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

Background

- Poly(ADP-ribose) polymerase (PARP) inhibitors exert their effect intracellularly within tumors; thus, sufficient tissue 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.
- 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 (Certa, Princeton, NJ, USA).
- The model assumptions were:
  - The tumor was represented by 3 homogeneous compartments: vascular space, interstitial space, and intracellular space
  - Unbound 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 unionized 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 OV134 tumor-bearing BALB/c nude mice. 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

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)

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