creatinine clearance) is a significant predictor for veliparib exposure in patients with cancer [23]. Similar to these studies, our results show CL_{CR} as the main covariate associated with veliparib clearance. However, instead of LBM, body weight was identified as a significant covariate on Vc/F. Both LBM and body weight are correlated and this difference could be, because the study population was different in the two studies with heavier

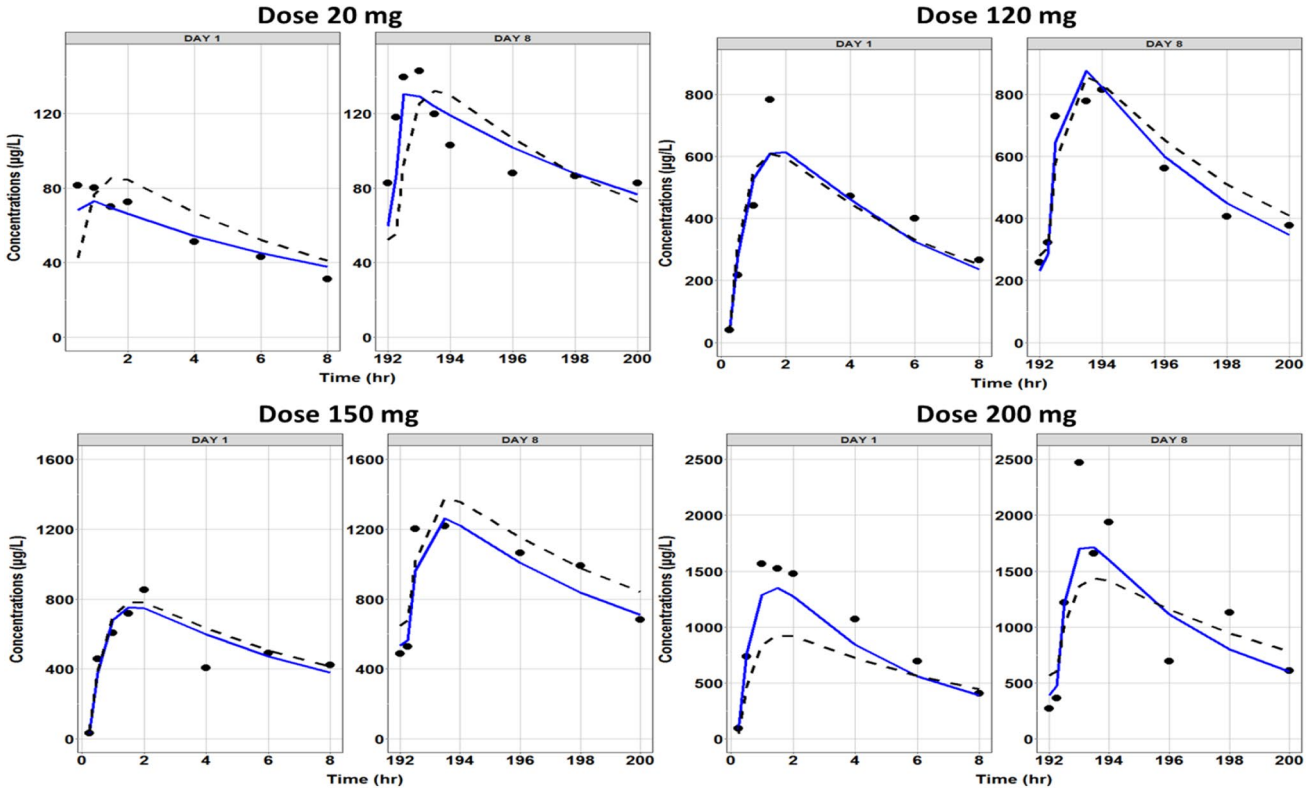

Fig. 2 Representative individual concentration–time plots derived from the final population pharmacokinetic model. Black circles represent the observed data; solid blue and dashed black lines represent the individual predicted and population predicted profiles

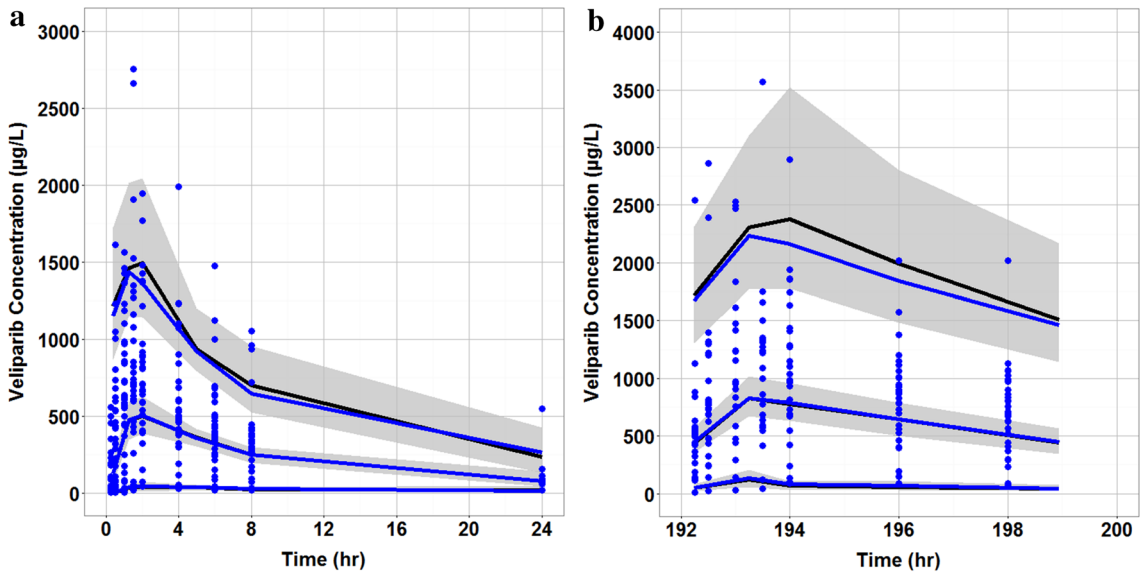

Fig. 3 Visual predictive check for day 1 (**a**) and day 8 (**b**). Circles represent observations, and lines represent the 5th, 50th, and 95th percentiles of observed (blue) and predicted (black) data with grey bands representing the 95% confidence bands for the predicted percentiles

patients in Salem et al. (body weight range of 42–170 kg). High variability in initial concentration was observed. Different absorption models (zero order, zero order followed by first order) were evaluated but did not result in improvement. Sparse data were collected in the absorption phase; hence, additional parameters for describing absorption were

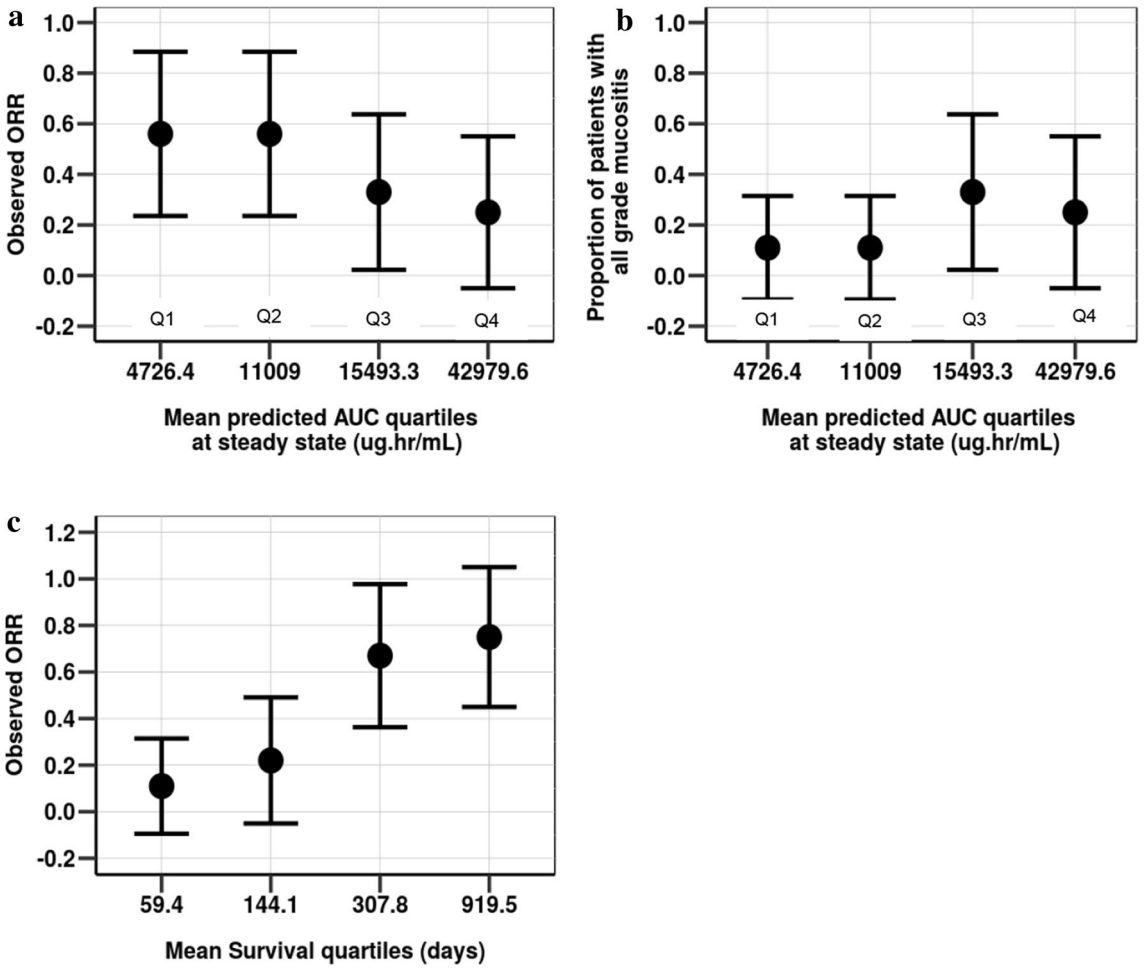

Fig. 4 Exposure–response analysis (top left-**a**) exposure–safety analysis (top right-**b**) and survival response (bottom left-**c**) for veliparib in combination with temozolomide. Data represents mean ± 95% confidence interval

not supported by the data. In addition, higher unexplained variability in initial concentrations could be due to other unobserved factors/covariates that were not accounted for in the population PK model.

The principal route of clearance of temozolomide is via the pH-dependent formation of a highly reactive metabolite 5-(3-methyltriazen-1-yl) imidazole-4-carboxamide (MTIC), with renal excretion playing a minor role in elimination. Thus, it is not surprising that there was no interaction seen between veliparib and temozolomide, given the different routes of elimination for each drug.

A phase I trial of veliparib in combination with topotecan plus carboplatin demonstrated a 33% ORR in patients with advanced myeloid malignancies, with a striking 64% ORR in those with aggressive or transformed myeloproliferative neoplasms and CMML-2 [21]. Efficacy, safety and PK data from 95 patients who were administered 10 to 100 mg BID doses of veliparib for either 8, 14, or 21 days demonstrated shallow exposure–efficacy and exposure–safety relationship. A veliparib dose of 80 mg administered for at least 14 days with topotecan and carboplatin in these patients was considered appropriate from a benefit–risk perspective and was recommended for future clinical studies. However, in the current study, no clear trend in exposure–ORR was observed, suggesting that multiple factors such as co-administered chemotherapy and disease condition may play an important role in determining the exposure–ORR relationship. Kaplan–Meier analysis suggested that survival did not change with exposure, which is in agreement with the exposure–ORR analysis. However, based on exposure–mucositis relationship, a mean steady-state AUC_{tau} of 11,000 µg h/L (approximately equal to dose of 120 mg) was relatively safer (11% all grade mucositis). On this basis, future clinical studies aimed at confirming exposure–efficacy/safety relationship would need to evaluate doses ranging up to 120 mg. In the publication by Gojo et al. 150 mg BID veliparib in combination with temozolomide was found to be the maximum tolerated dose based on grade 3 or 4 mucositis using a 3 + 3

design [14]. Our analysis is conservative as we are proposing a highest veliparib dose of 120 mg for future investigations based on all grade mucositis and the observed relatively flat exposure–efficacy relationship.

It should be noted that, although a high-fat meal has been shown to decrease veliparib C_{max} by 17% and delay T_{max} by approximately 1 h [29], our population pharmacokinetic analysis did not account for patient diet as a covariate. The decreased rate of absorption due to food consumption may occur because of delayed gastric emptying resulting in a delay of the administered veliparib to reach the small intestine, the main site of absorption for the majority of basic drugs. It is possible that accounting for diet could have helped to capture C_{max} more precisely in our population pharmacokinetic analysis; however, a 17% reduction in C_{max} in the presence of food is not considered clinically relevant [29], and AUC, our primary exposure parameter to correlate with response or toxicity, was not affected by food [29]. In addition, CYP2D6 poor metabolizer status and co-administration of OCT2 inhibitor (cimetidine) have been postulated to increase veliparib steady-state exposure by 20%, and 30%, respectively [23]. Our analysis did not account for different concomitant medications for this study.

Our data demonstrate that the pharmacokinetics of veliparib in a population of older patients with advanced myeloid leukemias is similar to that reported earlier in other cancer patient populations [8, 24, 25]. In addition, exposure–response analysis shows that, in the trial patient population, a lower dose of veliparib can be efficacious in combination with temozolomide. The exposure–response data are further supported by the correlation of complete response with pretreatment MGMT promoter hypermethylation, and treatment-induced H2AX phosphorylation that was observed at veliparib doses ranging from 20 to 150 mg [14]. While efficacy was not strictly exposure dependent at the doses evaluated in this study, the incidence of mucositis was related to exposure. It is possible that the decrease in ORR at higher exposure could be obscured by patients discontinuing therapy due to toxicity in the higher exposure groups before they could derive objective clinical benefit. The limited number of patients across the various exposure cohorts in this study precludes a definitive analysis of exposure–efficacy relationship. The population PK analysis indicates that patients with mild renal impairment may not need dose adjustment, since CL_{CR} of ≥ 60 mL/min is expected to result in $\leq 25\%$ increase in AUC. Nonetheless, since no patient in this study had CL_{CR} <30 mL/min, accurate prediction for veliparib PK in the setting of significant renal impairment cannot be made based on the current data. Studies in patients with moderate or severe renal impairment are ongoing and will assess the need for dose adjustment for these sub-populations (ClinicalTrials.gov Identifier: NCT01366144).

In conclusion, the exposure–response analysis, based on limited data, informed the veliparib dose range in combination with temozolomide that minimizes toxicity while preserving antileukemic efficacy. Veliparib doses ranging up to 120 mg (equivalent to mean steady-state AUC_{tau} of 11,000 µg h/L or lower) in combination with temozolomide could be explored in future clinical studies of older adults with advanced myeloid leukemias. This will better define the exposure–response relationship and lead to optimized dosing recommendations with maximized benefit–risk for the combination.

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Compliance with ethical standards

Conflict of interest All authors declare no potential conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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