Physiologically-Based Pharmacokinetic Modelling of Niraparib in Special Populations

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Introduction

- Poly ADP-ribose polymerase inhibitors (PARPi) have demonstrated significant efficacy in gynecological oncology. However, their clinical application is frequently limited by hematological adverse events, including thrombocytopenia, anemia, and neutropenia [1].
- Investigating the pharmacokinetics of niraparib and other PARP inhibitors across diverse populations is critical for elucidating mechanisms underlying observed adverse events and offering tailored dose justification strategies.

Aim

The key objective of the current work was to develop a physiologically based pharmacokinetic (PBPK) model of niraparib to predict optimal dosage in patients with hepatic impairment and evaluate main pharmacokinetic predictors of niraparib toxicity.

Methods

Systematic Literature Review

A comprehensive systematic literature review was conducted in PubMed and ClinicalTrials.gov, to gather all sources reporting niraparib PK data, in accordance with PRISMA guidelines.

Model Development

The niraparib PBPK model was built in PK-Sim® (v11.3). Six drug-specific parameters: LogP, pKa, intestinal permeability (Pint), renal plasma clearance (CLren), maximum reaction rate (Vmax) and Michaelis constant (Km) of carboxylesterase 2 (CE2) metabolic transformation were calibrated using Approximate Bayesian Computaion (ABC-SMC) approach [2] to match niraparib plasma concentration-time profiles from the Phase 1 study [3] and urinary excretion data from the mass balance study [4].

The calibration began with informative priors based on the available theoretical parameter estimates. The ABC-SMC algorithm was first applied to all six parameters, but then three were fixed due to high correlations between the parameters. A final ABC-SMC procedure optimized the Vmax, Pint, CLren.

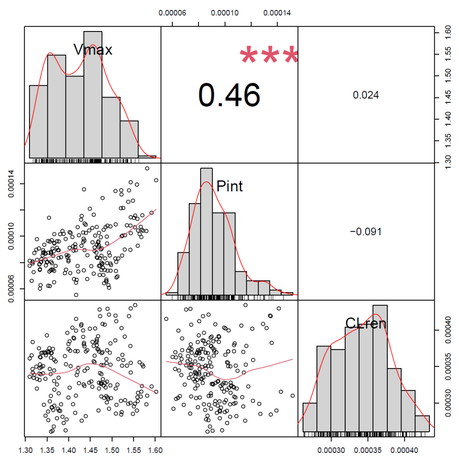

Figure 1 Parameters posterior distributions

Modelling of hepatic impairment

- Hepatic impairment stages were defined by NCI-ODWG criterion, which classify severity using total bilirubin (TBIL) and aspartate aminotransferase (AST) plasma levels.
- To model hepatic impairment effects on niraparib clearance, Vmax of CE2 metabolism was considered as a power function of TBIL and calibrated to describe mean plasma concentrations in patients with moderate hepatic impairment (Akce et al. [5]).

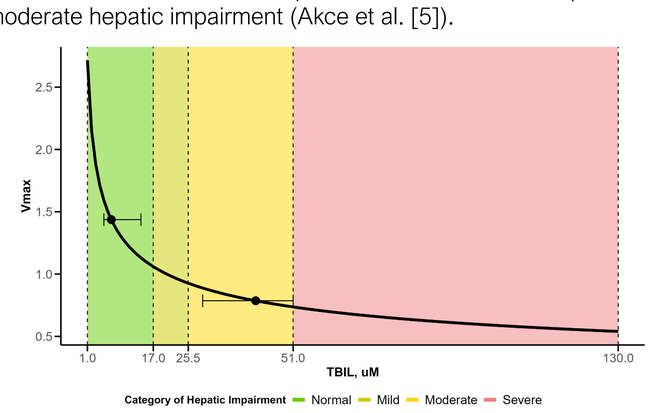

Figure 2 Dependence of Vmax on total bilirubin level

Results

Systematic Literature Review

The results of systematic literature review are summarized in the PRISM diagram (Figure 1). The 8 studies were selected for model development based on presence of relevant PK data in Caucasian patients. In total, these clinical trials aggregated data from 220 patients from 26 cohorts with 13 different dosing regimens, i.e. 30, 40, 60, 80, 110, 150, 210, 290, 300, 400 mg QD and 100, 200, 300 SD.

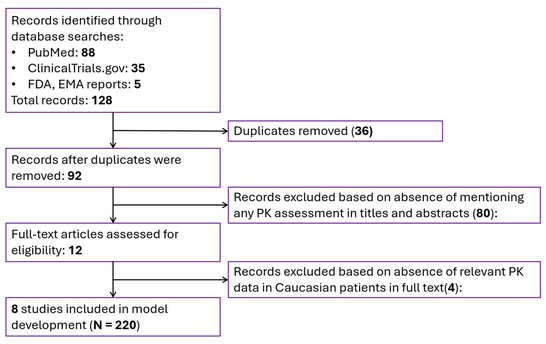

Figure 3 Prisma flow diagram for search and selection of clinical trials reporting niraparib PK measurements for PBPK model development

All the PK data were obtained in aggregated form, with concentration values reported as either the mean or median for each respective cohort.

Model Diagnostics and Validation

- Niraparib plasma PK profiles in female European patients under single dose and daily dosing regimens were predicted to consider parameters variability and compare them with available observed data.
- To estimate corresponding 95% prediction interval the calculations were repeated for each parameter combination from final posterior distribution set (n=207). Simulations with currently approved 300mg dose were performed to validate the developed model against independent data which were not used for model calibration.

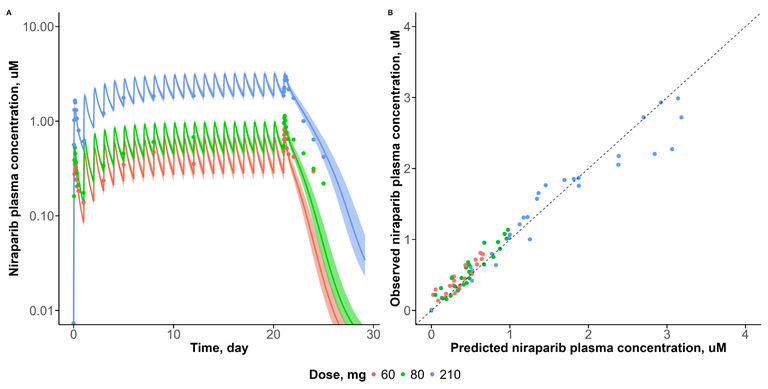

Figure 4 Model diagnostics — niraparib exposure under 60,80,210 mg QD regimen

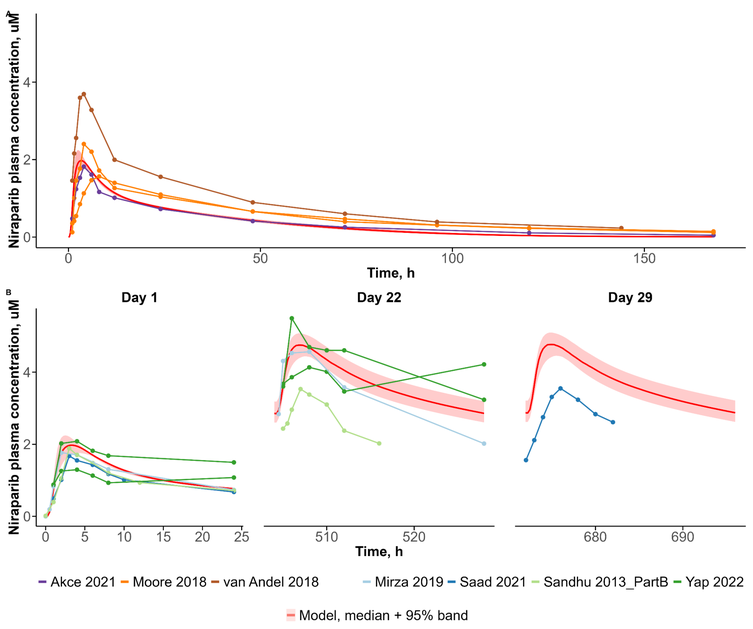

Figure 5 Model validation — niraparib exposure under a 300 mg QD regimen

PBPK simulations in patients with HI

- PK simulations under a 300 mg QD regimen across four hepatic impairment groups categorized by μM values of TBIL (mild, moderate, severe60, severe120) demonstrated an increase in steady-state plasma AUCs vs. the predicted normal value of 5315 μM●min by, respectively, 38%, 65%, 81%, and 113%.
- Upon dose adjustments to 250 mg for mild, 200 mg for moderate, and 150 mg for severe60 and severe120 stages, simulations predicted typical AUCs which remained within a ±20% range for all compartments, as compared to patients with normal hepatic function receiving the full dose of 300 mg.

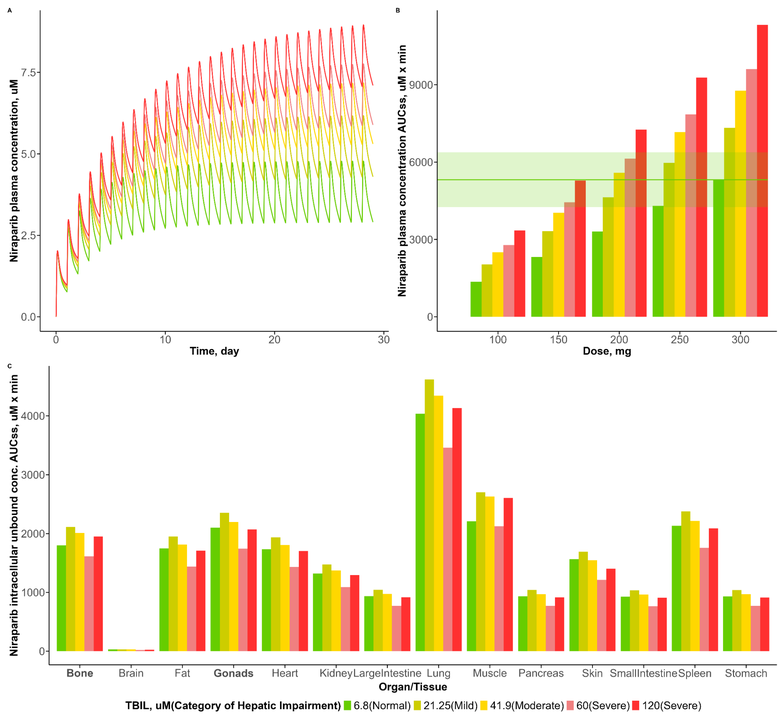

Figure 6 Simulations of niraparib exposure in patients with hepatic impairment

Exploration of niraparib therapeutic range

- The model predicted steady-state intracellular unbound AUCs in bone and gonads compartments to be equal to, respectively, 1183.99 μM●min and 1384.36 μM●min.
- Local sensitivity analysis of drug exposure in biologically relevant effect compartments (not shown) identified pKa and LogP as the most influential factors of niraparib toxicity — a 10% increase in pKa resulted in a 14% decrease in bone-to-gonads AUC ratio.

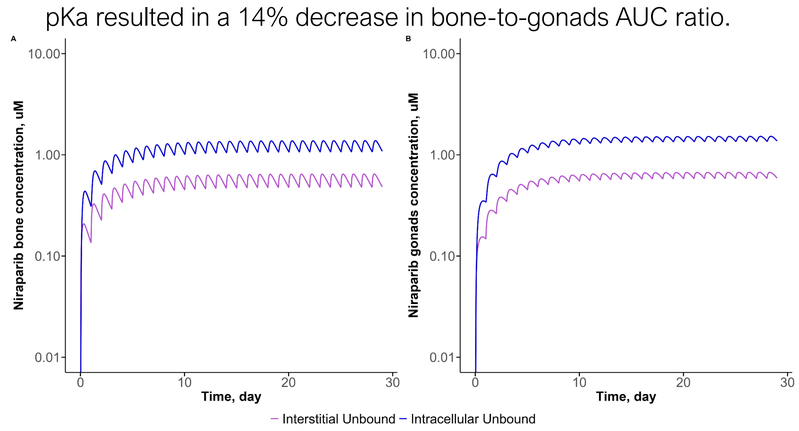

Figure 7 Simulations of niraparib exposure in bone and gonads

Conclusion

- The developed PBPK model of niraparib adequately reproduced mean niraparib plasma concentration-time profiles for various drug regimens administered clinically.
- The model justified the strategy for optimizing dosing regimens in patients with hepatic impairment, by integrating drug concentration predictions from different compartments across varying degrees of hepatic dysfunction.
- The proposed model can be used to further explore additional niraparib dosing regimens, in support of other safety challenges beyond hepatic impairment.

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