Population PK/PD modelling of platelet dynamics for dose selection in patients with haematological malignancies

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Introduction

Siremadlin – a MDM2 inhibitor

- Overexpression of murine double minute 2 (MDM2), a key negative regulator of the tumour suppressor protein p53, has been reported in a variety of cancers [1].
- Siremadlin, a MDM2 inhibitor, is being investigated as a new treatment for acute myeloid leukaemia (AML). The effect of siremadlin in patients with solid tumours has been previously reported, with delayed thrombocytopaenia being the primary dose-limiting toxicity [2].

Haematological malignancies and platelets

- The effect of siremadlin in patients with haematological malignancies, however, has not been fully evaluated. Specifically, the nature of the underlying disease may have different clinical manifestation of thrombocytopaenia than in solid tumour patients.
- A population PK/PD model characterising the relationship between the plasma pharmacokinetics (PK) of siremadlin and platelet counts in haematological patients can therefore be beneficial in supporting dose optimisation.

Objective

Model-informed dose optimisation

- This work aims to develop a population PK/PD model characterising the relationship between siremadlin plasma PK and platelet levels to support dose selection.

Methods

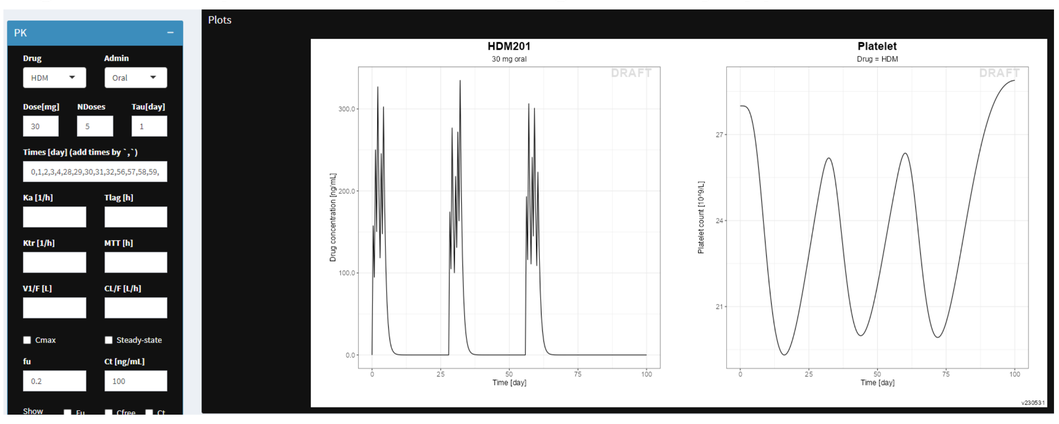
Model development

- Plasma drug concentrations and platelet data were obtained from a phase I study on patients with p53 wild-type solid tumours and haematological malignancies following different dosing regimens. Plasma drug concentrations and platelet data were analysed and modelled using a population approach in Monolix 2021R2.
- Previously, a population PK (PopPK) model was developed using the plasma PK data in the trial. The individual PK predictions from the PopPK model were used to drive drug effect on platelets. The platelet model was a cell maturation model adapted from Friberg et al (2002) [3] and different drug effect functions were evaluated.

Simulation

- During model evaluation, a Shiny application (Figure 1) [4,5] was developed to allow interactive exploration of the model and different dosing scenarios. Dosing regimens with different periods of drug holiday and number of cycles were evaluated.
- For the population simulation, Simulx was used and platelet profiles from 1000 virtual subjects were generated to assess the risk of thrombocytopaenia following siremadlin treatment from 5 to 40 mg QD for 5 days every 4 weeks for 6 cycles.

Figure 1 Example screenshot showing the Shiny application in action



Results

Modelling

- The plasma concentration-time profiles of siremadlin were well-described by a one-compartment disposition model with linear clearance (CL/F) and delayed absorption as described by a transit compartment model. Body weight was included as a covariate on volume of distribution (V/F) and the correlation between CL/F and V/F was considered (Figure 2, Table 1).
- Drug effect on platelets, driven by drug concentrations in the central compartment, was described by a drug effect function potentiating cell apoptosis in the proliferating precursor compartment representing bone marrow cells, leading to a reduced number of matured cells available for development into circulating platelets. Baseline platelet count (PLTZ) was noticeably lower than the ones in solid tumour patients (PLTZ: 28.0 vs 241 G/L) [2].

Figure 2 Schematic diagram of the PK/PD model

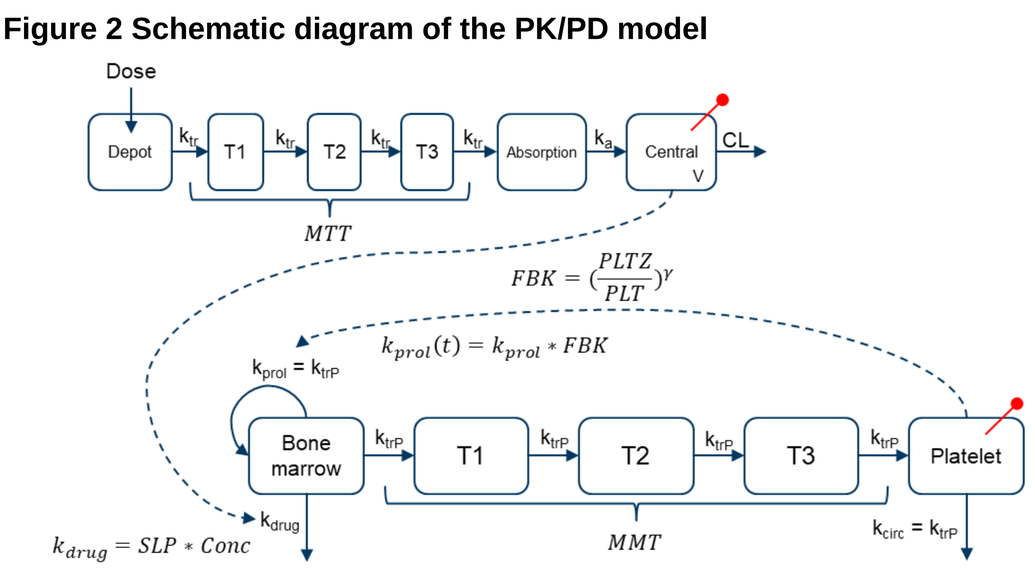


Table 1 Parameter estimates of the PK/PD model

Parameter	Unit	Description	Value (RSE%)	IIV (RSE%)
PK model				
Ktr	h^{-1}	Transit rate constant	6.28 (7.90)	0.618 (9.95)
MTT	h	Mean transit time	0.812 (4.06)	0.328 (8.35)
ka	h^{-1}	First order absorption rate constant	3.89 (17.8)	1.42 (9.44)
Cl/F	L/h	Apparent clearance	5.90 (4.20)	0.555 (5.76)
V/F	L	Apparent volume of distribution	116 (2.57)	0.315 (6.26)
beta_V_tBWKG	-	Body weight effect on V	0.888 (9.23)	-
corr_V_Cl	-	Correlation: V and CL	0.650 (7.85)	-
a1	ng/mL	Additive error	0.595 (15.6)	-
b1	-	Proportional error	0.346 (1.75)	-
PD model				
PLTZ	G/L	Baseline platelet count	28.0 (12.0)	0.864 (9.75)
MMT	h	Mean maturation time	177 (13.3)	0.673 (17.2)
gam	-	Sigmoidicity factor	0.145 (20.8)	0.883 (18.4)
SLP	-	Drug effect	0.000808 (15.2)	0.714 (15.0)
b2	-	Proportional error	0.346 (1.75)	-

NB: IIVs are reported in standard deviation scale.
IIV: Interindividual variability; RSE: Relative standard error

Simulation

- The model was able to simulate the delayed thrombocytopaenia resulting from different doses of siremadlin and showed that following a single cycle of treatment, platelet count decreased to the lowest level after approximately 15 days for a typical subject before a gradual recovery.
- Following different doses of siremadlin QD for 5 days every 4 weeks for 6 cycles, the dose level of siremadlin and baseline platelet count are the most influential factors on the proportion of patients with severe thrombocytopaenia (Figure 3).

Figure 3 Predicted platelet profiles following siremadlin treatment

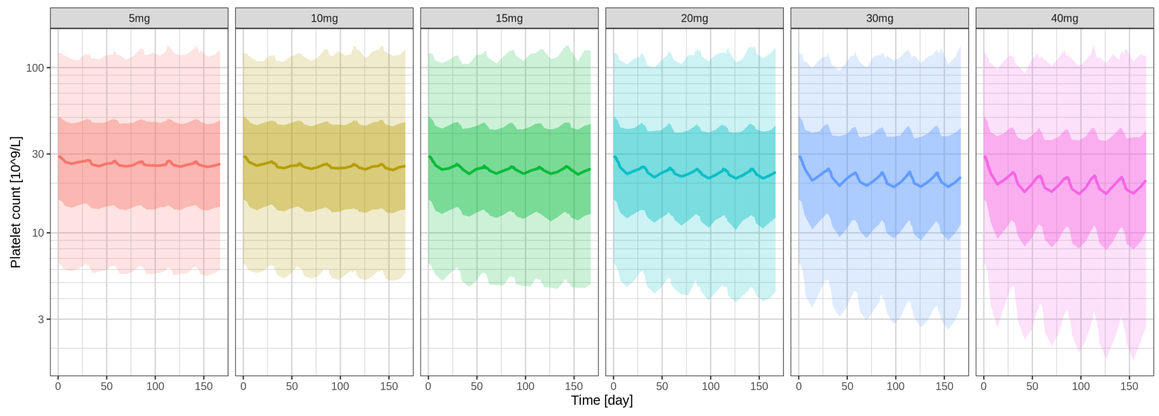


Figure 3. Predicted platelet profiles showing the median (line) and the 50% and 90% prediction intervals (shaded) computed from the virtual population (n=1000) following siremadlin treatment from 5 to 40 mg QD for 5 days every 4 weeks for 6 cycles.

Conclusions

Population PK/PD modelling for dose optimisation

- This work shows an application of a population PK/PD model with a safety endpoint in view of supporting dose selection, considering platelet dynamics and thrombocytopenia as a clinical constraint. Model development is ongoing to further support the evaluation of disease effect in haematological malignancies.

References

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