Modified model of drug induced thrombocytopenia efficiently projects safe starting dose in human from preclinical data

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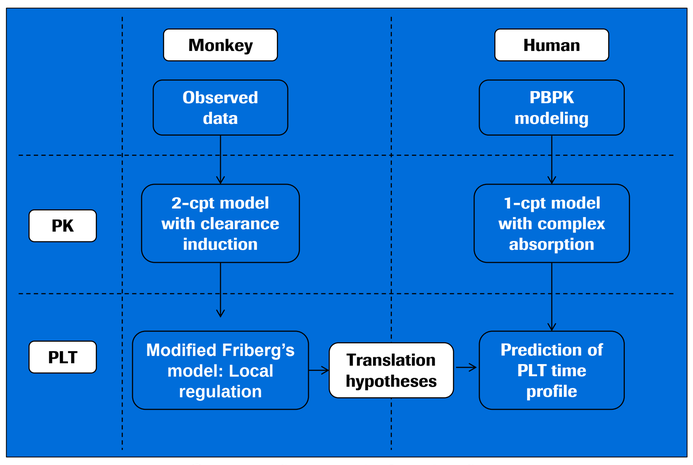
Introduction

RO_A is a new anticancer compound that caused thrombocytopenia in the cynomolgus monkey.
The aim of this study was:

- to guide the selection of a dosing regimen in humans
- to calculate the risk of grade 4 thrombocytopenia at the selected starting dose

A specific PK/PD model was developed to describe the effect of drug on the time-course of platelet (PLT) concentrations

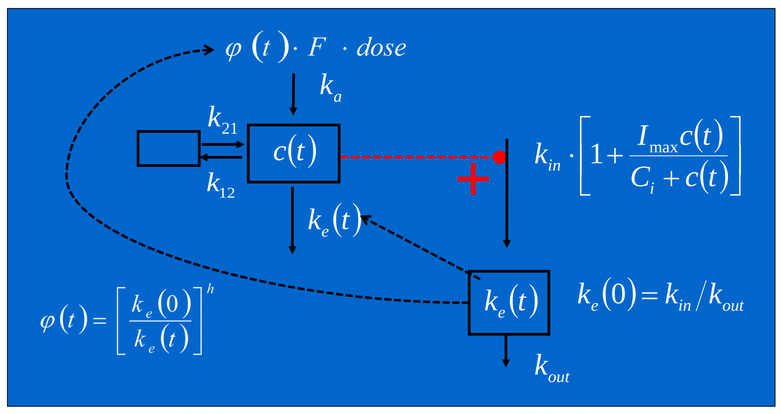


Strategy for translational safety

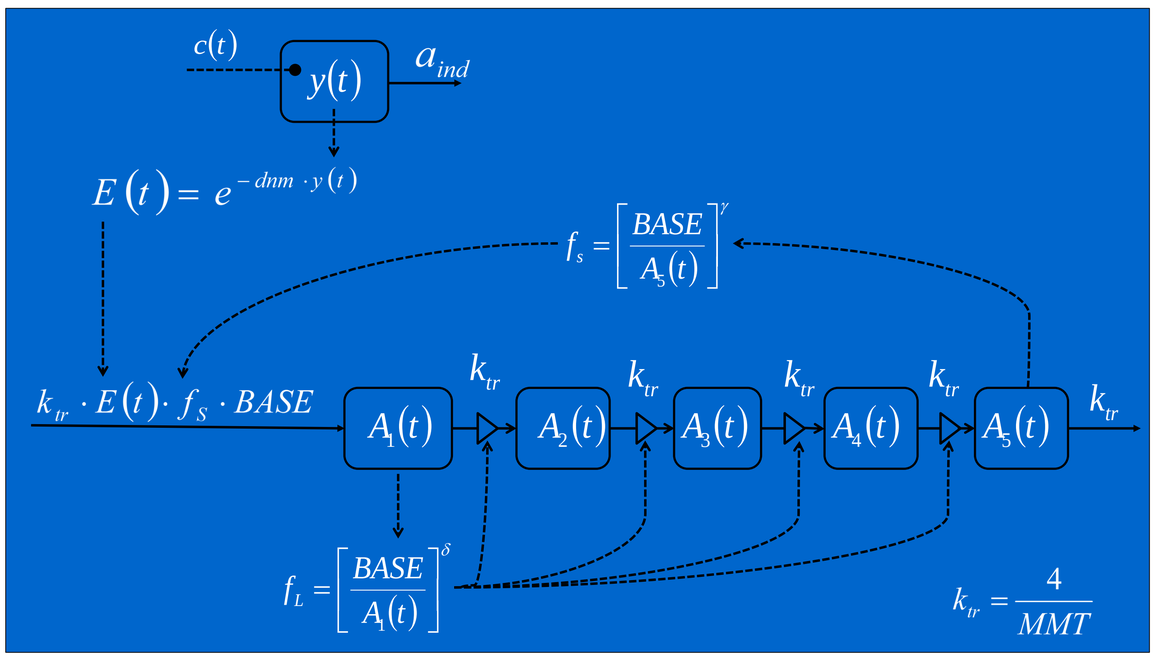
Materials & Methods

- The analysis included 244 PLT and 144 PK observations from 48 monkeys receiving single iv and repeated oral doses of RO_A ranging from 10 to 500 mg/Kg.
- Monkey PK was modeled using a 2-compartment model accounting for an enzyme induction effect
- The semi-mechanistic model quantifying hematotoxicity of anticancer agents was adapted from Friberg[1] as follows:
  - zero-order production of cells sensitive to treatment
  - addition of a local regulation mechanism, dependent of first compartment and affecting proliferation of cells in subsequent compartments
- The population approach was used to estimate PK and PD parameters with MONOLIX 3.2[2]
- Human PK of RO_A was predicted using physiologically based pharmacokinetic (PBPK) modeling in GastroPlus[3]. PBPK simulations for a range of pertinent doses were used to develop a one-compartment model with both linear and saturable absorption rates; this compartment model could be conveniently used with the PK/PD model to predict time-course PLT concentrations in humans administered RO_A

- Human PLT profiles were simulated with doses ranging from 30 to 2000 mg.
- The risk of grade 4 thrombocytopenia was assessed by Monte Carlo simulation.



PK induction model in monkey for RO_A



PD model for thrombocytopenia

Systemic regulation (f_S) associates circulating PLT in A_5 and production in first compartment A_1
Local regulation (f_L): associates cells in A_1 and amplification of transferred cells in the next compartments A_2 to A_5

Model equations

PK

Monkey

$C(t) = Qc/V$

$Q_a(0) = F\left[\frac{k_e(0)}{k_e(t)}\right]^h dose$

$\frac{dQ_a}{dt} = -k_a Q_a$

$\frac{dQ_c}{dt} = k_a Q_a - [k_e(t) + k_{12}]Q_c + k_2$

$\frac{dQ_p}{dt} = k_{12} Q_c - k_{21} Q_p$

$\frac{dk_e(t)}{dt} = k_{in}\left[1 + \frac{I_{max}\, c(t)}{C_i + c(t)}\right] - k_{out}\, k$

$k_e(0) = \frac{k_{in}}{k_{out}}$

Human

$C(t) = Qc/Vc$
$V_c = V \cdot \exp(0.00046 \cdot dose)$
$k_{ac} = k_a \cdot \exp(-0.000386 \cdot dose)$
$H = 4$
$G_{50} = 1080\ mg$
$k_{as} = 0.747 \cdot \exp(-0.000849 \cdot dose)$
$k_{anl} = k_{as} \cdot {G_{50}}^H / ({G_{50}}^H + {Q_a}^H)$

$\frac{dQ_a}{dt} = -(k_{ac}+k_{anl}) \cdot Q_a$

$\frac{dQ_c}{dt} = (k_{ac}+k_{anl}) \cdot Q_a - k_e \cdot Q_c$

PD

- Effect cpt:

$\frac{dy(t)}{dt} = -a_{ind} \cdot y(t) + \frac{c(t)}{1(4^5}$

- PDs:

$\frac{dA_1(t)}{dt} = -k_{tr} A_1(t) + k_{tr} \cdot BASE \cdot f_S \cdot exp[-dnm \cdot y(t)] \quad A_{1,i}(0) = BASE$

$\frac{dA_i(t)}{dt} = -k_{tr} \cdot A_i(t) + k_{tr} \cdot f_L \cdot A_{i-1}(t) \qquad i = 2{:}5$

  - Regulations:

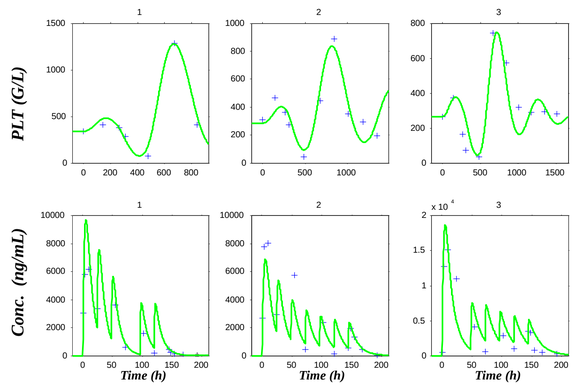
$f_S = \left[\frac{\mathrm{BASE}}{\mathrm{A_5}(t)}\right]^\gamma \qquad f_L = \left[\frac{\mathrm{BASE}}{\mathrm{A_1}(t)}\right]^\delta$

Results

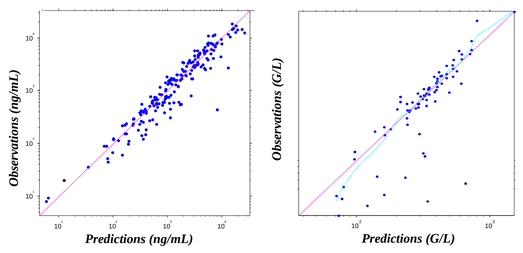
PK/PD model in CYNO

- Adding local regulation allowed a good description of a transient increase of PLT in monkeys. Thrombocytopenia including rebound was well described for all the dosing regimens.

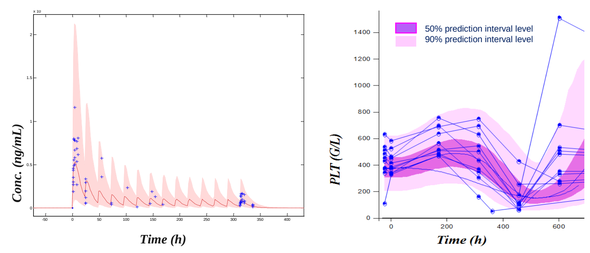
	Parameters		Fixed effects Estimation	r.s.e.(%)	Random effects Estimation	r.s.e.(%)	Description
PD	*MMT (h)*	:	**247**	5	**0.209**	17	Mean Maturation Time
	BASE (G/L)	:	**367**	4	**0.226**	14	PLT baseline
	aind (h-1)	:	**0.012**	22	**0**	×	Exit rate constant from effect compartment
	dnm (mL/µg)	:	**0.0228**	40	**0**	×	Drug toxicity potency
	γ	:	**1.97**	14	**0.302**	37	Systemic regulation exponent
	δ	:	**0.13**	7	**0.147**	52	Local regulation exponent
PK	*F*	:	**0.18**	×	**0.559**	18	Bioavailability
	ka (h-1)	:	**0.0739**	11	**0.339**	22	Absorption rate
	V (L/Kg)	:	**0.21**	16	**0**	×	Central volume of distribution
	ke (h-1)	:	**0.185**	27	**0**	×	Elimination rate constant
	kout (h-1)	:	**0.018**	25	**0.627**	24	Induction recovery rate
	Imax	:	**4.54**	55	**0.1**	×	Maximum induction factor
	Ci (ng/mL)	:	**218**	82	**0**	×	Threshold concentration for induction
	k12 (h-1)	:	**0.23**	×	**0**	×	Distribution rates
	k21 (h-1)	:	**0.19**	×	**0**	×	
	h	:	**0.886**	39	**0**	×	Bioavailbility induction exponent
Residual error	*b_1*	:	**0.362**	6			PK residual error model
	a_2 (G/L)	:	**15.9**	0			PD residual error model
	b_2	:	**0.175**	14			



Individual fit examples: PK (bottom row) and PD (top row)



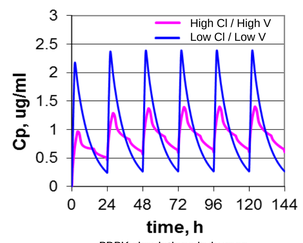
OBS vs. PRED using the individual parameters



Visual predictive check for 100 mg dose group

Translation to HUMAN

- Assumptions:
  - Monkey is a relevant specie for thrombocytopenia prediction
  - Same structural model of PLT is applicable both species
  - Physiological parameters are specific to the specie
  - Drug potency on progenitors is translational across species.
- PBPK model projections considered two scenarios (low Cl low V and High Cl and high V). Low Cl/ Low V simulations were used for conservative PK/PD projections
- PK/PD model in human:
  - System related parameters in human were obtained through the analysis of human data of a same class compound: 11 patients with complete PLT profiles
  - The effect cpt parameter aind was scaled allometrically



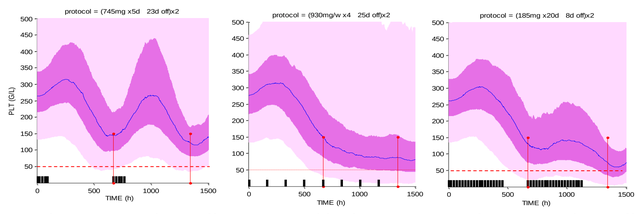
PBPK simulations in human

Parameter	Fixed effect	IIV
MMT (d)	**15.2**	0.3
BASE (G/L)	**270**	0.3
γ	**1.72**	0.5
aind (h-1)	**0.00609**	-
dnm (mL/µg)	**0.0228**	-
ka (h-1)	**0.916**	0.4
V	**0.0373**	0.4
ke (h-1)	**0.124**	0.2
δ	**0.1**	0.5

PK/PD parameters for simulations in human

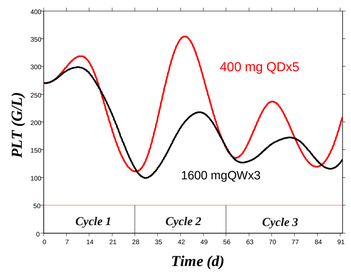
Dosing regimen selection

- Schedule impact on safety in human was simulated
- Concentrated administration allows better recovery than distributed dosing during the cycle



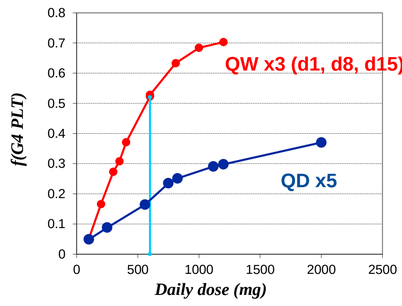
5 days on, 23 days off | Weekly dose | 20 days on, 8 days off

- Two regimens, once a day for 5 days (QDx5) and once a week for 3 weeks (QWx3) have been selected
- 400 mg QDx5 and 1600 mg QWx3 have close average concentrations during the cycle (641 versus 582 ng/mL)



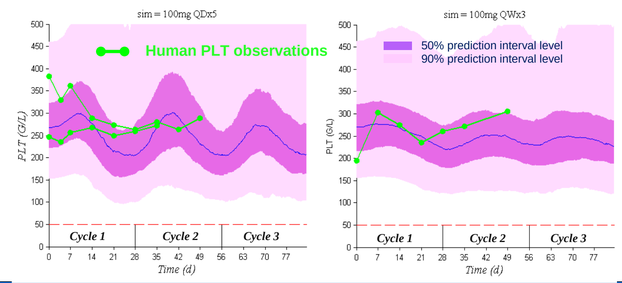
Risk of thrombocytopenia Grade 4

- At 100 mg, risk of grade 4 thrombocytopenia during the first 2 cycles was estimated to be 4%
  - For each dose level, 1000 simulations of 2 first cycles with PK and PD variability
  - Cycle duration: 28 days
- Support to adaptive design (dose-risk prior)



Overlay with clinical data at starting dose

- M&S supported 100mg starting dose
- Human PLT profiles are in line with the predictions
- The model predicted no thrombocytopenia was expected for the 100 mg dose, and none was observed



Conclusion

- A translational model for thrombocytopenia was successfully implemented in this anticancer project for human prediction.
- A local bone marrow regulation was implemented in the hematopoiesis model resulting in amplification of cell number in the maturation process
- Conservative PK variability was assumed. The worst case scenario was considered for the PBPK model. The model proved to correctly capture the platelet profiles in monkey and human
- A model based approach was successfully used to support the selection of the 100mg starting dose

References

1. Friberg L. et al. J Clin Oncol. 2002 Dec 15;20(24):4713-21
2. Kuhn E., Lavielle M. "Maximum likelihood estimation in nonlinear mixed effects models" Computational Statistics and Data Analysis, vol. 49, No. 4, pp 1020-1038, 2005
3. GastroPlus v6.1, www.simulations-plus.com

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