Integration of a Tumour Growth Inhibition Model within a Mouse Physiologically-Based Pharmacokinetic Model

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Background

Erlotinib is a tyrosine kinase inhibitor which exerts its action intracellularly. Integrating the dynamic tumour growth inhibition within the physiologically-based pharmacokinetic (PBPK) model allows to better understanding of drug kinetics and investigation of the operative concentration. The **objective** of this work is to build a tumour model in mice and predict local drug concentration at site of action using erlotinib as a probe and to predict tumour volume after modifying the dosing regimen.

Methods

A compound file for erlotinib in mice was built within the Simcyp Animal Simulator V18 that includes a permeability-limited tumour model. Published parameter values for erlotinib absorption and clearance [1] as well as tissues-to-plasma partition ratio (Kp) for brain, liver, kidney, heart and lung [2] were used during model building. Other tissues Kps were predicted within the simulator [3] and scaled by 5 to match the reported overall distribution volume [1]. The passive permeability (PS) for the tumour was optimized to describe the reported tumour homogenate concentration after the first dose of 100 mg/kg [1]. No target binding was considered, while binding to cellular acidic phospholipids, neutral lipids and neutral phospholipids was predicted and included in the model. The Simeoni model built-in within the simulator was used to describe the natural growth of the tumour in the absence of the drug using published parameters [1]. Tumour growth inhibition (TGI) effect after pulsed dosing of 100mg/kg/day was assumed to have a linear inhibition rate (k2) on the tumour growth using the predicted intracellular free drug concentration. The k2 value was estimated using reported TGI data for the 100mg/kg dosing schedule. The established TGI model was used to predict tumour volume after continuous administration of 6.25 and 25 mg/kg/day and compared to observations [1].

Results

Predicted plasma concentrations after single and multiple doses of 100mg/kg match observations [1] reasonably well (Figure 1 A & C). Prediction of erlotinib concentration in tumour tissue homogenate after single dose of 100mg/kg is given in Figure 1B. Estimated parameter values for PS and k2 were 0.1 ml/min/ml of tumour volume, and 0.7 1/uM*day, respectively. The model was able to predict tumour growth in the control and after inhibition after both 25 and 6.25 mg/kg adequately (Figure 2). PBPK Predicted vs original predicted [1] mean % TGI defined as

$$\% \text{ TGI} = ((TV_{control} - TV_{treated})/TV_{control}) \times 100$$

for all the investigated doses, ie., 100, 25 and 6.25 mg/kg at the end of the dosing regieme (on day 16) were 67 (vs 83), 38 (vs 56) and 11 (vs 18) %, respectively. Comparison between predicted erlotinib concentration in mice plasma, whole tumour tissue and unbound concentration in the intracellular compartment are given in Figure 3.

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 be used to optimise study design and translational modelling .

References

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[3] Rodgers T et al. Physiologically based pharmacokinetic modelling 2: predicting the tissue distribution of acids, very weak bases, neutrals and zwitterions. J Pharm Sci. 2006;95(6):1238-57.

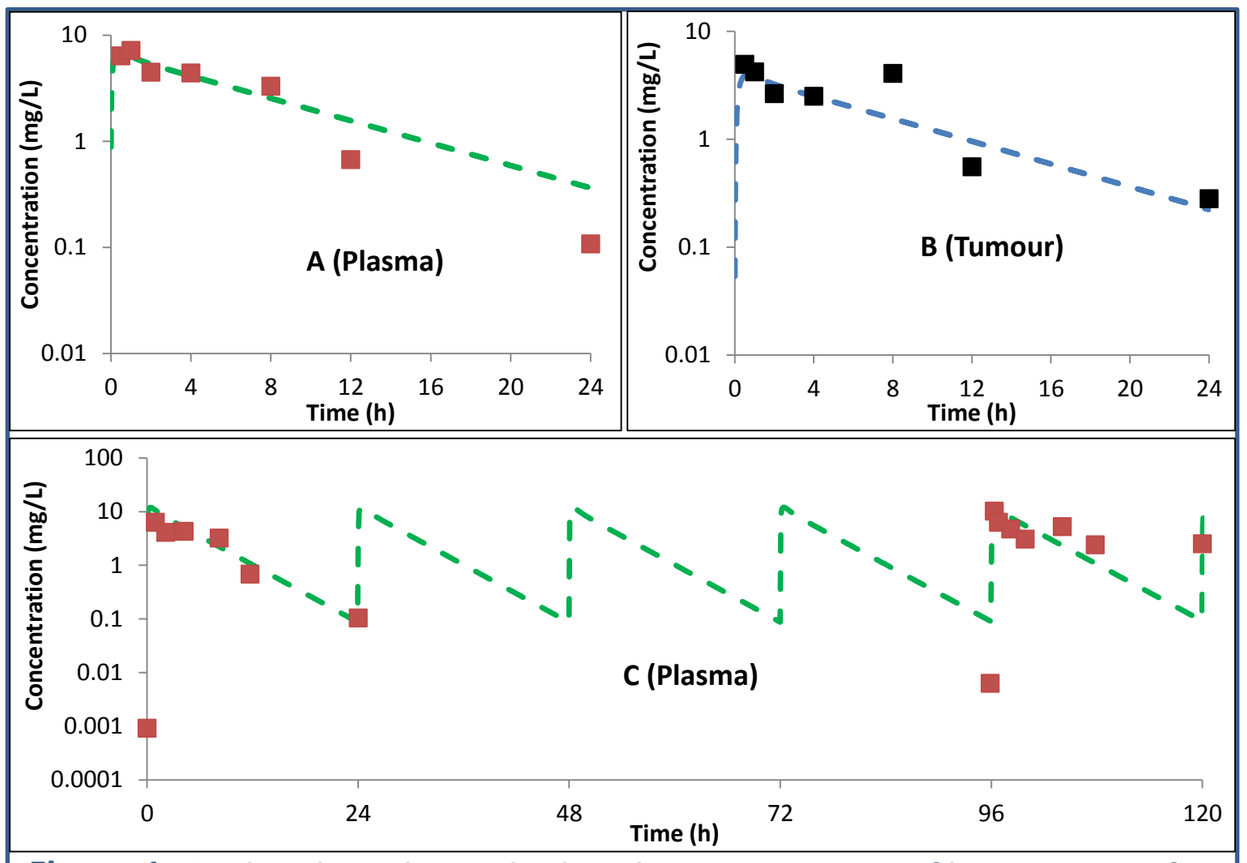

Figure 1. Predicted vs Observed erlotinib concentration profiles in mouse after single (A: Plasma, B: Tumour tissue homogenate) and multiple (C: Plasma) oral doses of 100mg/kg. Lines are predicted and squares are observations [1]

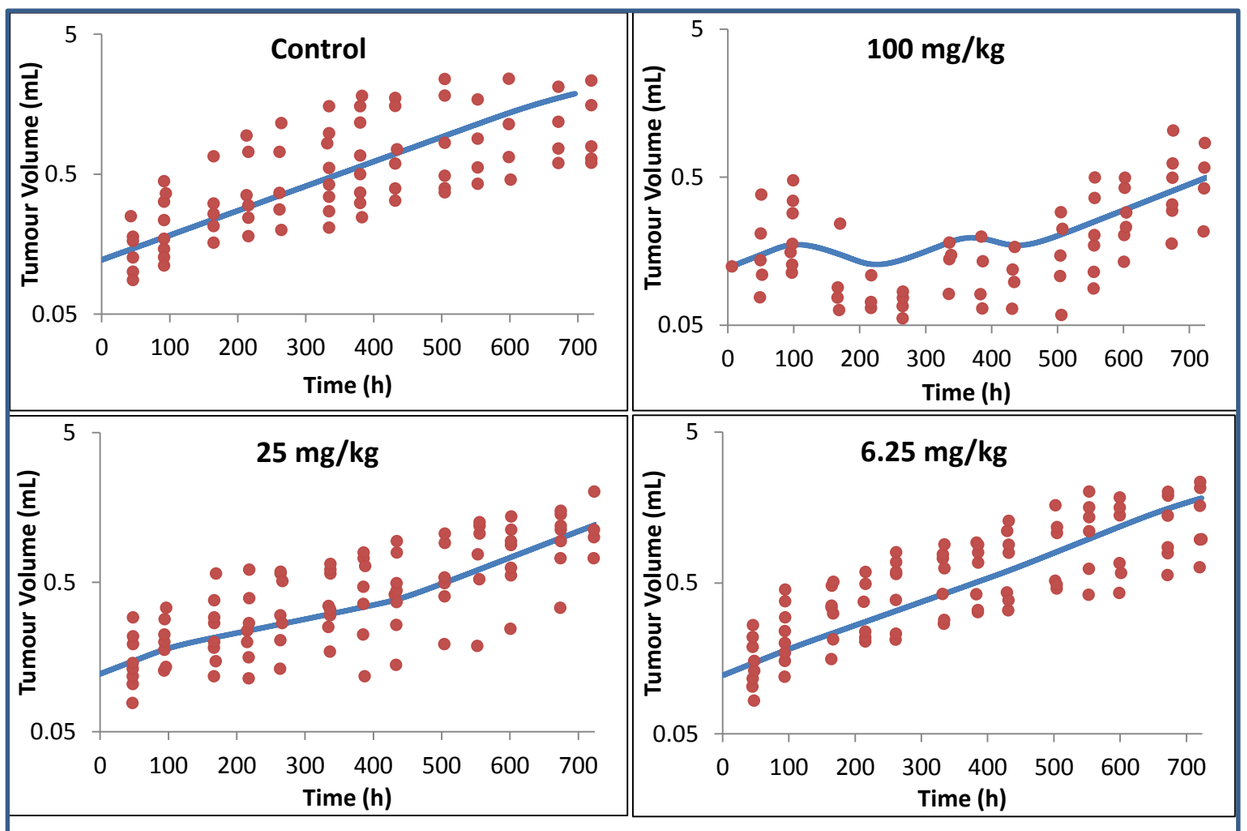

Figure 2. Prediction of Tumour volume in mice using growth inhibition model after different oral doses . Circles are observed values [1].

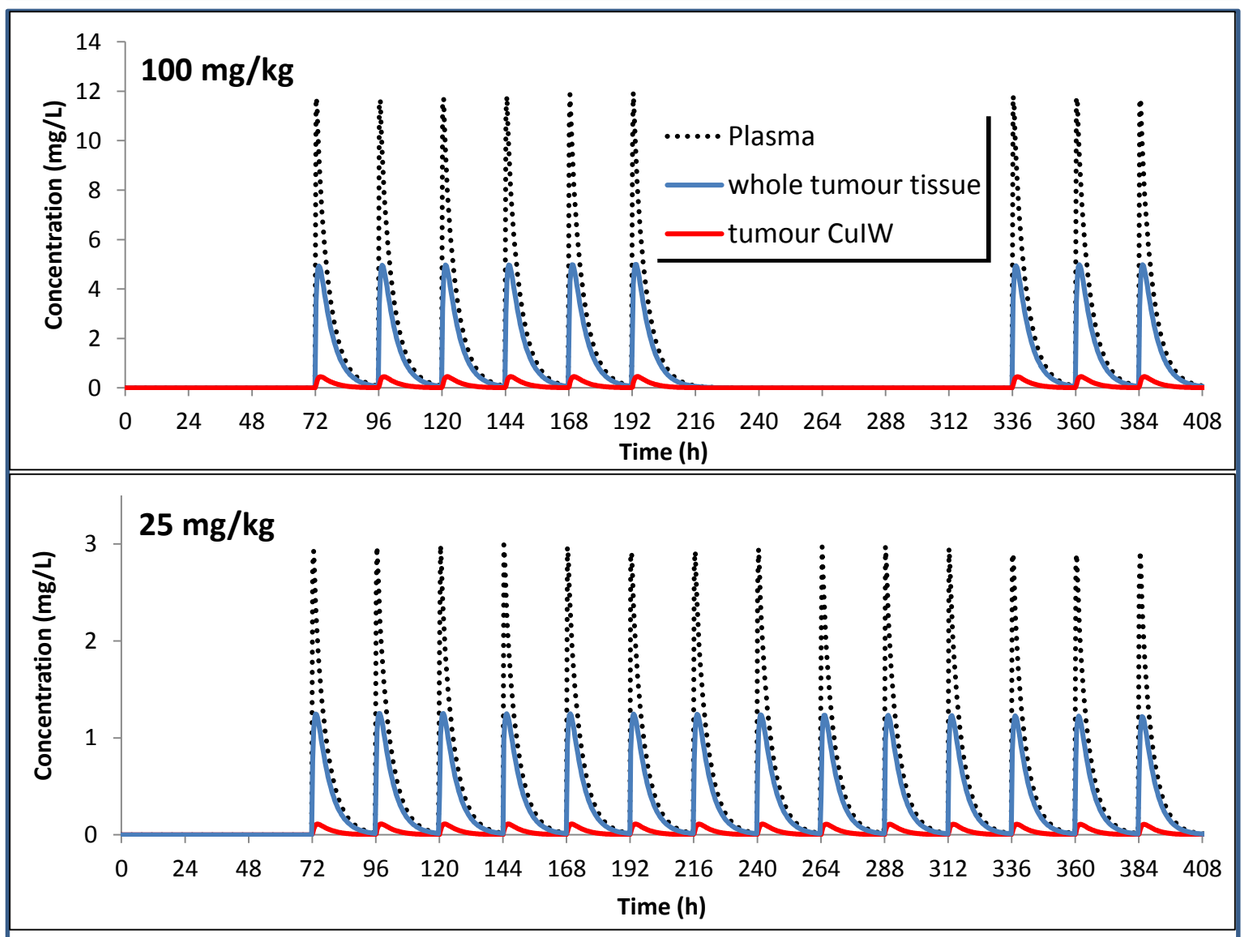

Figure 3. Comparison between predicted erlotinib concentration in mouse plasma, whole tumour tissue and unbound concentration in the intracellular compartment.