Abstract #2952

Predicting the Concentration of PARP Inhibitors in Human Tumor Tissue Using PBPK Modeling

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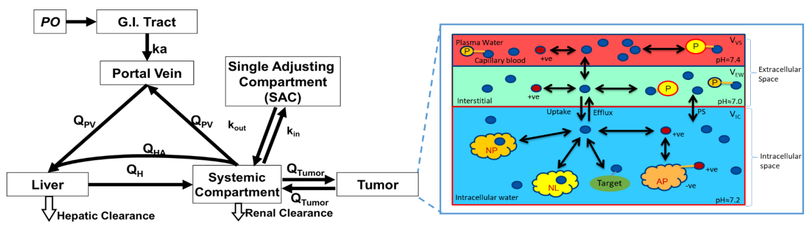
Background

- Poly(ADP-ribose) polymerase (PARP) inhibitors exert their effect intracellularly within tumors; thus, sufficient tumor penetration is essential for a pharmacological response
- Preclinical mouse xenograft data show a 3.3-fold higher tumor versus plasma exposure of niraparib, while olaparib tumor exposure had 60% plasma exposure[1]
- This study aimed to build a physiologically-based pharmacokinetic (PBPK) model extended with a tissue composition-based permeability-limited tumor model to:
  - Gain a mechanistic understanding of the differences in tumor exposure of niraparib and olaparib
  - Predict clinical tumor exposure in patients with ovarian cancer at clinically relevant dosing regimens

Methods

- A minimal PBPK model was extended to include a permeability-limited tumor model (**Figure 1**) that integrated data on tumor composition (**Table 1**) and drug physicochemical properties (**Table 2**) analogous to the established permeability-limited organ model available for the liver in the Simcyp Simulator (Certara, Princeton, NJ, USA).[2,3] Key model assumptions were:
  - The tumor was represented by 3 homogenous compartments: vascular space, interstitial space, and intracellular space
  - Unbound unionized drug was in equilibrium between the vascular and interstitial compartments
  - Movement of the drug between the interstitial and intracellular space was via passive diffusion of the unbound unionized drug or active transport of the unbound drug
  - Drug binding to PARP, neutral lipids, neutral phospholipids, and acidic phospholipids in the intracellular space could be accounted for
  - Clinical and preclinical tumor physiological parameters such as volume, blood flow, and tissue composition were defined using published data and albumin in the interstitial space
- PBPK models were built to describe the plasma and tumor concentrations of niraparib and olaparib in OVC134 tumor-bearing BALB/c nude mice.[1] For both drugs, passive permeability between the interstitial and intracellular space were estimated from the preclinical data, and estimation of active efflux or acidic phospholipid concentration was also required. Other parameters were fixed based on available data from multiple sources

Figure 1. Minimal PBPK Model With a Single Adjusting Compartment Extended to Include a Permeability-limited Tumor Model



Left panel: Q_H, Q_{PV}, Q_{HA}, and Q_{Tumor} are blood flows in the liver, portal vein, hepatic artery, and tumor, respectively; k_{in} and k_{out} are first-order rate constants that act on the masses of drug within the systemic compartment and the single adjusting compartment, respectively.
Right panel: PS, IW, NL, NP, and AP represent passive permeability–surface area product, intracellular water, neutral lipids, neutral phospholipids, acidic phospholipids, and the remaining fraction, respectively; P represents protein; blue and red circles represent unionized and ionized drug, respectively.
G.I.=gastrointestinal; PO=oral.

- Simulations were performed to predict the clinical tumor concentrations of niraparib and olaparib at steady state when administered at a standard dosing regimen by accounting for available data on tumor composition in patients with ovarian cancer, differences in pharmacokinetics, and parameters estimated from preclinical data

Table 1. Physiological Input Parameters for the Permeability-limited Tumor Model

Parameter	Mouse Xenograft	Clinical	Reference
Tumor volume (mL)	0.323	5 (1.5)	[1]
Tumor blood flow (mL/min/mL)	0.9	0.686 (0.481)	[4,5]
Vascular volume fraction	0.054	0.204 (0.124)	[5,6]
Interstitial volume fraction	0.269	0.296 (0.288)	[5,6]
Neutral lipid content (fraction wet weight)	0.0089	0.0089 (0.0035)	[3]
Neutral phospholipid content (fraction wet weight)	0.0096	0.0096 (0.0038)	[3]
Acidic phospholipid content (mg/g)	2.4	2.4 (0.52)	[3]
Total water volume fraction	0.862	0.862 (0.024)	[7,8]
Albumin interstitial:plasma concentration ratio	0.425	0.425	[9]
Interstitial pH	6.8	7.0 (0.4)	[10,11]
Intracellular pH	7.1	7.3 (0.2)	[11,12]
PARP concentration (pg/mL)	16	16	Data on File

Clinical data are reported as mean (standard deviation).

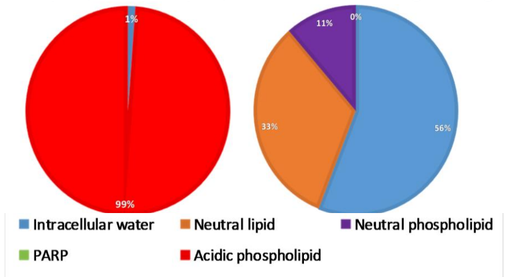
Table 2. Key Physicochemical Inputs for Niraparib and Olaparib

Parameter	Niraparib	Olaparib
Molecular weight	320.4	434.5
Log P	2.46	1.55
Compound type	Monoprotic base	Neutral
pKa	9.95	—

Results

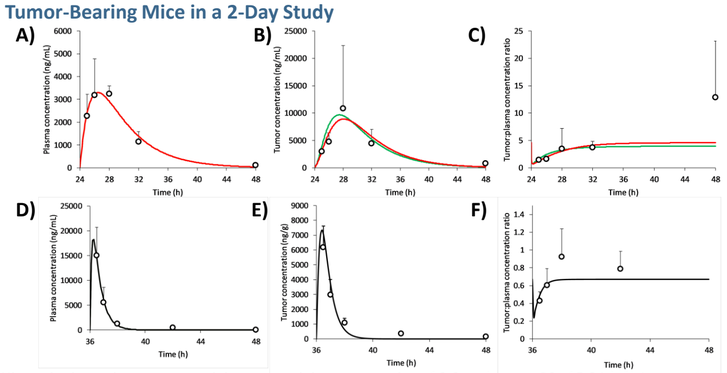
- High acidic phospholipid binding results in high tumor distribution of niraparib
- The model predicted increased tumor distribution of niraparib compared with olaparib in mice, primarily due to extensive acidic phospholipid binding of niraparib, which is highly ionized in the tumor intracellular space, but not olaparib (**Figure 2**)

Figure 2. Fraction of Niraparib (left) and Olaparib (right) Unbound in Intracellular Water and Bound to Lipids, Phospholipids, and the Pharmacological Target PARP



- Fitting passive permeability alone was insufficient to recover the tumor concentration of niraparib. However, uncertainty in the acidic phospholipid concentration, which has not been measured in tumors from OVC134 tumor-bearing mice, or the potential for active efflux by breast cancer resistance protein (BCRP) or P-glycoprotein were identified as potential mechanisms for the difference. Either reducing the concentration of acidic phospholipids or accounting for active efflux transport enabled recovery of niraparib plasma and tumor concentrations consistent with preclinical data (**Figure 3**)
- A 1.8- to 6.5-fold higher tumor exposure and 5.5- to 36.0-fold higher tumor:plasma exposure ratio was predicted for niraparib compared to olaparib in patients with ovarian cancer, depending on the assumptions made regarding acidic phospholipid concentration and efflux transporter activity (**Table 3**)
- Model predicted niraparib tumor exposure is 4 to 13-fold higher than plasma
- For olaparib, but not niraparib, clinical tumor concentrations have been measured. The predicted tumor:plasma concentration ratio (**Table 3**) is consistent with the reported mean ratio of 0.41 (range 0.05–1.54)[13]

Figure 3. Simulated (lines) and Observed (open circles[1]) Plasma and Tumor Concentration Profiles and Tumor:Plasma Concentration Ratios Following (A–C) Niraparib 50 mg/kg Once Daily and (D–F) Olaparib 67 mg/kg Twice Daily in OVC134 Tumor-Bearing Mice in a 2-Day Study



Niraparib simulations used an acidic phospholipid concentration of 0.6 mg/g and a PS of 5.8 L/h/mL tumor (green line) or an efflux transporter $CL_{int,T}$ of 0.024 L/h/mL and a PS of 5.8 L/h/mL tumor (red line). Olaparib simulations used a PS of 0.005 L/h/mL. $CL_{int,T}$=intrinsic clearance over time; PS=passive permeability–surface area product.

Table 3. Predicted Steady-State 24-Hour Tumor Exposure and Tumor:Plasma Exposure in Patients With Ovarian Cancer Following Niraparib 300 mg Once Daily or Olaparib 300 mg Twice Daily

Drug	Scenario	Tumor $AUC_{ss,24h}$ (µg/mL/h)	Tumor:plasma $AUC_{ss,24h}$ Ratio
Niraparib	A	272 ± 154 (50.0–919)	13.4 ± 6.21 (3.50–36.8)
	B	76.7 ± 40.4 (17.7–250)	3.77 ± 1.59 (1.39–9.94)
	C	94.4 ± 48.7 (30.3–255)	4.64 ± 1.73 (1.91–10.6)
Olaparib	—	41.6 ± 22.0 (8.49–129)	0.372 ± 0.0614 (0.277–0.572)

Results are reported as mean ± standard deviation (range). Scenarios: A) AP = 2.4 mg/g and $CL_{int,T}$ = 0; B) AP = 0.6 mg/g and $CL_{int,T}$ = 0; C) AP = 2.4 mg/g and efflux $CL_{int,T}$ = 0.024 L/h/mL. AP=acidic phospholipid; AUC=area under the concentration–time curve at steady state over 24 hours; $CL_{int,T}$=intrinsic clearance over time.

Conclusions

- Niraparib had higher steady state tumor exposure and tumor:plasma exposure as compared with olaparib
- A permeability-limited tumor model was developed using current knowledge of tumor lipid, phospholipid, and water content. The model predicts that increased tumor accumulation of niraparib versus olaparib is due to acidic phospholipid binding of niraparib but not olaparib. The predicted clinical tumor:plasma concentration ratio of olaparib is consistent with clinical data
- Tumor blood flow did not appear to have any impact on the model
- The developed mechanistic model may be used to predict the tumor exposure of other small-molecule anticancer drugs

References

1. Sun K, et al. *Oncotarget*. 2018;9:37080–37096; 2. Jamei M, et al. *Clin Pharmacokinet*. 2014;53:73–87; 3. Poulin P, et al. *J Pharm Sci*. 2015;104:1508–1521; 4. Kallinowski F, et al. *Cancer Res*. 1989;49: 3759–3764; 5. Thomassin-Naggara I, et al. *J Magn Reson Imaging*. 2017;46:1776–1785; 6. Kim YR, et al. *Magn Reson Med*. 2004;52:485–494; 7. Bhujwalla ZM, et al. *Br J Cancer*. 1998;78:606–611; 8. Kiricuta I-C, et al. *Cancer Res*. 1975;35:1164–1167; 9. Reed RK, Wiig H. *Scand J Clin Lab Invest*. 1983;43:503–512; 10. Vaupel P, et al. *Cancer Res*. 1989;49:6449–6465; 11. Raghunand N, et al. *Neoplasia*. 2001;3:227–235; 12. Ng TC, et al. *Radiology*. 1989;170:875–878; 13. Bundred N, et al. *Invest New Drugs*. 2013;31:949–958.