Exposure–Response of Veliparib to Inform Phase II Trial Design in Refractory or Relapsed Patients with Hematological Malignancies

Shailly Mehrotra1, Mathangi Gopalakrishnan1, Jogarao Gobburu1, Jiuping Ji2, Jacqueline M. Greer5, Richard Piekarz4, Judith E. Karp3,5, Keith W. Pratz3,5, and Michelle A. Rudek3,5,6

Abstract

Purpose: A phase I trial of veliparib in combination with topotecan plus carboplatin (T+C) demonstrated a 33% objective response rate in patients with hematological malignancies. The objective is to perform exposure–response analysis to inform the phase II trial design.

Experimental Design: Pharmacokinetic, efficacy, and safety data from 95 patients, who were administered 10 to 100 mg b.i.d. doses of veliparib for either 8, 14, or 21 days with T+C, were utilized for exposure–efficacy (objective response and overall survival) and exposure–safety (≥grade 3 mucositis) analysis. Multivariate Cox proportional hazards and logistic regression analyses were conducted. The covariates evaluated were disease status, duration of treatment, and number of prior therapies.

Results: The odds of having objective response were 1.08-fold with 1,000 ng/hr/mL increase in AUC, 1.5-fold with 1,000 ng/hr/mL increase in AUC, 1.5% for 1,000 ng/hr/mL increase in AUC, 39% with >8 days treatment, 2.8-fold in patients with myeloproliferative neoplasms (MPN), and 0.5-fold with >2 prior therapies. Based on analysis of overall survival, hazard of death decreased by 1.5% for 1,000 ng/hr/mL increase in AUC, 39% with >8 days treatment, 44% in patients with MPN, while increased by 19% with >2 prior therapies. The odds of having ≥grade 3 mucositis increased by 29% with 1,000 ng.h/mL increase in AUC.

Conclusions: Despite shallow exposure–efficacy relationship, doses lower than 80 mg do not exceed veliparib single agent preclinical IC50. Shallow exposure–mucositis relationship also supports the 80-mg dose. Based on benefit/risk assessment, veliparib at a dose of 80 mg b.i.d. for at least 14 days in combination with T+C is recommended to be studied in MPN patients.

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Translational Relevance

Veliparib is an orally bioavailable PARP inhibitor that potentiates toxicity of diverse chemotherapeutic drugs, including topoisomerase I inhibitors and platinating agents. A phase I trial of veliparib in combination with topotecan plus carboplatin demonstrated promising efficacy in patients with advanced myeloproliferative neoplasms (MPN). This study illustrates the utility of assessing exposure–efficacy, exposure–safety, and the effect of covariates to inform future clinical investigations. While a shallow exposure–efficacy and exposure–safety were observed, veliparib exposure did not exceed single-agent preclinical IC50, supporting the 80 mg dose for future studies. Additionally, a subset of patients with MPNs was identified as being more likely to benefit with at least 14 days of veliparib treatment. This quantitative information is useful not only in the design of a future phase II clinical trial with this combination but also in terms of assessing exposure–response data to rationally design clinical trials.

Materials and Methods

Data

The pharmacokinetic, efficacy and safety data for the current analysis were obtained from the phase I trial of veliparib in combination with topotecan plus carboplatin. This analysis informs dose selection, patient population, and treatment duration for future clinical investigations of this regimen.

120-hour intravenous continuous infusion from days 3 to 7. The doses of topotecan and carboplatin for the current trial (9) were based on a previous phase I study (19) where the MTD was determined as 1.6 mg/m²/day for topotecan and 150 mg/m²/day for carboplatin. When the lowest dose of veliparib in combination with topotecan 1.3 mg/m²/day and carboplatin 150 mg/m²/day was associated with dose-limiting GI mucositis, an exploration of altering topotecan and carboplatin doses was performed. The doses of topotecan and carboplatin were then fixed at 1.2 mg/m²/day and 150 mg/m²/day, respectively, which allowed for escalation of veliparib dose. The doses of veliparib were 10, 20, 40, 80, 90, and 100 mg b.i.d. The MTD was determined to be 80 mg b.i.d. for 8 days, with mucositis being dose limiting. To further investigate tolerability for a longer duration, the veliparib treatment was extended to 14 or 21 days for MPN and CMML patients. Plasma veliparib concentrations were collected predose and until 8 hours post dosing on days 1 and 4. Two measures of clinical outcome: objective response (OR) and overall survival (OS) were available. OR included complete response (CR), complete response with incomplete count recovery (CRi) and partial response (PR) (9). OS was defined as the time from the start of the treatment to date of death or censored at the last follow-up date (9).

Exposure metric

A two-compartment population pharmacokinetic model with absorption lag adequately described the concentration profile of veliparib with topotecan plus carboplatin (20). Using individual pharmacokinetic parameter estimates obtained from the model, a rich pharmacokinetic profile was simulated for each patient with doses administered every 12 hours. The Cmax (maximum concentration) and AUCltau (area under the curve until 12 hours) were obtained using noncompartmental analysis for single dose and at steady state. A strong correlation was observed between Cmax and AUCltau both at single dose and at steady state (Supplementary Fig. S1). Therefore, model-predicted AUCltau at steady state was utilized as the exposure metric for conducting exposure–response analyses for efficacy and safety.

Assessment of risk factors (MPN status and number of prior therapies) and treatment duration on OR rate (ORR) and OS

Risks factors including number of prior therapies (≥2 and <2) and disease status (MPN versus no MPN) were evaluated as univariate covariates on ORR using logistic regression. Since duration of treatment was different among the 80-mg dose group, treatment duration (8 and >8 days) was also evaluated as a binary covariate using logistic regression as described in equation 1 below.

\[ P_i = \frac{e^{a+b \text{predictor}}}{1 + e^{a+b \text{predictor}}} \]  

where \( P_i \) is the probability of observing objective response in a subject, \( a \) is the intercept, and \( e^\beta \) represents the odds ratio of the event occurring for every unit increase in the predictor variable. Specific prior therapies administered to the patients included only cytotoxic agents and therefore were not evaluated as a risk factor. Kaplan–Meier (K-M) analysis was conducted to explore relationship between risk factors and treatment duration on OS.

Information across doses and adjust for various risk factors for benefic–risk assessment. Idelalisib is a PI3Kδ kinase inhibitor was approved by the FDA in 2015 (14). Exposure–response analysis indicated increased tumor reduction with increasing exposures with a plateauing effect observed at the exposures from 150 mg b.i.d. dose (approved dose), indicating that doses beyond 150 mg b.i.d. may not offer additional benefit. Furthermore, lack of any exposure–safety was pivotal to recommend no dose adjustment in patients with hepatic impairment and with concomitant administration of strong CYP3A4 inhibitors despite increase in exposures (14). Similarly, lack of exposure–efficacy, but a significant exposure–safety (anemia) relationship was crucial in FDA’s decision to question the sponsor on the use of a tablet formulation (300 mg b.i.d.) of olaparib in confirmatory clinical trials. Previously, the capsule formulation (400 mg b.i.d.) of olaparib was granted accelerated approval (15, 16) and the exposures from the tablet formulation were found to be 50% higher than that of the capsule formulation. These examples and others demonstrate the utility of exposure–response to support a wide variety of decisions including dose selection and future trial designs in oncology (17, 18).

The objective of our current research was to perform exposure–response analysis for efficacy and safety utilizing the information obtained from the phase I trial of veliparib in combination with topotecan and carboplatin. This analysis informs dose selection, patient population, and treatment duration for future clinical investigations of this regimen.

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Dose and exposure–response for ORR

The dose–response for ORR was explored graphically by plotting the proportion of patients achieving objective response against dose. The distribution of baseline risk factors (number of prior therapies and disease status) and treatment duration was compiled for each dose group. The exposure–response for ORR was first explored graphically using quantile plots (21). The steady-state AUCs were arranged in ascending order and then divided into 4 quartiles. The mean (95% CI) objective response rate (ORR) for each quartile was plotted against mean AUC of each quartile to assess the underlying shape between exposure and response (21). A univariate logistic regression as described in equation 1 was then conducted using individual patient level data to quantify exposure–response relationship for ORR. Multivariate logistic regression was conducted to quantify the effect of number of prior therapies, disease status, treatment duration, and exposures of veliparib on ORR.

Dose and exposure–response for OS

K-M analysis was conducted to explore dose–OS relationship and evaluate the relationship between exposure quartiles of veliparib to OS as described above. The survival curves for a given covariate (univariate) were compared using the log rank test. Multivariate cox proportional hazard analysis was conducted to quantify the effect of number of prior therapies, disease status, treatment duration, and exposures of veliparib on OS as described in equation 2 (22).

\[
\ln h(t) = \ln h_0(t) + b_1 x_1 + b_2 x_2
\]

where \(h(t)\) is the hazard at time \(t\); \(x_1\) and \(x_2\) are the explanatory variables; and \(h_0(t)\) is the baseline hazard when all the explanatory variables are zero and coefficients \(b_1\) and \(b_2\) are estimated from the data.

Exposure–response for PAR inhibition in PBMC

Poly-adenosine ribose (PAR) levels were measured in peripheral blood mononuclear cells (PBMC) at baseline and at 2, 4, 7, and 24 hours after the first dose on days 1 and 4. Maximum PAR suppression was observed at 2 hours on day 1. An exploratory graphical analysis using quantile plots was conducted to evaluate the relationship between percent PAR suppression in PBMC with observed veliparib concentrations at 2 hours on day 1. The distribution of risk factors (number of prior therapies, disease status, and treatment duration) was calculated in each quartile as follows:

\[
\% \text{ CFB in PAR at } 2 \text{ hour on day } 1 = \frac{(\text{PAR at 2 hours on day 1} - \text{Baseline PAR}) \times 100}{\text{Baseline PAR}}
\]

Relationship between PAR suppression in PBMC and objective response rate

Furthermore, the relationship between % CFB in PAR at 2 hours versus ORR was explored using quantile plots. A total of 37 subjects had both PAR levels (baseline PAR>100 pg/10⁷ cells) and OR information. The % CFB in PAR levels was divided into 4 quartiles and ORR was plotted for each quartile.

Dose and exposure–response for safety

The exposure–safety analysis was conducted for the most clinically relevant adverse events with an attribution of possibly, probably, or definitely related to the investigational agent. The adverse events were assessed using NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. For the most part, severity grade of 3 or higher for a nonhematologic adverse event was considered as dose-limiting toxicity (DLT). Mucositis was identified as the DLT and grade 3 or greater mucositis was the adverse event of interest (9). Mucositis grade was converted into binary variable (mucositis none or grade ≤2 versus grade ≥3). Logistic regression as described in equation 1 was conducted to quantify relationship between proportion of patients with mucositis and AUC. Similar analysis was also conducted for all grade mucositis. Using the exposure–mucositis relationship, the risk of mucositis was assessed in patients with mild renal impairment who had 28% higher AUC as compared with patients with normal renal function (20).

Software

Pharmacokinetic model for veliparib was developed using Phoenix NLME 1.4 (Pharsight a Certara Company). All graphical and statistical analyses were conducted using R version 3.3.0.

Results

Efficacy and safety data were evaluable from 95 of the 99 patients. The demographic characteristics across different doses are shown in Table 1. Eleven of the 95 patients had missing pharmacokinetic information; therefore, the exposure–response dataset consisted of 84 patients. The characteristics of the patients in the exposure–response dataset were representative of the entire population (Supplementary Table S2).

Because this was not a randomized trial, the effect of confounding factors on ORR and OS was evaluated first. Dose and exposure were then correlated to two efficacy endpoints (ORR and OS) to assess the dose/exposure–response relationship after adjusting for the confounding factors. Next, ORR–OS relationship was explored to assess the ability to use ORR to predict OS for planning future trials. Because veliparib suppresses PAR levels, analysis was conducted to determine the exposure levels needed for maximum PAR suppression and to assess if higher PAR suppression was related to higher ORR. Finally, the relationship between dose and exposure with mucositis was explored to assess overall benefit/risk.

The distribution of risk factors (number of prior therapies and disease status; MPN versus non-MPN) and treatment duration are shown in Table 1. At the 80-mg dose group, 30% of patients received >8 days treatment of veliparib and 43% patients (16/37) has MPN while at the 10 mg dose, no patient had >8 days treatment and only 4% (1/26) had MPN. The number of patients with >2 prior therapies was 43% (16/37) at 80 mg as compared with 65% (17/26) at the 10-mg dose group. Therefore, the effect of number of prior therapies, treatment duration, and disease status on efficacy was explored further. The doses of topotecan ranged from 1.0 to 1.3 mg/m²/day, while carboplatin dose range was 120 to
150 mg/m²/day given for all dose levels except 1 and 2 (Supplementary Table S1). Higher doses of topotecan (1.3 mg/m²/day) were associated with dose-limiting mucositis. Therefore, for veliparib doses of ≥40 mg, the dose of topotecan (1.2 mg/m²/day) plus carboplatin (150 mg/m²/day) was fixed. No definitive trend in ORR with topotecan and carboplatin doses was observed and thus the effect of topotecan and carboplatin doses on efficacy was not explored in further analysis.

Effect of risk factors (MPN status and number of prior therapies) and treatment duration on ORR and OS

As previously reported, patients with MPN, >8 day treatment duration, and <2 prior therapies had higher ORR and longer OS (9). Similar results were obtained in our analysis after excluding four non evaluable subjects. Based on univariate logistic regression, the odds of having a response for patients with MPN was 5.8-fold higher than non-MPNs ($P = 0.001$) and 6.3-fold higher for patients with >8 day treatment as compared with 8 day treatment ($P = 0.01$). In contrast, the odds of OR decreased by 0.43-fold in patients with ≥2 prior therapies ($P = 0.06$).

The patients with extended duration of veliparib treatment (14 or 21 days) had greater efficacy without added toxicity (9). It is important to note that all patients with extended duration of veliparib (>8 day) had MPN and received 80 mg b.i.d. Therefore, ORR and OS were compared in MPN patients on 80 mg dose with 8 days ($n = 5$), 14 days ($n = 5$), and 21 days ($n = 6$) of treatment duration. The ORR and OS were 60% and 8 months for 8 days, 100% and 33.9 months for 14 days, and 50% and 11.8 months for 21 days treatment, respectively. The ORR was 60% and 73% for 8 days and >8 days treatment, respectively (Supplementary Table S3).

Of 21 patients with MPN, 11 had >8 days of veliparib. MPN patients with 8 day treatment duration received 10 mg ($n = 1$), 20 mg ($n = 2$), 40 mg ($n = 1$), 80 mg ($n = 5$), or 100 mg ($n = 1$) doses, while all MPN patients ($n = 11$) with >8 day veliparib received 80 mg. In order to compare the ORR and OS across the spectrum of dose escalation, we examined only those patients receiving 8 days of veliparib. ORR and OS were compared between MPN ($n = 10$) and non-MPN ($n = 74$) patients. The ORR and OS were higher in MPN relative to non-MPN patients, as shown in Supplementary Table S4.

Dose–response for OR and OS

As depicted in Fig. 1A, a modest dose-related increase in ORR was observed. The ORR was 27% ($n = 26$), 29% ($n = 17$), and 43% ($n = 37$) for 10-, 20-, and 80-mg dose groups, respectively. These dose groups had the maximum number of patients compared to other dose groups. The ORs were 0% at 90 mg and 75% at 100 mg, both doses exceeding the MTD.

Similarly for OS, a numerical trend in increase in median OS with increase in dose was observed except for the 90-mg dose group (Fig. 2A). The median OS was 5.1, 6.9, 7.2, 7.2, 2.8, and 10.6 months for 10, 20, 40, 80, 90, and 100 mg doses, respectively. Due to the small number of patients in the 40-, 90-, and 100-mg dose arms, the survival curves for these dose groups were not informative.

Exposure–response for OR and OS

Figure 1B shows the quantile plot for steady-state AUC and ORR. Consistent with dose–response, increasing ORR was observed with increasing veliparib exposure. Based on univariate logistic regression with steady-state AUC as predictor of ORR, the odds of having ORR increased by 15.5%, with every 1000 ng.h/mL increase in AUC ($P = 0.08$).

Similarly, OS for the highest quartile of exposure was higher as compared with OS for the lower quartiles (Fig. 2B). Based on univariate cox proportional hazard analysis, the hazard of death was 41% less in Q4 patients as compared with Q1 ($P = 0.22$).

The distribution of number of prior therapies, disease status, and treatment duration was evaluated in four quartiles (Supplementary Table S5). The highest quartile (Q4) had a greater proportion of MPN patients and patients with >8 days of treatment, suggesting that the higher ORR observed in this quartile may be attributable to MPN status and longer duration of treatment independent of higher exposure.

Multivariate exposure–response analysis for OR and OS

After adjusting for MPN status, treatment duration, and prior therapy, ORR increased by 8% with every 1000 ng.h/mL increase
in AUC, 1.8-fold with >8 day treatment, and 2.8-fold for patients with MPNs and decreased 0.5-fold with ≥2 prior therapies (Supplementary Table S6). However, none of the predictor variables was found to be statistically significant. After adjusting for number of prior therapies, disease status, and treatment duration, the exposure–response for ORR appears shallow, indicating that there is minimal benefit with the increase in exposures (Fig. 3). It is also evident that the group with MPN, <2 prior therapies and >8 day duration had a higher ORR at any particular AUC relative to those with no MPN, ≥2 prior therapies and 8 days of treatment duration.

Supplementary Table S7 shows the results of multivariate cox proportional hazard analysis for the OS endpoint. The hazard of death decreased by 1.5% for 1,000 ng·h/mL increase in AUC, 39% with >8 day treatment, and 44% in patients with MPN, but increased by 19% with ≥2 prior therapies indicating that the magnitude of the effect of AUC on OS was less than the other predictor variables. Figure 4 shows the effect of increase in veliparib exposures on OS after adjusting for number of prior therapies, disease status, and treatment duration. To evaluate the effect of increased AUC on OS, the survival probabilities were predicted from the multivariate cox proportional hazard model at the AUC of 555, 1,117, 3,772, and 6,266 ng·h/mL in patients who had MPN, with <2 prior therapies and >8-day duration. The AUC values represent the median AUC of the AUC quartiles in Figs. 1b and 2b. Similar plots were made for patients on no MPN, ≥2 prior therapies, and 8 days of treatment duration. The OS was similar between different exposures for a given patient population. Also, the group with MPN, <2 prior therapies, and >8 day duration has higher OS at any particular exposure as compared to the group with no MPN, ≥2 prior therapies, and 8 days of treatment duration.

**Relationship between ORR and OS**

A clear positive trend was observed between ORR and OS as depicted in Supplementary Fig. S2, indicating that patients with...
higher ORR also had higher OS. The median OS was 15.5 months and 4.5 months for responders and nonresponders, respectively.

Exploratory analysis of relationship between veliparib concentrations, PAR suppression, and ORR

An exploratory analysis using quantile plot was conducted to identify the relationship between (i) veliparib concentrations and PAR suppression at 2 hours and (ii) PAR suppression at 2 hours and ORR as shown in Supplementary Fig. S3. In general, the ORR, OS, and proportion of MPN patients in this subgroup were comparable to that of the overall dataset (Supplementary Table S2). Veliparib exposures resulted in suppression of PAR levels; however, a shallow trend in increase in PAR suppression with increase in veliparib exposures was observed. The results were consistent when AUICtau was used as the exposure metric (data not shown). Furthermore, a slight trend was observed between PAR suppression and ORR. Patients with less than 50% inhibition of PAR levels had lower ORR as compared with patients with >50% inhibition of PAR.

Dose or exposure–response for mucositis

Because grade ≥3 mucositis defined the MTD, we conducted dose–response and exposure–response analyses or mucositis. A total of 15% (15/99) of the patients had grade ≥3 mucositis. Figure 5A and B show that the proportion of patients with all grade or grade ≥3 mucositis increases with an increase in veliparib dose, respectively. Furthermore, the exposure–response analysis was conducted for all grade and grade ≥3 mucositis as shown in Fig. 5C and D, respectively. The odds of having any grade mucositis increased by 27.6% with 1,000 ng.h/mL increase in veliparib AUC (P = 0.004). Also, the odds of having grade ≥3 mucositis increased by 29% with 1,000 ng.h/mL increase in veliparib AUC (P = 0.01). Based on the exposure–mucositis relationship, a 28% increase in veliparib AUC in a patient with mild renal impairment would result in only 7% increased probability of mucositis.

Discussion

Aggressive and transformed MPNs and CMML are refractory to diverse therapies with median overall survival in patients with leukemic transformation from MPN less than 6 months (9, 23–25). The phase I dose escalation trial of veliparib in combination with topotecan and carboplatin demonstrated that patients with antecedent or aggressive MPNs and CMMLs achieved a 64% ORR, consistent with the preclinical findings that these disorders exhibit homologous repair deficits conferring sensitivity to PARP inhibition ex vivo (10). The goal of the current analysis was to evaluate the exposure–response for efficacy, safety, and the effect of number of prior therapies, disease status and treatment duration on clinical outcome in order to inform the trial design for future clinical investigations of this combination.

From the current analyses, patients with MPN, ≤2 prior therapies, and >8 days treatment were found to have higher ORR supporting the notion that future trials should investigate MPN patient population and longer treatment duration. In addition, as with other neoplasms associated with HR, MPNs exhibit PARP inhibitor hypersensitivity compared with normal marrow (10). Treatment duration of 14 days had higher ORR and OS as compared with 8 and 21 days treatment. A decreasing trend in OS and ORR when treatment duration was increased from 14 to 21 days may be due to limited sample size in each treatment duration group. Nonetheless, the totality of our exposure–response analyses support continued bidirectional translational investigations of PARP inhibitors in MPNs.

We acknowledge certain limitations of our analysis. First, the aim of the analysis was to identify the trends in the data and extract information to inform future clinical investigations of veliparib.
Therefore, statistical significance to identify the potential risk factors was not considered at this stage of drug development. Second, a majority of patients (~70%) who did not achieve OR only received one course of treatment but were followed long term for OS, raising the possibility that longer duration of OS observed in some patients cannot be attributed solely to short-term veliparib treatment. Therefore, exposure–response analysis of ORR was considered as the primary analysis to support dosing recommendations while exposure–response analysis for OS was considered exploratory and supportive. It is important to note that the exposure–response analysis for both ORR and OS were internally consistent and showed similar trends.

Since veliparib was studied in the combination setting, the efficacy and safety outcomes observed in this trial are attributed to the combination and not veliparib alone. It is not possible to tease out the differences in efficacy and safety of veliparib from topotecan plus carboplatin since all patients were administered topotecan plus carboplatin in this single arm trial. Nonetheless, since the majority of the patients were administered similar doses of topotecan and carboplatin, it is reasonable to speculate that the relative change in efficacy and safety over various veliparib doses or exposures is related to veliparib alone, thereby justifying the use of veliparib exposures for the exposure–response analysis.

A relatively shallow exposure–response for OR was observed after adjusting for the MPN status, treatment duration, and number of prior therapies. For the median AUC at 80 mg dose (MTD), the model predicted a 75% ORR for patients with MPN, <2 prior therapies and >8-day treatment and a mucositis rate of 19%. A shallow exposure–response for efficacy would suggest that a dose lower than 80 mg (e.g., 40 mg) would show similar efficacy as that of 80 mg. Indeed, at a lower dose of 40 mg, the model predicted 71% ORR in patients with MPN, <2 prior therapies, and >8-day treatment and a 10% mucositis rate. However, as shown in Fig. 4, there is uncertainty as to whether or not the mean ORR...
predictions indicate that doses lower than 80 mg could result in loss of efficacy. Furthermore, the incidence and severity of transient mucositis at 80 mg dose is clinically acceptable in this relapsed and/or refractory patient population. We acknowledge that because of substantial pharmacokinetic variability at the 80 mg dose, there will be patients who may have higher probability of experiencing grade ≥3 mucositis (Fig. 5D). Furthermore, from a preclinical perspective, the median IC₅₀ of veliparib as a single agent in colony-forming assays of primary MPN samples was ~3 μmol/L (732.9 ng/mL) (10). Interestingly, the clinical exposures of veliparib at the steady state at 80 mg b.i.d. dose overlap with the preclinical IC₅₀. Based on our current understanding of mechanism of action of topotecan, carboplatin, and veliparib, the IC₅₀ of veliparib in combination will be either similar to or lower than the IC₅₀ of veliparib as a single agent, because the exposures are likely to be higher in the combination setting than in the in vitro IC₅₀ of single-agent veliparib. Therefore, we conclude that lower exposures resulting from 40 mg b.i.d. dose are not justified based on preclinical single-agent IC₅₀.

Furthermore, exposures in patients with mild renal impairment were 48% higher AUC compared with patients with normal renal function. These increased exposures are within the range of exposures observed at 80 mg dose and on an average would result in only 7% increased probability of mucositis. Therefore, it is reasonable to include patients with mild renal impairment in the subsequent trials without the need for veliparib dose adjustment.

Because veliparib can inhibit PARP in PBMC, as measured by PAR formation, we attempted to characterize the relationship between veliparib exposure and PAR suppression. While more than 50% inhibition of PAR levels was observed at all dose levels, a shallow relationship was observed between veliparib exposures and PAR suppression possibly due to the variability in leukemic blast populations in the PAR assay samples. PAR suppression in nonleukemic PBMCs is no longer done due to poor correlation with PK in solid tumor studies. The exposures observed with 80 mg b.i.d. fall into the plateau of the exposure–response relationship. In addition, suppression in PAR levels was plotted against ORR. Patients with less than 50% inhibition of PAR levels had lower ORR as compared to patients with >50% inhibition of PAR. These relationships (Supplementary Fig. S3A and B) need to be interpreted carefully due to limited sample size. Nevertheless, these relationships support the choice of 80-mg b.i.d. dose for future clinical investigations.

Based on the totality of evidence that includes exposure–response analysis, severity of disease, available treatment options and preclinical evidence and PAR inhibition, a dose of 80 mg b.i.d. administered for at least 14 days with topotecan and carboplatin is appropriate for further clinical investigations in patients with aggressive MPNs and CMML. A phase II trial (NCI#10147) planned will evaluate safety and efficacy of veliparib in combination with topotecan plus carboplatin to topotecan plus carboplatin.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Authors’ Contributions

Conception and design: J.E. Karp, K.W. Pratz, M.A. Rudek
Development of methodology: S. Mehrotra, J. Ji, K.W. Pratz, M.A. Rudek
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): J. Ji, J.M. Greer, J.E. Karp, K.W. Pratz, M.A. Rudek
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): S. Mehrotra, M. Gopalakrishnan, J. Gobburu, J. Ji, J.E. Karp, K.W. Pratz, M.A. Rudek
Writing, review, and/or revision of the manuscript: S. Mehrotra, M. Gopalakrishnan, J. Gobburu, J. Ji, R. Piekarsz, J.E. Karp, K.W. Pratz, M.A. Rudek
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): J. Ji, J.M. Greer, M.A. Rudek
Study supervision: J. Ji, J.M. Greer, R. Piekarsz, K.W. Pratz, M.A. Rudek

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