APPLICATION OF PBPK MODELING TO ASSESS THE VICTIM DDI POTENTIAL OF PACLITAXEL IN ONCOLOGY COMBINATION THERAPIES

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Introduction

- Paclitaxel is the backbone of standard chemotherapeutic regimens used in a number of malignancies. It is cleared through CYP2C8, CYP3A4 and P-gp mediated pathways.
- Newly developed oncolytic agents, including tyrosine kinase inhibitors are often shown to be CYP3A4 and P-gp inhibitors.
- Therefore, it is of interest to assess *a priori* the combination of new agents and paclitaxel with respect to pharmacokinetic (PK) interactions.

Aims

- The aim of this study was to develop a PBPK model for intravenously administered paclitaxel to estimate the DDI potential as a victim.

Methods

- Non-linear pharmacokinetics in the dose range of 60-200 mg/m^2 has been reported, and this apparent non-linearity has been largely attributed to formulation effects (i.e., cremophor).
- For model qualification purposes, two paclitaxel models were developed: the 135 mg/m^2 model and the 175 mg/m^2 model.
- *In vitro* data (Wang et al., *Drug Metab Dispos* 2014) were used initially to assign the fraction metabolized (fm) by CYP2C8 and CYP3A4 as 73% and 9%, respectively.
- To verify fm_{CYP2C8}, the pharmacogenetic effect of CYP2C8 on paclitaxel PK (175 mg/m^2) was assessed (Bergmann *Pharmacogenomics* 2011). The reported 58% reduction in CYP2C8*3 variant intrinsic activity determined *in vitro* was incorporated in the model.
- To verify fm_{CYP3A4}, DDI data were utilized to investigate the effect of

  a) the CYP3A4 and P-gp inhibitor R-verapamil (225 mg every 4 h for total of 12 doses) on paclitaxel (200 mg/m^2 3-h infusion on day 2) (Berg *J Clin Oncol* 1995); R-verapamil model incorporated *in vitro* data on CYP3A4 inactivation (K_I:2.21 µM and k_{inact}:2.0 hr^{-1}), CYP2C8 inactivation (K_I:17.5 µM and k_{inact} : 3.9 hr^{-1}) and hepatic P-gp inhibition (K_i: 0.1 µM).

  b) the CYP3A4 inhibitor pazopanib (800 mg QD for 21 days) on paclitaxel (135-175 mg/m^2 3-h infusion on day 21) (Kendra *Mol Cancer Ther* 2015). The pazopanib model incorporated *in vitro* data on CYP3A4 inactivation (K_I:2.9 µM and k_{inact}:1.26 hr^{-1} (Kenney et al., *Pharm Res* 2012)

Table 1. Initial input parameter values used to simulate the kinetics of paclitaxel 175 mg/m^2

Parameter Name	Value	Method/Source
Phys Chem and Blood Binding		
MW (g/mol)	853.9	Product label (Bristol-Myers-Squibb, 2015)
logP	3.54	Predicted, Chemaxon
Compound type	Neutral	Reported (Wattanachai et al., 2011)
B/P	0.69	Reported (Sparreboom et al., 1999), dose-dependent due to formulation effect
fu_p	0.054	Time-averaged value determined in patient plasma samples (Brouwer et al., 2000)
Main plasma binding protein	Albumin	Reported (Wattanachai et al., 2011)
Distribution		
Model	Full PBPK	
Vss – predicted (L/kg)	1.3	Global Kp scalar of 0.155 was applied to match the observed Vss (Brouwer et al., 2000)
Elimination		
CL_{IV} (L/h)	23.6 (40%)	Weighted mean literature value using clinical PK data obtained following 175 mg/m^2 paclitaxel administered as a 3-h infusion (n=99 subjects)
Enzyme kinetics – CYP2C8 CLint (µl/min/pmol)	5.0	Retrograde calculation– assign 85% of hepatic CL (Wang et al., 2014)
Enzyme kinetics – CYP3A4 CLint (µl/min/pmol)	0.1	Retrograde calculation– assign 10% of hepatic CL (Wang et al., 2014)
Biliary CL (µl/min/millions)	2.72	Assign 5% of hepatic CL based on mass balance data (Bristol-Myers-Squibb, 2015)
CL_R (L/h)	3.4	Estimated from literature data (Walle et al., 1995)

Results

- Two paclitaxel models which allowed recovery of the observed paclitaxel non-linear pharmacokinetics following 135 and 175 mg/m^2 given as a 3-h infusion were developed.
- The paclitaxel base model predicted 15% reduction in paclitaxel CL in CYP2C8 *1/*3 individuals, which was comparable to the observed reduction of 11.4%.

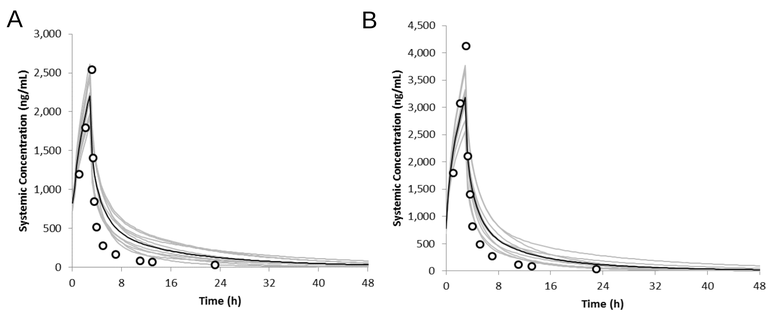

Fig. 1. Simulated (solid black line) and observed (data points; Tan et al., 2010; Brouwer et al., 2000) mean plasma concentrations of paclitaxel following a single 135 mg/m^2 (A) or 175 mg/m^2 3-h infusion (B). The solid grey lines are the individual trials.

Results Cont'

- The R-verapamil model was qualified against observed PK data (Fig. 2A).
- The "fit-for-purpose" pazopanib model was qualified against observed PK data (Fig.2B). The CYP3A4 k_{inact} was optimized from 1.26 hr^{-1} to 0.22 hr^{-1} to recover the observed midazolam AUCR of 1.35 (Goh et al., 2010).

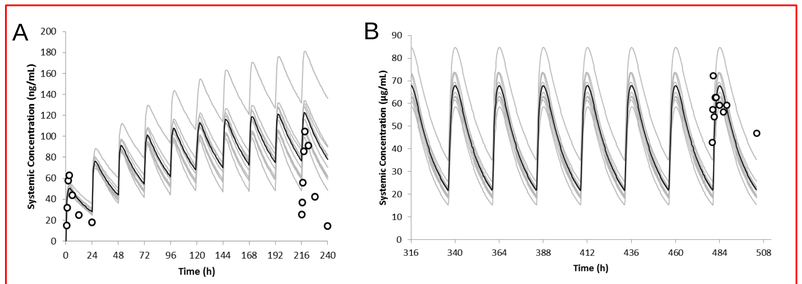

Fig. 2. A) Simulated (solid black line) and observed (data points; Lemma et al., 2006) mean plasma concentrations of R-verapamil on day 1 and day 10 following daily oral dosing of 120 mg R-verapamil to healthy volunteers. B) Simulated (solid black line) and observed (data points; Plummer et al., 2013) mean plasma concentrations of pazopanib on day 21 following daily oral dosing of 800 mg pazopanib to oncology patients.

- DDI predictions between paclitaxel and R-verapamil/pazopanib indicated that fm_{CYP3A4} and fm_{CYP2C8} are likely to be 30% and 50%, respectively, and the overall contribution of P-gp (hepatic+renal) is approximately 20%.

  a) the predicted paclitaxel (200 mg/m^2) AUCR due to R-verapamil treatment was 1.61, compared to the observed paclitaxel AUC ratio of 1.76.

  b) the predicted paclitaxel (175 mg/m^2) AUCR due to pazopanib treatment was 1.20 (trial range 1.16-1.27), compared to the observed paclitaxel AUCR of 1.26-1.41.

Conclusions

PBPK modeling using robust qualified models allows *a priori* prediction of DDIs involving complex combination therapies which are often utilized in an oncology setting.

References

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