Pharmacokinetic-Directed Dosing of Vandetanib and Docetaxel in a Mouse Model of Human Squamous Cell Carcinoma

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Supplementary Information

Docetaxel Pharmacokinetic Study. For the development and validation of a PBPK model for intraperitoneal (IP) injection of DTX a plasma and tissue distribution study of DTX was conducted in mice at doses of 10 mg/kg, 20 mg/kg and 40 mg/kg. DTX was administered by IP injection as a single bolus dose. Three mice were sacrificed at 5, 15, 30 min and 1, 2, 4, 8, and 24 hours by cardiac stick exsanguinations under isoflurane anesthesia. Analysis of DTX in plasma and tissues was done using an LC/MS/MS method based on a previously established method from our laboratory (1,2).

PBPK Model Development:

We developed a flow-limed model for docetaxel plasma and tissue distribution following IP administration utilizing seven compartments; liver, intestine, kidney, slowly perfused tissues, rapidly perfused tissues, blood and an ip cavity. The liver, kidney and intestine were specific compartments utilized since these are the organs primarily responsible for metabolism and excretion of

docetaxel. An IP compartment was added to serve as a reservoir for absorption of docetaxel to the liver, intestine and directly into the blood. Grouping the remaining tissues into rapidly perfused and slowly perfused compartments minimized complexity of the model while still allowing for accurate prediction of a range of doses of docetaxel. A schematic representation of the PBPK model is shown in figure S1. Since DTX was delivered to the peritoneal cavity, we assumed that the majority of the drug would be absorbed directly through the intestine, liver and blood. We assumed first order absorption of DTX, which was initially estimated from linear regression of the absorption phase of the DTX time-course distribution. The absorbance rate constants used in the model were 1.2, 1.5 and 1.5 h^{-1} for the intestine, liver and blood respectively (Table S2). Simple timing commands were also added to the IP DTX model and the IV DTX to allow for repeated dosing. The predictive capability of the model was determined by calculation of performance errors as well as comparison of PK parameters calculated from simulation data to actual data.

The PBPK model was written and simulations conducted with Advanced Continuous Simulation Language (ACSL) Tox version 11.8.4 (AEgis Technologies Group, Inc., Huntsville, AL) on a PC-based computer. PK modeling and calculation of PK parameters was performed with WinNonlin version 4.1 (Pharsight Corp.).

Validation of IP PBPK Model

To validate the change in the route of administration made to the PBPK model, we performed a PK study in female balb/c mice to obtain docetaxel plasma and tissue concentrations after a single IP dose of 10, 20 or 40 mg/kg. The median absolute performance error (MAPE%) was calculated to determine the predictive accuracy of the modified PBPK model (2,3). The MAPE% values for plasma varied between 55.4 and 84.3% and the CV% of the actual measured data sets for plasma ranged from 55.4 to 104.5%. This indicates that the model predictions are generally within the dispersion of the data set. The MAPE% for simulations of intestinal docetaxel levels varied from 35.7 to 62.0% and the CV% of the actual measured data sets ranged from 12.7 to 73.5%. The MAPE% for the IP simulations indicates that our modified PBPK model generates simulations that reasonably predict actual data.

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(4) Brown R, Delp M, Lindsted S, Rhomberg L, Beliles R. Physiological parameter values for physiologically based pharmacokinetic models. Toxicol Ind Health 1997;13:407-484.

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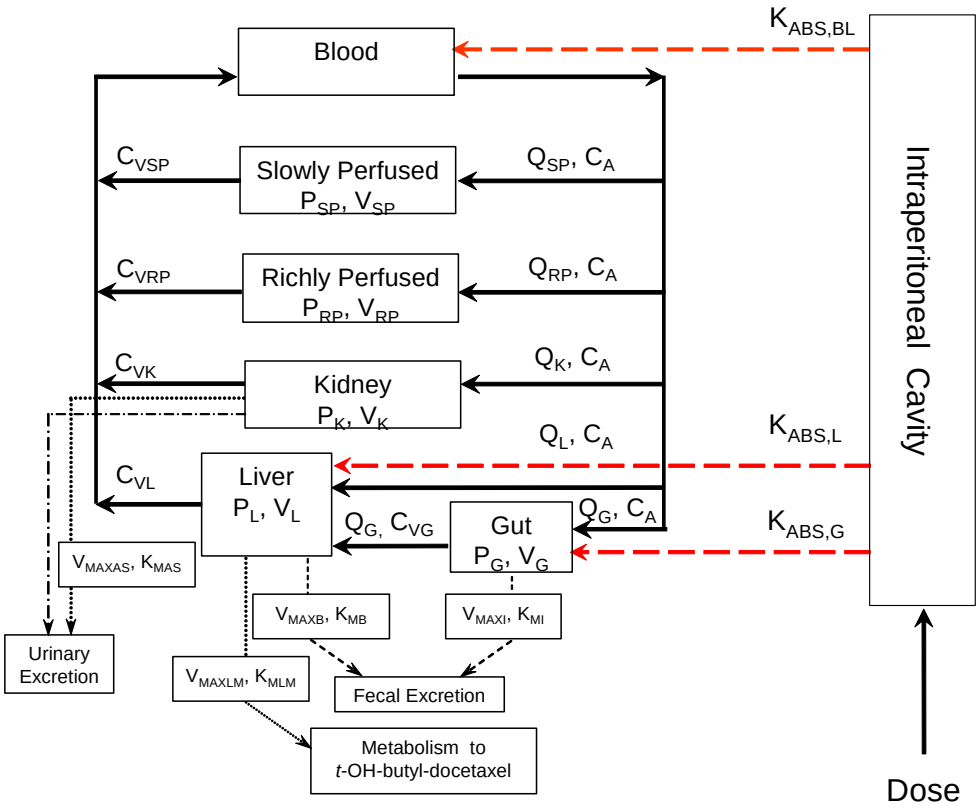

Figure S1. Schematic representation of a PBPK model for docetaxel with IP administration. Values used for compartment parameters are shown in Table S1 and Table S2.

Table S1. Mouse Organ Weight Parameters*	
Organ Volume (% of body weight)	
Blood	4.9
Liver	5.5
Gut	4.2
Kidney	1.7
Slowly Perfused	74.3
Rapidly Perfused	9.4
Organ Blood Flow (% of cardiac output)	
Liver	2.0
Gut	14.1
Kidney	9.1
Slowly Perfused	40.0
Rapidly Perfused	34.8

*Physiologic parameters were obtained from Brown *et al* (4).

Table S2. PBPK Model Parameters		
Parameter	Notation (Units)	Value
Absorption Rate Constants	$K_{ABS, BL}$ (h^{-1})	1.5
	$K_{ABS, L}$	1.5
	$K_{ABS, G}$	1.2
Liver Metabolism*	K_{mLM} (nM)	5000
	V_{maxLM} (nM/h)	5×10^6
Fecal Elimination†		
Biliary Transport	K_{mB} (nM)	75
	V_{maxB} (nM/h)	1.5×10^4
Intestinal Transport	K_{mI} (nM)	75
	V_{maxI} (nM/h)	1.5×10^4
Urinary Excretion†		
Active Secretion	K_{mAS} (nM)	75
	V_{maxAS} (nM/h)	1.5×10^5
Fractional Blood Flow Cleared	KGF	0.1
Plasma Protein Binding‡	KAB	0.9
Intracellular Binding Affinity§	K_D (nM)	10
Intracellular Binding Capacity§		
Liver	B_L (nmol/kg tissue)	15000
Gut	B_G (nmol/kg tissue)	10000
Kidney	B_K (nmol/kg tissue)	10000
Slowly Perfused	B_{SP} (nmol/kg tissue)	5000
Rapidly Perfused	B_{RP} (nmol/kg tissue)	8000
Tissue Partitioning**		
Liver	P_L	12.4
Gut	P_G	14.5
Kidney	P_K	17.0
Slowly Perfused	P_{SP}	17.0
Rapidly Perfused	P_{RP}	17.75

*Liver metabolic parameters estimated from Marre *et al.* (5) and Vaclavikova *et al*. (6) and optimized to achieve 70-80% metabolism of total administered dose.

†Fecal and urinary elimination parameters were optimized within the model to best describe the plasma and tissue distribution data, taking into account published fecal and urinary elimination information.

‡Plasma protein binding of docetaxel was estimated from Urien *et al.* (7)

[§]Docetaxel binding to intracellular macromolecules was estimated from Kuh *et al.* (8), Wierzba *et al*. (9) and Sherline *et al*.(10) as described in ref (2).

[**]Docetaxel tissue partitioning was determined experimentally in our laboratory as described in ref (2).