



UPPSALA
UNIVERSITET

Semi-mechanistic PKPD model of a new histone deacetylase inhibitor in co-administration with doxorubicin

C. Vong^{1,2}, Q. Chalret du Rieu², S. Fouliard², E. Roger³, I. Kloos³, S. Depil³, M.Chenel², LE. Friberg¹

¹Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden;

²Clinical Pharmacokinetic department, Institut de Recherches Internationales Servier, Suresnes, France,

³Oncology business Unit, Institut de Recherches Internationales Servier, Suresnes, France



Background and Objectives

The combination of histone deacetylase inhibitor (HDACi) and DNA-damaging agents has demonstrated potential clinical applicability [1, 2] but is hampered by the development of dose-limiting thrombocytopenia. The ability to anticipate this haematological toxicity is hence of great value for optimizing future dosing strategies. The aim of this project was to develop a semi-mechanistic thrombocytopenia model to describe a new HDACi in development, co-administered with doxorubicin (DOXO), and assess the drug-induced apoptosis effects on circulating platelets.

Methods

Study design and Patient data

- “3+3” dose-escalation Phase I clinical trial
- 8 patients treated over six 4-week cycles
- Oral twice-daily administration given 4 hours apart for HDACi (3 dose levels 60-90-120 mg/m²/day)
- 25 mg/m² IV 15min-infusion administration for doxorubicin
- 230 HDACi PK samples with a median of 30 per patient (range 21-31)
- 160 DOXO and its metabolite doxorubicinol (DOXOL) PK samples (20 per patient)
- 202 platelet measurements with a median of 26.5 per patient (range 6-42)

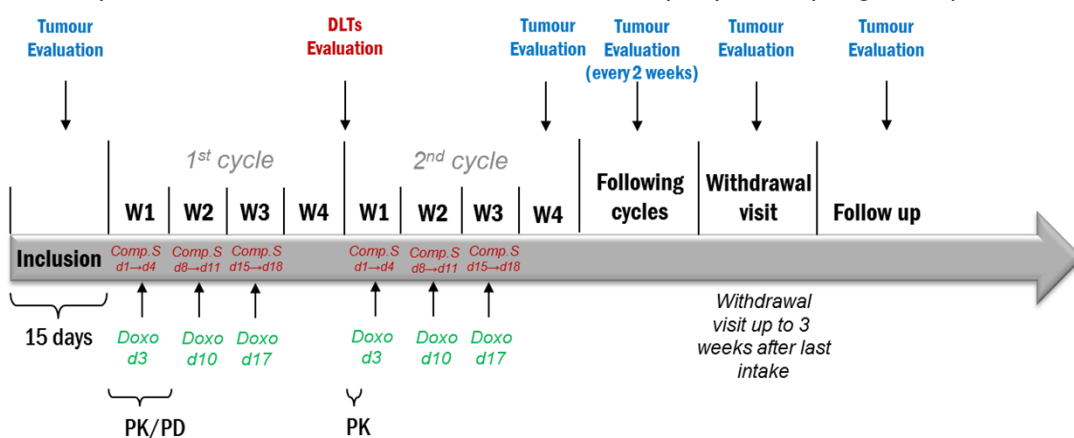


Fig.1: Dosing regimen and study plan for the six 4-week cycles study

Drugs were administered 3 weeks out of 4 with a 4 hours-apart BID administration of HDACi the first 4 days of each week and an IV infusion of doxorubicin at the third day of each week, 2 hours after the second intake of HDACi.

Population model building

- Sequential modeling was performed, where individual Bayesian estimates of PK parameters obtained from PK analysis of both compounds were fixed for subsequent PD modeling
- Patient baseline characteristics were modeled using the B2 method as described in Dansirikul et al. [3].
- Estimations were performed using FOCE-I in NONMEM 7.2

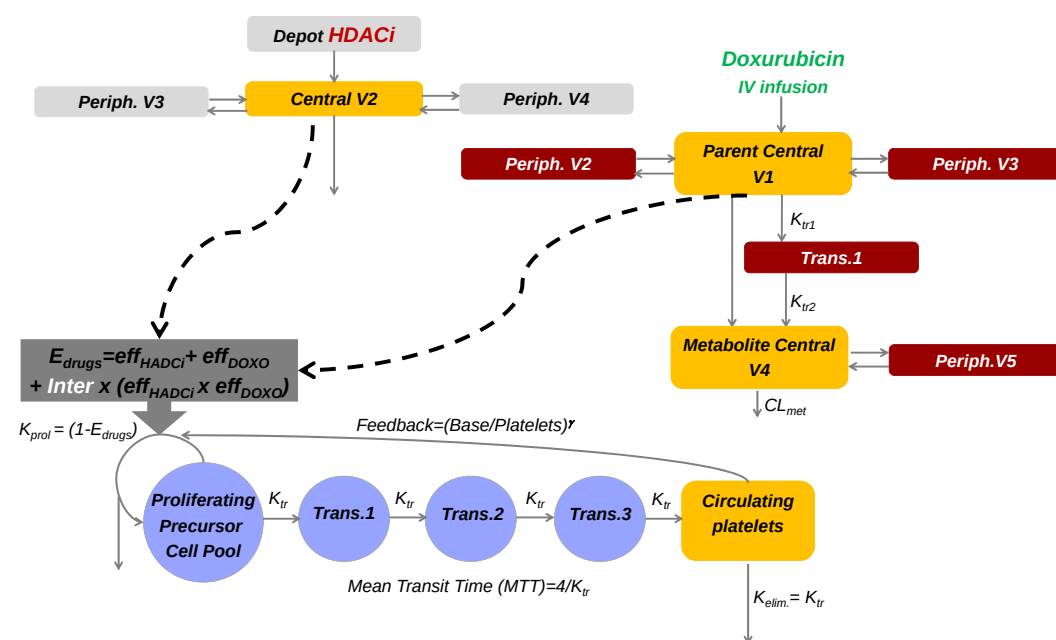


Fig.2: Schematic representation of the final PKPD thrombocytopenia model

4 types of data (yellow boxes) were utilized in this model building. An external validation using a 3-cmp model with 1st order absorption previously developed using internal data was found adequate to describe HDACi's disposition. A 3-cmp IV infusion model and a 1-cmp model [4] were used respectively, to characterize the time courses of DOXO and DOXOL. Two metabolic clearance pathways, one direct and one delayed modeled as a transit compartment were used to relate the parent to the metabolite observations. A semi-physiologic model [5], incorporating stem cell proliferation inhibition drug effect from HDACi previously developed from the same structure as the semi-mechanistic myelosuppression model described by Friberg et al. [6,7], was further refined and the effect of doxorubicin was added. Emax, slope and power models were tested for both drug effects and an interaction term was estimated.

Results

PK models for HDACi and DOXO/DOXOL

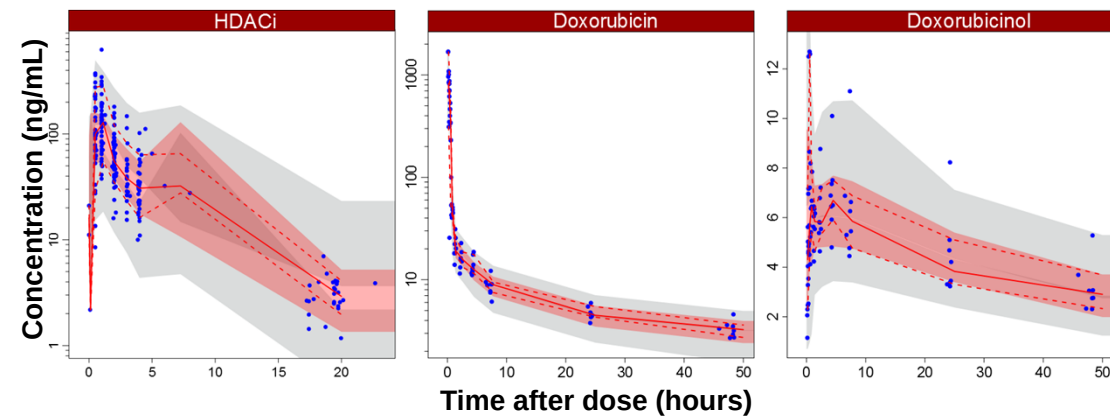


Fig.3: Visual Predictive checks for the final models describing the PK of HDACi, doxorubicin and doxorubicinol vs. time. Median (solid line), 10th and 90th percentiles (dashed lines) of the observed data are compared to the 95% confidence intervals (shaded areas) for the simulated data's 10th, 90th percentiles and median.

PKPD model for thrombocytopenia

- An extended myelosuppression model with an I_{max} and a power models describing respectively HDACi and doxorubicin acting on the inhibition of proliferative cells by the drugs were found to best characterize the platelet data.
- Incorporation of a synergistic interaction implemented as $Eff_{HDACi} + Eff_{DOXO} + INT \times Eff_{HDACi} \times Eff_{DOXO}$ were not found significant.

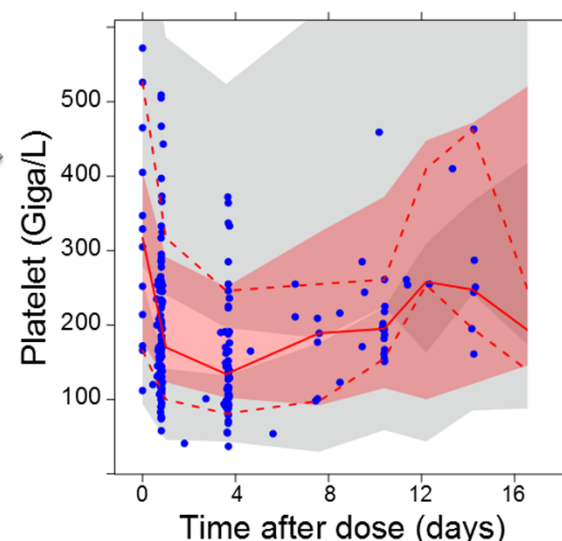
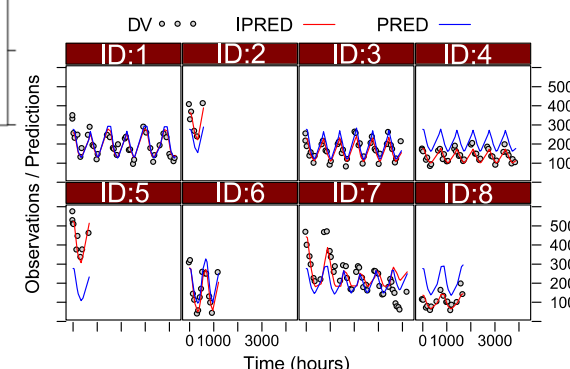


Fig.4 & 5: Visual Predictive checks for the thrombocytopenia model describing the platelet counts vs. time (same description as above) and individual predictions vs. time. Open circles represent the individual observations. Population prediction are represented by the blue solid line, individual prediction by the red solid line.

Table 1: Final parameter estimates (RSE%) for PD

Parameter	Estimate	IIV (CV %)
IMAX _{HDACi}	1 FIX	-
IC50 _{HDACi} (ng/mL)	0.405	-
HILL _{HDACi}	0.543	29.5
SLOP _{DOXO} (•10 ⁻³ ng/mL)	0.197	-
HILL _{DOXO}	0.184	-
MTT (h)	104	-
GAMMA	0.239	31.0
BASE (•Giga/L)	277	42.9
Add Err. (•Giga/L)	0.305	-
Prop Err. (%)	0.202	-



PKPD simulations of Toxicity probability

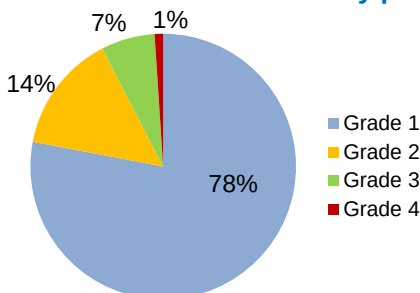


Fig.6: Probability of hematological toxicity in the current study settings based on the nadir values derived from the 1000 simulated profiles using the estimated PK and PD parameters from the developed PKPD model

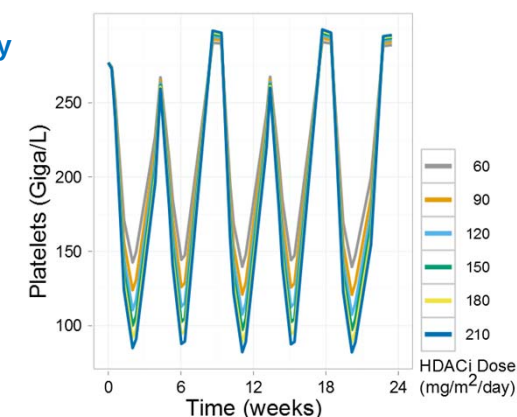


Fig.7: Simulation of higher HDACi doses

Conclusion

A PKPD model was developed that integrated the PK of HDACi and doxorubicin to describe their combined effects on the time-course of platelets. The thrombocytopenic effects were adequately predicted assuming an additive effect between the two drugs on the proliferative cells. Future refinements of the model and link to efficacy with tumor data are expected with additional dosing regimens.

References

- [1]. Lopez et al. Clin Cancer Res. 2009;15(10):3472-83.
- [2]. Yang et al. Cancer Chemother Pharmacol. 2011;67(2):439-46.
- [3]. Dansirikul et al. J Pharmacokinet Pharmacodyn. 2008;35(3):269-83
- [4]. Callies S. et al. Cancer Chemother Pharmacol. 2003; 51(2): 107-118.
- [5]. Chalret du Rieu et al. PAGE 21 (2012) Abstr 2503 [www.page-meeting.org/?abstract=2503]
- [6]. Friberg et al. J Clin Oncol. 2002;20(24):4713-21.
- [7]. Friberg and Karlsson. Invest New Drugs. 2003;21(2):183-94.