

The influence of erythrocyte accumulation on everolimus pharmacokinetics and pharmacodynamics in cancer patients

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Background

Everolimus is an anti-cancer drug from the class of mTOR-inhibitors and is used for treatment several solid malignancies, like breast cancer and renal cell carcinoma [1]. Everolimus pharmacokinetics toxicity and efficacy correlate with pharmacokinetics in the clinically relevant concentration range [2,3]. Everolimus extensively accumulates in erythrocytes and, therefore, hematocrit (HT) is a confounder for everolimus whole blood pharmacokinetics. HT is highly variable in cancer patients, but the impact of varying hematocrit on the PK/PD of everolimus remains unknown.

Objectives

- To develop a semi-physiological population pharmacokinetic model for everolimus in cancer patients.
- To investigate the impact of varying hematocrit on pharmacokinetics (PK) and pharmacodynamics (PD) of everolimus.

Methods

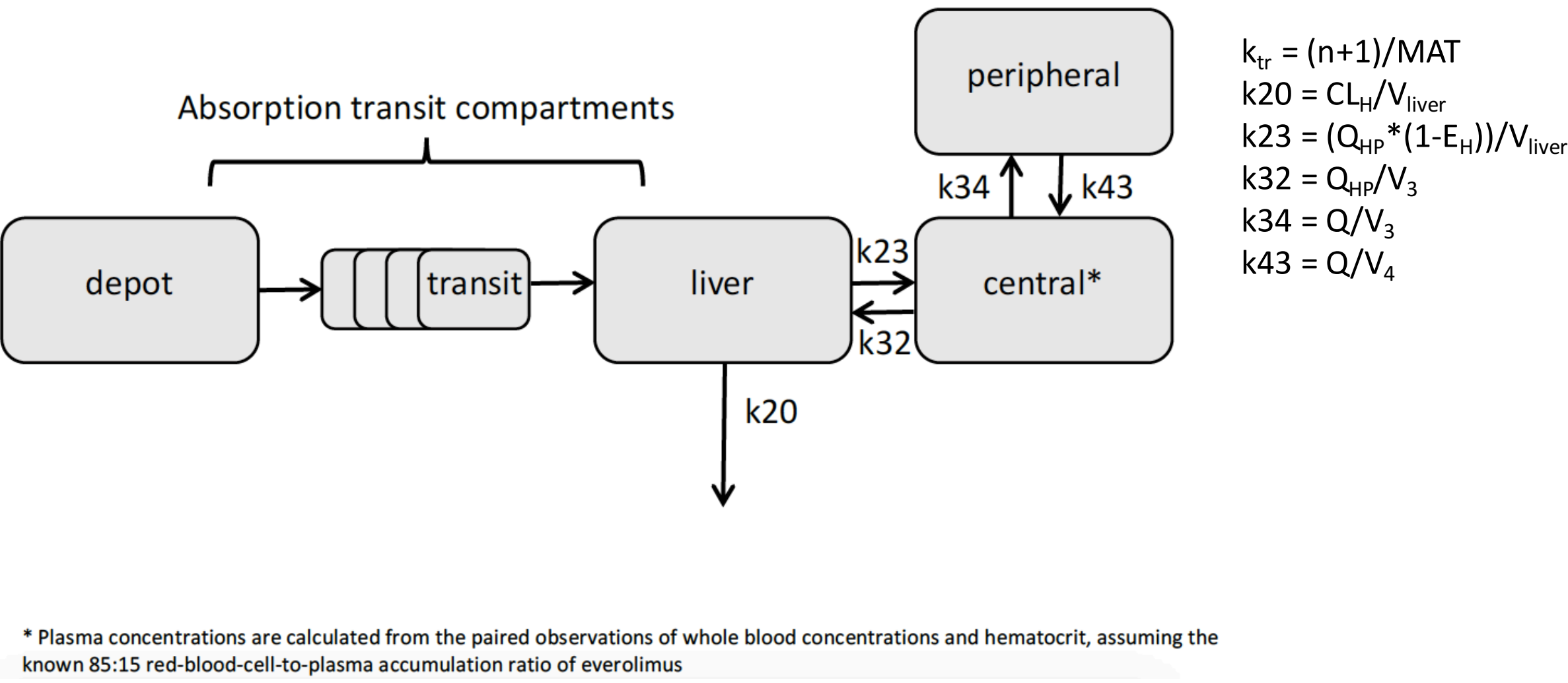
Study: Intensively sampled whole blood PK data were obtained from two clinical studies (915 time-concentration observations in 73 patients) studying everolimus in renal cell and breast carcinoma (clinicaltrials.gov identifiers NCT01118065 and NCT01948960).

PK analysis: All data were log-transformed and analysis was performed by means of semi-physiological non-linear mixed effects modelling with NONMEM V7.3. A well-stirred liver model as implemented to describe hepatic metabolism [4] and HT was introduced *a priori* as a predictor for plasma PK as demonstrated earlier for tacrolimus [5], assuming a known erythrocyte-to-plasma concentration ratio of 85:15 [6]. The unbound fraction in plasma was fixed to a known value of 27% [6]. Liver plasma flow (Q_{HP}) was assumed to be 90*HT L/h and liver volume (V_{liver}) was assumed to be 1 L.

Mean Absorption Time (MAT) trough a chain of transit compartments was estimated.

PK/PD simulation study: A previously developed PK/PD model [7] was used for simulation studies to explore the impact of hematocrit changes on inhibition of S6K1 (an mTOR downstream pathway), which was described with an E_{max} model: $S6K1 inhibition (\%) = I_{max} * C_u / (IC_{50} + C_u) \cdot I_{max}$, where IC_{50} , and C_u are the maximum S6K1 inhibition (97%) in tumor tissue, the unbound everolimus plasma concentration that inhibits 50% of S6K1 activity (0.05 ng/mL), and the unbound everolimus plasma concentration from the PK model, respectively. We simulated whole blood and plasma PK and S6K1 inhibition at steady state for a 10 mg QD dose at 20% and 45% hematocrit levels.

Figure 1 – Pharmacokinetic model



Results (continued)

Table 1 – Plasma pharmacokinetic parameters

Model parameter	Final model parameter estimates		Bootstrap results (n=500)	
	Estimate	Relative standard error of estimate (CV %)	Mean	Relative standard error (CV %)
Mean absorption time (MAT) through 4 transit compartments (h)	0.544	6.4%	0.549	8.4%
Intrinsic clearance (CL_{int}/F) (L/h)	198	4.3%	198	4.7%
Volume central compartment (V_3/F) (L)	207	5.0%	207	6.1%
Inter-compartmental clearance (Q) (L/h)	72.1	3.2%	72.9	5.0%
Volume peripheral compartment (V_4/F) (L)	485	4.2%	489	5.6%
IV mean absorption time (%)	62.0%	23.5%	61.8%	21.7%
IV intrinsic clearance (%)	38.9%	24.8%	37.0%	22.5%
IV volume central compartment (%)	36.1%	63.4%	35.9%	71.8%
Correlation between IV intrinsic clearance and volume of central compartment	0.347	90.6%	0.292	98.0%
IOV on relative bioavailability (F1)	15.2%	43.1%	15.8%	32.5%
Erythrocyte-to-plasma concentration ratio	85:15 (fixed)	-	-	-
Unbound fraction in plasma	0.27 (fixed)	-	-	-
Hepatic plasma flow (L/h)	90*HT (fixed)	-	-	-
Liver volume (L)	1 (fixed)	-	-	-
Residual error (%)	26.0%	20.8%	25.9%	18.2%

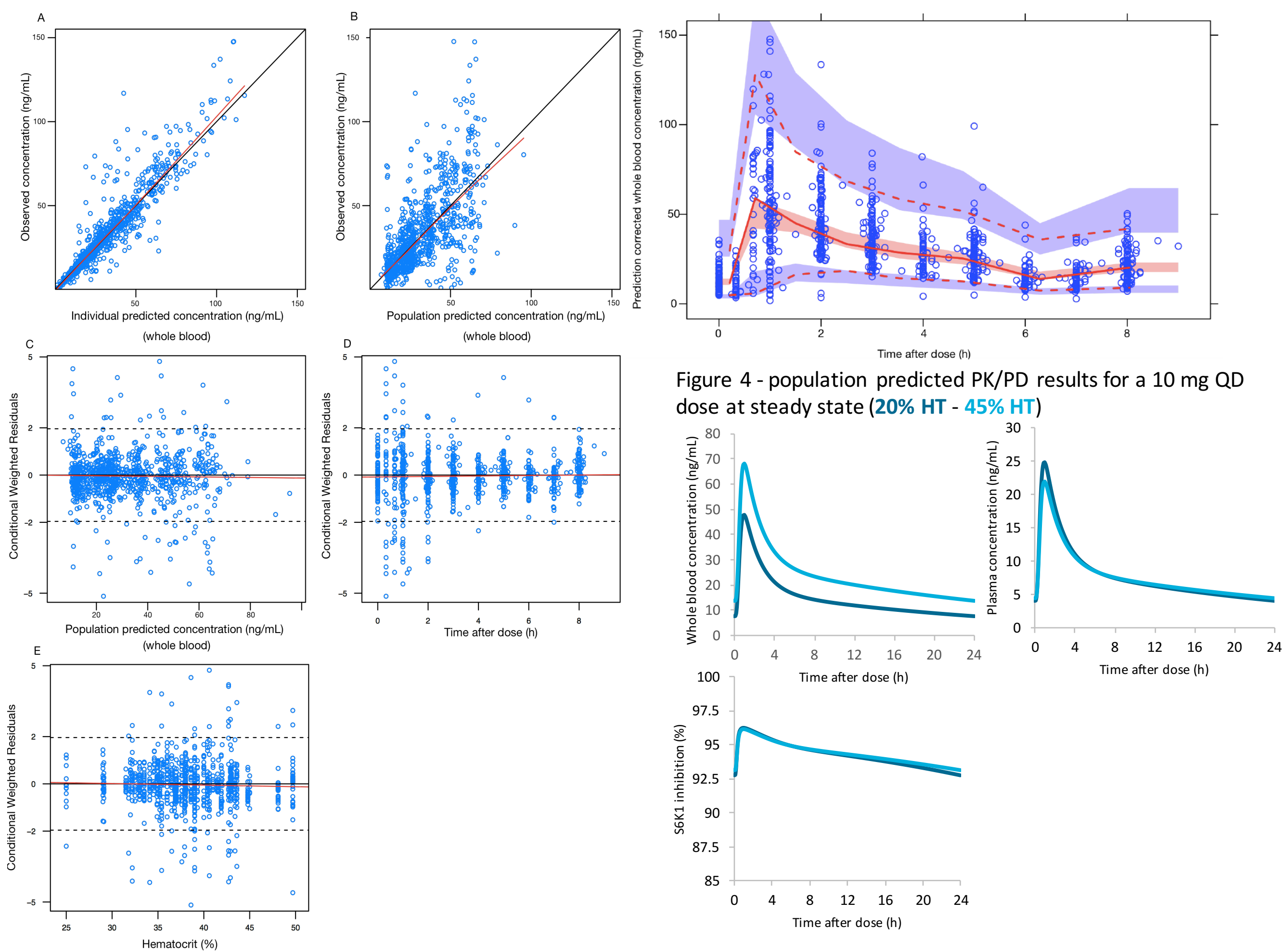


Table 2- Monte Carlo trough level simulations (n=2000) for 10 mg QD dose with varying hematocrit

hematocrit	20%			45%		
	Whole blood (ng/L)	Plasma (ng/L)	S6K1 inhibition (%)	Whole blood (ng/L)	Plasma (ng/L)	S6K1 inhibition (%)
Trough level	7.85	4.06	92.8	14.0	4.51	93.2
90% Prediction interval	3.31-18.7	1.71-9.65	87.5-95.2	6.19-30.6	2.00-9.86	88.9-95.2

As observed in the goodness of fit plots, our model captured the observed whole blood concentrations unbiased and precisely accross the hematocrit range. Our simulation results show that natural variation in the hematocrit level relevantly impacts whole blood pharmacokinetics, but not plasma pharmacokinetics or pharmacodynamics (S6K1 inhibition). Furthermore, at the approved dose of 10 mg QD, there is considerable pharmacokinetic variability but limited variability in S6K1 inhibition that was predicted to be at a plateau level.

Conclusions

- We have succesfully developed a semi-physiological population pharmacokinetic model for everolimus in patients with solid tumors.
- Variability in hematocrit relevantly impacts everolimus whole blood pharmacokinetics, but not its plasma pharmacokinetics or pharmacodynamics, showing that whole blood concentrations should preferably be corrected for hematocrit when performing pharmacological studies or therapeutic drug monitoring.
- S6K1 inhibition is predicted to be at a plateau phase in the approved dose. This warrants investigations for dose reductions in case of severe toxicity.

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