Development of Paclitaxel PBPK Model to Predict Tumour Concentration in Cancer Patients

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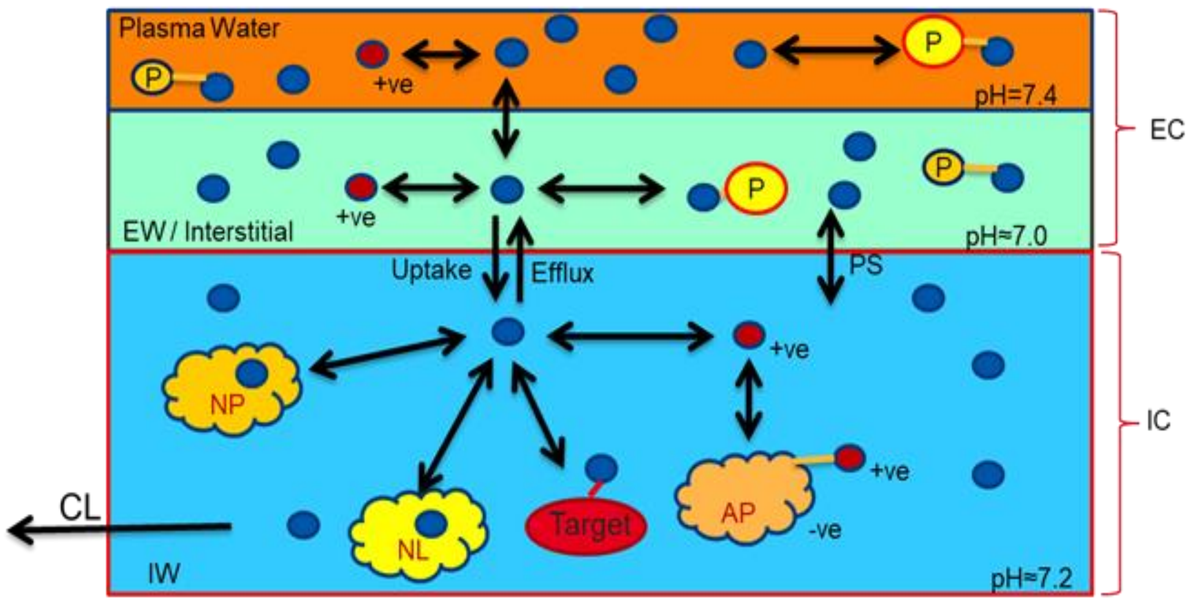
Background

Tubulin targeting drugs such as paclitaxel exert their effect intracellularly within tumor, thus sufficient intracellular drug concentrations are essential for a pharmacological response, and the ability to predict the concentrations of drug at site of action has the potential to improve dose and dosage regimen finding. This study aimed to build a PBPK model extended with a tissue composition based permeability limited tumor model to (a) gain a mechanistic understanding of the paclitaxel distribution in tumor and (b) to predict clinical tumor exposure in breast cancer patients.

Methods

A full PBPK model extended with a permeability-limited tumor model that integrates data on tumor composition and drug physiochemical properties was used to simulate paclitaxel plasma and tumour concentrations using the Simcyp Simulator V18.

The tumour is divided into extracellular (EC) and intracellular compartments (IC). The extracellular space is the sum of the interstitial space and the vascular space. The model assumes that unbound drug is in instantaneous equilibrium between the vascular and interstitial compartments, so that drug partitioning between these two spaces is governed by ionisation and concentration dependent nonlinear equilibrium binding to protein(s). The drug movement between the interstitial and intracellular space is via passive permeability (PS). Intracellular space is the sum of intracellular water, neutral lipids (NL), neutral phospholipids (NP) and the residual intracellular component (REM). Intracellular drug in various sub-compartments are also instantaneously at equilibrium so that concentration dependent nonlinear binding to these sub-compartments is governed by drug affinities, abundances (concentrations) of binding components which constitute these compartments and the concentration of drug. The nonlinear binding to all the components in the EC and IC compartments is calculated by the Simulator using the Newton-Rapson method.



A RES-Paclitaxel file which was developed in Simcyp Simulator using the Sim–Cancer population and verified with the clinical studies PK data at doses 80 mg/m^2, 135 mg/m^2 and 175 mg/m^2 (Figure 1) was used. "Generic Tumour" is selected as the tumour type so that that it receives a blood supply from the arterial compartments, and outflow is to the venous compartment. Clinical tumor physiological parameters such as volume, blood flow and tissue composition are defined using published data (Default values for tumor model in Simcyp Simulator V18), the published Intracellular tubulin concentration[2] and tubulin-binding affinity [3] determined in cell cultures were used. The PS for the tumour was calculated using passive intrinsic permeability (Ptrans0) predicted from Simcyp ADAM Mechanistic Permeability (MechPeff) model and surface area of tumour calculated from cell volume based calculations.

Results

Consistent with clinical data, where 4-70 fold higher drug concentration are measured in tumor biopsy compared to plasma taken at ~ 20 hours after initiation of a 3 hour 175 mg/m^2 infusion in six previously untreated locally advanced breast cancer patients[4], the model predicts a 28.9 – 76.8 fold higher tumor exposure relative to plasma at 20 hours in six female patients (Figure 2 & 3B). A 48.5 fold change in the fraction unbound in the intracellular space was observed (Figure 3A), indicating concentration dependent nonlinear binding of paclitaxel to tubulin, and from sensitivity analysis, drug accumulation in tumour was found to be highly sensitive to the tubulin concentration, therefore inter-individual difference in the tubulin concentrations could be one of the reasons for observed variability in drug accumulation in tumour. The high variability in the observed tumour concentrations could also be a result of difference in P-glycoprotein expression in the patients, as paclitaxel is a substrate for P-glycoprotein, however tumour P-gp efflux has not been accounted in this study due to lack of absolute abundance data.

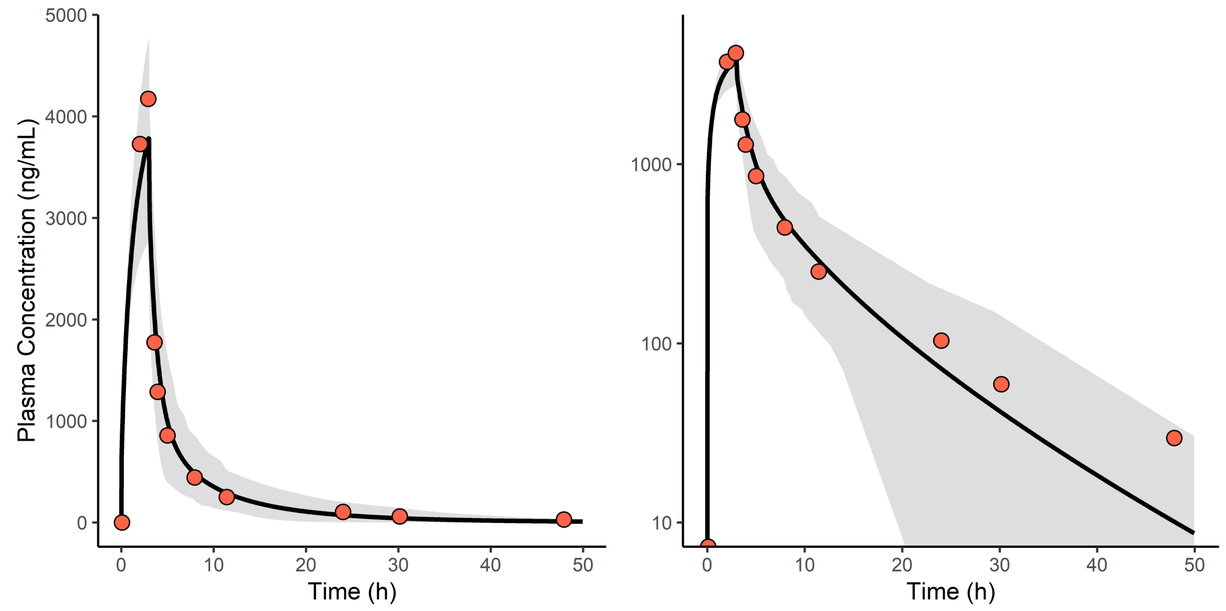


Figure 1. Simulated (black line) and observed (data points [1]) mean plasma concentration-time profile of paclitaxel after an intravenous dose (175 mg/m^2 infused over 3 hours). Shaded area represent the 5th and 95th percentile of the total virtual population (10 trials x 8 subjects; 48 – 72 years, 24% female).

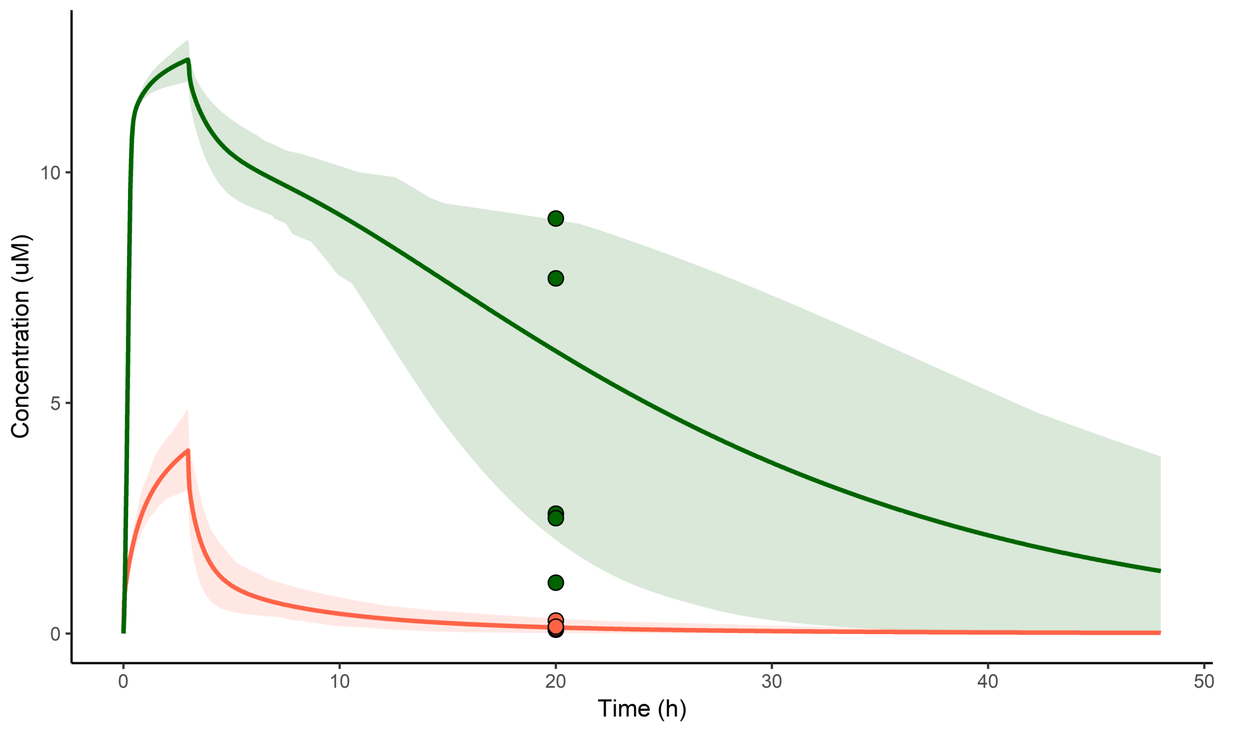


Figure 2. Simulated mean plasma (Red) and total whole tumour (Green) concentration profiles of paclitaxel after an intravenous dose (175 mg/m2 infused over 3 hours). Circles are observed individual values [4]. Shaded area represent the 5th and 95th percentile of the total virtual population (10 trials x 6 subjects; 42 – 65 vears. 100% female).

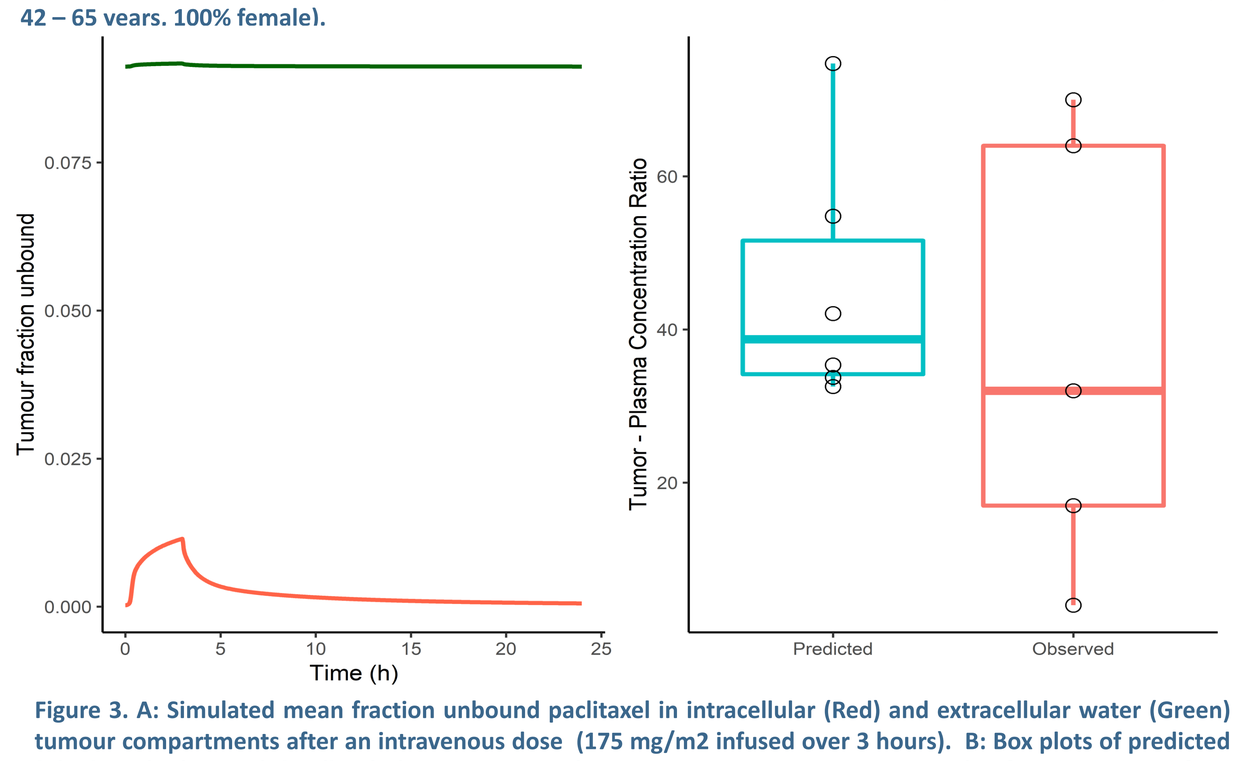


Figure 3. A: Simulated mean fraction unbound paclitaxel in intracellular (Red) and extracellular water (Green) tumour compartments after an intravenous dose (175 mg/m2 infused over 3 hours). B: Box plots of predicted (Blue) and observed (Red) whole tumour to plasma concentration ratios at 20 h after initiation of an intravenous dose (175 mg/m2 infused over 3 hours) (1 trials x 6 subjects; 42 – 65 years, 100% female). Circles are individual values.

Conclusions

PBPK modelling offers an approach to investigate the drug exposure in the total tumour tissue and the tumour intracellular compartment. The ability to predict accurately the pharmacologically active operating concentration can facilitate understanding of the molecular mechanism of drug action and can be used to optimise study design and translational modelling.

References

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