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

Leonid Gibiansky, Ekaterina Gibiansky

QuantPharm LLC, North Potomac MD, USA (www.quantpharm.com)

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BACKGROUND

Pharmacokinetics (PK) of drugs that target B-cells is often described by a model with time-dependent clearance that is influenced by 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 [3], where drug elimination was described as a combination of linear clearance and elimination via free receptors on neutrophils.

OBJECTIVES

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

METHODS/RESULTS

It was assumed that PK of the drug is described by a two-compartment model with parallel linear and target-mediated elimination with (a) **irreversible binding**; (b) **receptor recycling** (resulting in constant number of receptors on each cell), and (c) **and limited access of the drug to the target cells** (leading to relatively slow effective binding rate).

Then TMDD equations can be written as:

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

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

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

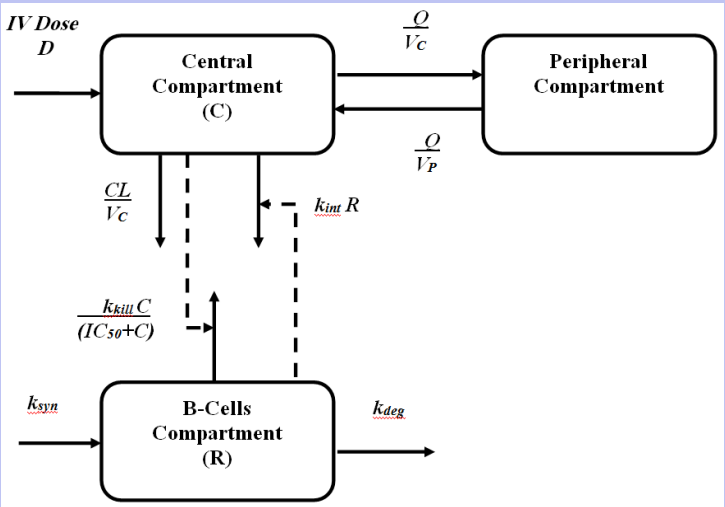
Here target-mediated elimination $k_{int}*A_1*R$ is proportional to the drug amount A_1, the target cell concentration R, and internalization rate k_{int} that may depend on drug-target binding rate k_{on}, density and turnover of target receptors. Target cells are in equilibrium prior to drug administration; kill rate of target cells can be described by Emax 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

$$dR/dt = k_{syn} - (k_{\text{deg}} + k_{kill})R; \qquad t > 0; \quad R(0) = R_0 = k_{syn}/k_{\text{deg}},$$

that has a solution

$$R = R_0\left(\frac{k_{\text{deg}}}{k_{\text{deg}}+k_{kill}} + \frac{k_{kill}}{k_{\text{deg}}+k_{kill}}e^{-(k_{\text{deg}}+k_{kill})\cdot t}\right); \quad t > 0.$$



METHODS/RESULTS (continuation)

Substituting expressions for the concentration of target cells in the equation for A_1, one can arrive at the equation

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

The expression for clearance in this equation can be rewritten as

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

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

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

Thus, CL_{SS} and CL_T may be higher at higher baseline target cell concentration R_0, higher synthesis rate k_{syn}, and higher receptor density (that would lead to increase of k_{int}) and may be lower with concomitant chemotherapy (that decreases k_{syn}). In addition, concomitant chemotherapy may increase kill rate k_{kill} (synergy), leading to decrease of CL_{SS}, but increase of 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 relationship 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

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