Use of a minimal PBPK model to investigate the effect of shed antigen on simulated Trastuzumab in humans

AAPS 2013 (Nov) Poster: T3202
Submission ID: AM-13-3536

Linzhong Li, Iain Gardner, Rachel Rose

Simcyp (Certara), Sheffield, UK

PURPOSE

The ectodomain of HER2, the pharmacological target of trastuzumab, can be shed from the surface of tumor cells with levels of up to 2.21 μg/ml detected in the plasma of cancer patients in contrast to levels of less than 15 ng/mL in healthy subjects [1,2]. The impact of the existence of shed, soluble HER2 in plasma and tumor interstitial space on the PK of trastuzumab is not well characterized. A modeling study was performed to study the interplay of target shedding, lymph transport of shed antigen, elimination of HER2-trastuzumab complex, and the relative concentration of the drug and soluble receptor.

METHODS

Membrane bound targets in tissues or on circulating cells in blood, can be subject to ectodomain shedding or cell breakdown, generating soluble target that co-exists with the membrane bound target. In order to mechanistically model this more realistic target-mediated drug disposition (TMDD), existing TMDD models have been modified to take account of the ectodomain shedding of membrane bound target in the interstitial space of tissues [3]. Here we further extend this model to include a specific compartment for tumor tissue.

The right hand diagram in Figure 1 schematically shows the shedding model used in this study, where the membrane target shedding is represented by first-order rate constant (k_{shed}). The soluble targets R_S (in tumor interstitial space) and R_P(in plasma) are assumed to have their own synthesis and degradation processes in addition to being formed by shedding. Assuming that the system is at equilibrium before drug administration, we can derive the steady state solutions, as shown below in equations (1), (2), and (3), to serve as initial conditions for the soluble and membrane bound receptor in the tumor and the soluble receptor in the plasma. Furthermore, we allow the drug to modify the shedding rate by incorporating inhibitory or stimulatory effect into parameter k_{shed}.

Equations for both the full TMDD model and the quasi-steady-state approximation TMDD (Qss TMDD) were extended to account for shedding and the governing equations of total targets for Qss TMDD are given below. This set of equations are coupled with the equations of a minimal PBPK model for mAbs developed previously [4] with a further extended tumor compartment (see Figure 1 for model structure and table 1 for parameter values).

$$\frac{d[R_M]_T}{dt} = k_{syn,m} - \left\{\frac{(k_{\deg,m}+k_{shed})K_{M,SS}}{K_{M,SS}+\hat{C}_I^{ex}} + \frac{k_{\text{int},m}\hat{C}_I^{ex}}{K_{M,SS}+\hat{C}_I^{ex}}\right\}[R_M]_T \qquad (1)\quad [R_M]_T(0) = [R_M]_{SS} = \frac{k_{syn,m}}{k_{shed}+k_{\deg,m}}$$

$$\frac{d[R_S]_T}{dt} = k_{syn,s} - \left(\frac{(\lambda+k_{\deg,s})K_{S,SS}}{K_{S,SS}+\hat{C}_I^{ex}} + \frac{k_{elm,s}\hat{C}_I^{ex}}{K_{S,SS}+\hat{C}_I^{ex}}\right)[R_S]_T + \frac{k_{shed}K_{M,SS}}{K_{M,SS}+\hat{C}_I^{ex}}[R_M]_T \qquad (2)\quad [R_S]_T(0) = [R_S]_{SS} = \frac{k_{syn,s}+k_{sh,p}[R_M]_{SS}}{\lambda+k_{\deg,s}}$$

$$\frac{d[R_P]_T}{dt} = k_{syn,p} + \frac{\hat{V}_I}{V_p}\lambda\frac{K_{S,SS}}{K_{S,SS}+\hat{C}_I^{ex}}[R_S]_T - \left(\frac{k_{\deg,p}K_{P,SS}}{K_{P,SS}+C_P^{ex}} + \frac{k_{elm,p}C_P^{ex}}{K_{P,SS}+C_P^{ex}}\right)[R_P]_T \qquad (3)\quad [R_P]_T(0) = [R_P]_{SS} = \frac{1}{k_{\deg,p}}\left(k_{syn,p} + \frac{\hat{V}_I}{V_p}\lambda[R_S]_{SS}\right)$$

$$K_{M,SS} = \frac{k_{off,m}+k_{\text{int},m}}{k_{on,m}}, \quad K_{S,SS} = \frac{k_{off,s}+k_{elm,s}}{k_{on,s}}, \quad K_{P,SS} = \frac{k_{off,p}+k_{elm,p}}{k_{on,p}}.$$

$$(4)\quad \hat{C}_{I,T}^{ex} = \hat{C}_I^{ex}\left(1+\frac{[R_M]_T}{K_{M,SS}+\hat{C}_I^{ex}}+\frac{[R_S]_T}{K_{S,SS}+\hat{C}_I^{ex}}\right), \quad C_P^{ex} = \frac{1}{2}\left(C_{P,T}^{ex}-[R_P]_T-K_{P,SS}+\sqrt{\left(C_{P,T}^{ex}-[R_P]_T-K_{P,SS}\right)^2+4K_{P,SS}C_{P,T}^{ex}}\right).$$

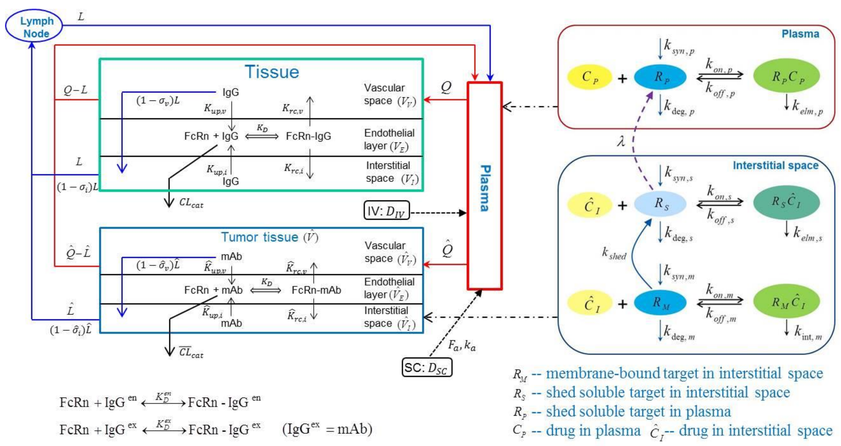

Figure 1. Schematic representation of the minimal PBPK model with a tumour compartment coupled with an extended TMDD model, taking account of target shedding.

Case study: *simulating PK of trastuzumab with the absence and presence of shed ectodomain of HER2 (ECD^{HER2}) in both tumor interstitial space and in plasma.*

Trastuzumab is a humanized IgG1 mAb that binds to HER2, a 185kDa transmembrane tyrosine kinase receptor. The soluble ectodomain protein of HER2 (soluble $P105^{HER2}$, ~97-115 kDa) is shed from tumor cells and can be detected in serum [5,6]. The standard dosing schedule of trastuzumab is a 4 mg/kg loading dose followed by 2 mg/kg weekly by intravenous infusion. The PBPK-TMDD model described above was parameterised using values obtained from the literature to simulate the kinetics of trastuzumab that accounts for binding to membrane-bound and soluble receptors (see Table 1 for the parameter values used for the simulation). Simulations were performed using Matlab (MathWorks, USA, version (R2012a)).

RESULTS

Simulations were performed assuming different membrane bound concentrations of HER-2 receptor. Initial simulations were performed without considering the effect of receptor shedding. Figure 2 shows that the simulated free trastuzumab serum concentrations after the standard dosing schedule are influenced by the level of pharmacological target and that inter-patient variability in the target-mediated trastuzumab clearance pathway leads to differences in plasma concentrations between individuals consistent with the findings in a population PK study [8].

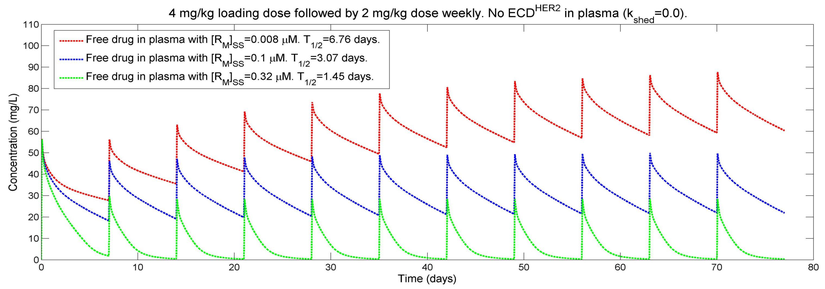

Figure 2. Simulation of trastuzumab kinetics with absence of soluble ECD^{HER2} in both plasma and tumor interstitial space, by setting shedding rate constant k_{shed} to be zero.

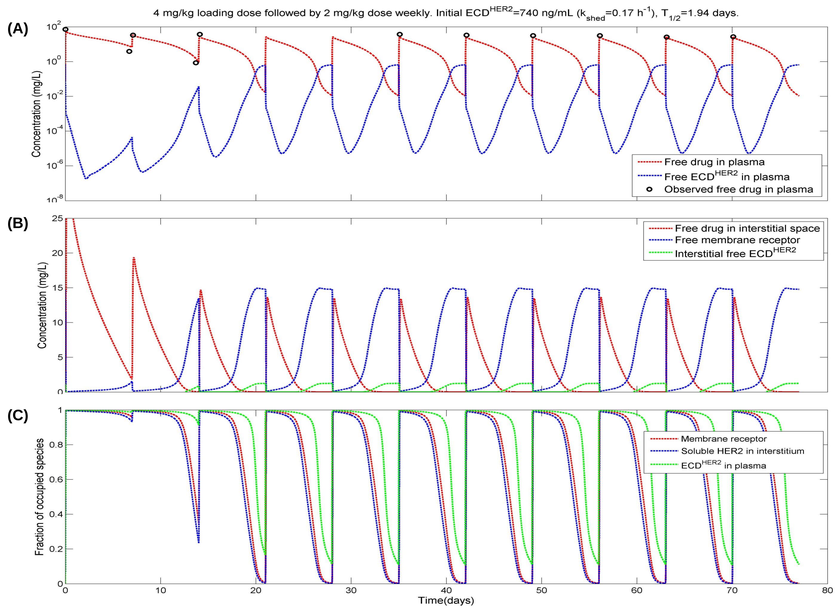

Figure 3. Simulation of trastuzumab kinetics with presence of soluble ECD^{HER2} in both plasma and tumor interstitial space. Assume $[R_M]_{SS}$= 0.08 μM, k_{shed} =0.17 h^{-1}. Correspondingly, $[R_P]_{SS}$= 740 ng/mL (i.e., initial ECD^{HER2} in plasma) and $[R_S]_{SS}$= 1254 ng/mL (i.e., initial ECD^{HER2} in tumor tissue interstitial space), calculated by equations (2) and (3). The observed data was taken from [5]. Due to the lower limit of the assay used there are only initial two pair of peak and trough level available.

In a second set of simulations the influence of high levels of shed receptor in the plasma were investigated and the resultant plasma levels of Trastuzumab were compared to the reported pharmacokinetics from a patient with high ECD HER2 level in plasma (>700 ng/mL) [5].

The value of membrane HER2 level was fixed as 0.08 μM (i.e., $[R_M]_{SS}$), and the shedding rate constant k_{shed} was systematically varied. Using a k_{shed}=0.17 h^{-1} **matches the** observed plasma concentration profile very well. For other values of $[R_M]_{SS}$, it is possible to have a similar fit, but in these instances the corresponding initial ECD^{HER2} level might drop below 700 ng/mL.

A sensitivity analysis was then conducted (Figure 4) to show the impact of varying membrane HER2 expression level $[R_M]_{SS}$ and initial plasma ECD^{HER2} levels on trastuzumab trough plasma concentrations and half-life. This analysis shows that in the absence of soluble receptor the level of membrane bound receptor influences both trough plasma concentration (left panel) and half-life (right panel). As the concentration of soluble, shed receptor increases for all of the scenarios there is a point where a sharp drop in trough concentration is observed (typically this is in the range of 250-1000 ng/mL). Interestingly concentrations of soluble receptor > 500 ng/mL have been associated with poorer clinical outcome [7].

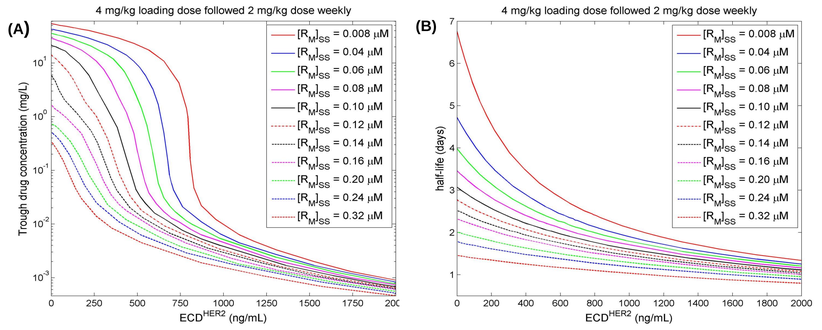

Figure 4. Sensitivity analysis. (A) Plasma trough level against initial plasma ECD^{HER2} for different membrane HER2 levels. (B) Half-life of plasma concentration profiles against initial plasma ECD^{HER2} for different membrane HER2 levels

CONCLUSION

Published TMDD models have been extended to take into account the effect of target shedding on the behavior of a typical monoclonal antibody in a minimal PBPK model with an extended tumor compartment. The simulation study showed that high concentrations of shed soluble target can result in alterations in both binding to membrane bound target (PD) and drug clearance (PK). When high levels of soluble (shed) target exist this should be factored in when determining optimal dosing regimens of therapeutics.

REFERENCES

[1] Tokuda et al. *Br. J. Cancer*. 1999; 81(8):1419-1425.
[2] Lennon et al. *J. Clin. Oncol*. 2009; 27(10):1685-1693.
[3] Li,L, Gardner, I, Rachel, R, Jamei, M. Incorporating target shedding into a minimal PBPK-TMDD model for mAbs. Poster presentation at *American Conference on Pharmacometrics* 2013 (12 – 15 May).
[4] Li L, Chetty M, Gardner I, Dostalek M, Grist E, Machavaram K. development of a minimal-PBPK model for simulating monoclonal antibody pharmacokinetics in human. Poster presentation at *AAPS National Biotechnology Conference* 2012 (21st—23rd May).
[5] Baselga et al. J. *Clin. Oncol*. 1996; 14: 737-744.
[6] Baselga, *Ann. Oncol.* **12 Suppl 1**, *S49-55* (2001).
[7] Pegram et al. *J Clin Oncol*. 1998; 18: 2657-71.
[8] Bruno et al. *Cancer Chemother Pharmacol* 2005; 56: 361-369.
[9] Suzuki et al. *J Immunol*. 2010; 184:1968-76.
[10] Bostrom et al. *PLoS One* 2011; 6(4): p. e17887.
[11] Astin et al. *Mol Biol Cell* 2004; 15(12): 5268-82.
[12] Harwerth et al. *J Biol Chem* 1992; 267(21): 15160-7.

Table 1. Model parameters

Parameter	Value	Parameter	Value	Parameter	Value	Parameter	Value
σ_v	0.62	$\hat{\sigma}_v$	0.4	$\hat{V}$	1.0 (L)	$k_{deg,s} = k_{syn,s}$	0.0 (1/h)
σ_i	0.2	$\hat{\sigma}_i$	$=\sigma_i$	$\hat{V}_V$	$0.05\hat{V}$	$k_{elm,s}$	$= \lambda$
Q	190 (L/h)	$\hat{Q}$	$0.05Q$	$\hat{V}_E$	$0.005\hat{V}$	$k_{syn,p}$	0.0 (1/h)
L	0.12 (L/h)	$\hat{L}$	$0.04\hat{Q}$	$\hat{V}_I$	$0.35\hat{V}$	$k_{deg,p}$	0.2 (1/h)
$K_{up,v}$=$K_{up,i}$	0.02979 (1/h)	$\hat{K}_{up,v}$=$\hat{K}_{up,i}$	$=K_{up,v}$	λ	$=\hat{L}/\hat{V}_I$ (1/h)	$k_{elm,p}$	0.2 (1/h)
$K_{rc,v}$	0.2999 (1/h)	$\hat{K}_{rc,v}$	$=K_{rc,v}$	$k_{on,m}$	2520 (1/μM/h) [10]	$k_{on,s} = k_{on,m}$	$k_{off,s} = k_{off,m}$
$K_{rc,i}$	0.1196 (1/h)	$\hat{K}_{rc,i}$	$=K_{rc,i}$	$k_{off,m}$	1.26 (1/h) [10]	$k_{on,p} = k_{on,m}$	$k_{off,p} = k_{off,m}$
CL_{cat}	0.0175 (L/h)	$\overline{CL}_{cat}$	$=CL_{cat}$	$k_{deg,m} = k_{\text{int},m}$	0.1 (1/h) [11] [12]	FcRn K_D	774 (nM) [9]

Correspondence : Dr. Linzhong Li, l.li@simcyp.com