The Relationship between Target-Mediated Drug Disposition (TMDD) and Models with Time-Dependent Clearance

Leonid Gibiansky, Ekaterina Gibiansky; QuantPharm LLC, North Potomac, Maryland

Background: Pharmacokinetics (PK) of drugs that target malignant B-cells is often described by a model with time dependent clearance that depends on disease characteristics [1, 2]. Dependence of clearance on expression, accessibility, and amount of target is indicative of target-mediated elimination, similarly to the example provided in [2] where drug elimination was described as a combination of linear clearance and elimination via free receptors on neutrophils.

Objective: To provide a possible mechanistic explanation of the observed time dependency of PK and dependency of time-dependent clearance on disease characteristics.

Methods: It was assumed that PK of the drug is described by a two-compartment model with parallel linear and target-mediated elimination with irreversible binding, receptor recycling (resulting in constant number of receptors on each cell), and limited access of the drug to the target cells (leading to relatively slow effective binding rate). Then TMDD equations can be written as:

$$\frac{dA_1}{dt} = -\left(\frac{CL_{ns}+Q}{V_c}\right)A_1 + \frac{Q}{V_P}A_2 - k_{\text{int}}A_1R; \qquad A_1(0) = D_{IV};$$

$$\frac{dA_2}{dt} = \frac{CL_{ns}}{V_c}A_1 - \frac{Q}{V_P}A_2; \qquad A_T(0) = 0; \qquad C = \frac{A_1}{V_c};$$

$$\frac{dR}{dt} = k_{syn} - k_{\text{deg}}R - k_{kill}R\frac{C}{IC_{50}+C}; \qquad R(0) = k_{syn}/k_{\text{deg}}.$$

Here target-mediated elimination $k_{int}*A_1*R$ is proportional to the target cell concentration R with internalization rate k_{int} that may depend on drug-target binding rate k_{on}, density and turnover of target receptors; target cells are in equilibrium prior to drug administration; kill rate of target cells can be described by E_{max} function of drug concentrations $k_{kill}*R*C/(IC_{50}+C)$. If IC_{50} is significantly lower than trough concentration C_{trough}, then one can derive equation $dR/dt = k_{syn} - (k_{\text{deg}} + k_{kill})R; \quad t > 0; \quad R(0) = R_0 = k_{syn}/k_{\text{deg}},$ that has a solution

$R = R_0\left(\frac{k_{\deg}}{k_{\deg}+k_{kill}} + \frac{k_{kill}}{k_{\deg}+k_{kill}} e^{-(k_{\deg}+k_{kill})\cdot t}\right); \quad t > 0.$ Substituting expressions for the concentration of target cells in the equation for A_1, one can arrive at the system

$$\frac{dA_1}{dt} = -\left(\frac{CL+Q}{V_c}\right)A_1 + \frac{Q}{V_P}A_2 - \frac{CL_R}{V_c}A_1; CL_R = k_{\text{int}}R_0\left(\frac{k_{\deg}}{k_{\deg}+k_{kill}} + \frac{k_{kill}}{k_{\deg}+k_{kill}} e^{-(k_{\deg}+k_{kill})\cdot t}\right)\cdot V$$

The expression for clearance in this equation can be rewritten as

$CL(t) = CL_{SS} + CL_T e^{-k\cdot t}, \quad where \quad k = k_{\deg} + k_{kill};$

$$CL_{SS} = CL_{ns} + k_{\text{int}}R_0 \cdot V_c \frac{k_{\deg}}{k_{\deg}+k_{kill}} = CL_{ns} + \frac{k_{\text{int}}k_{syn}}{k_{\deg}+k_{kill}}V_c;$$

$$CL_T = k_{\text{int}}R_0 \cdot V_c \frac{k_{kill}}{k_{\deg}+k_{kill}} = \frac{k_{\text{int}}k_{syn}k_{kill}/k_{\deg}}{k_{\deg}+k_{kill}}V_c;$$

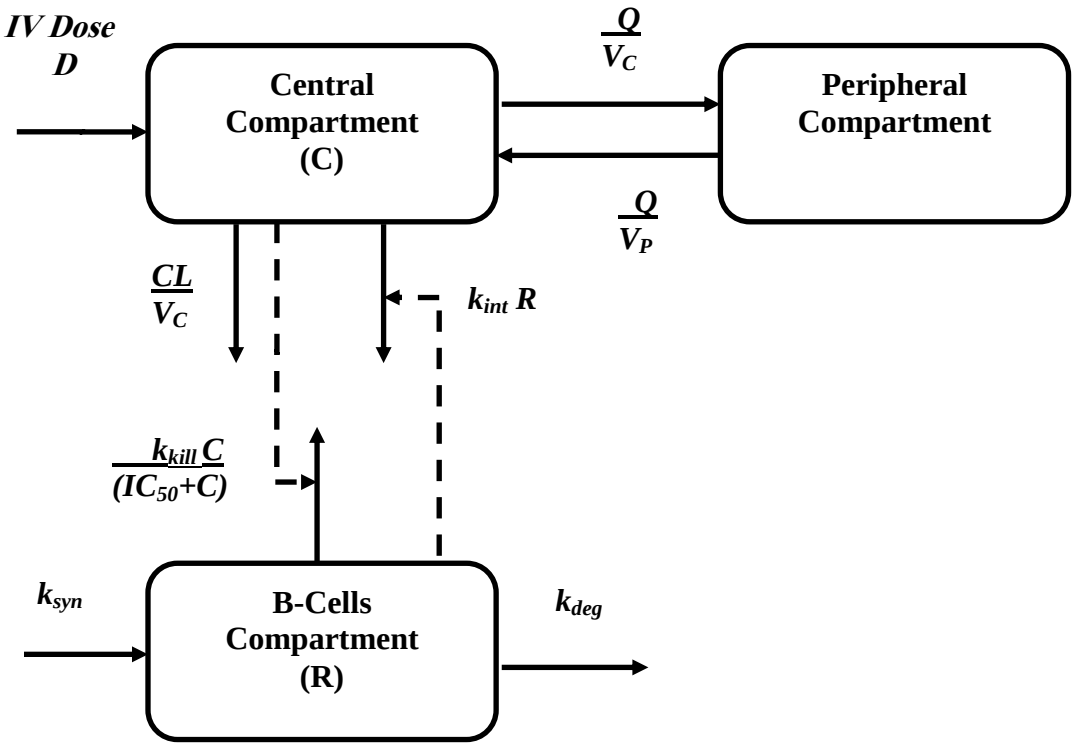
Thus CL_{SS} and CL_T may increase with increase of target cell concentration R_0, synthesis rate k_{syn}, receptor density (that would lead to increase of k_{int}) and may decrease with concomitant chemotherapy (that decreases k_{syn}). In addition, concomitant chemotherapy may increase kill rate k_{kill} (synergy), thus decreasing CL_{SS}, increasing CL_T and k. For subjects with low kill rate (non-responders), CL_{SS} would be higher leading to lower exposure. Thus, the often observed PK-PD relationships where lower exposure leads to lower probability of response could be a consequence of being non-responder rather than the cause of non-response.

Conclusions: Under reasonable assumptions, equations of the linear system with time-dependent clearance can be derived from target-mediated drug disposition equations. This explains the PK structural model and covariate dependencies that are typical for drugs that target B-cells.

References

1. Gibiansky E, et al., CPT PSP 2014 Oct 29;3:e144. doi: 10.1038/psp.2014.42.
2. Li J, et al., JCP 2012 Dec;52(12):1918-26. doi: 10.1177/0091270011430506.
3. Jonsson EN, et al., Pharm Res. 2005 Aug;22(8):1236-46

Graphical Representation and Equations of the Population Pharmacokinetic Model



Graphical Representation and Equations of the Population Pharmacokinetic Model