Physiologically-based PK/PD of targeted drug delivery by monoclonal antibodies

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Abstract- For the last few decades, modern pharmacology, in general, and hematological cancers, in particular, largely benefited from the development of molecular targeted drugs on the basis of monoclonal antibodies (MA). Cancer cells can develop resistance to the conjugated antibodies by several mechanisms such as low expression of the target membrane antigen, rapid metabolism, rapid excretion from the cell, or resistance to the conjugate toxin. All the aforementioned resistance mechanisms contribute to the high response variability already seen in MA-based drugs (MA-BD). We present a physiologically-based MA-BD PK/PD mathematical model that includes blood PK and detailed model of MA-BD interactions with its target receptor. It can be coupled with various indirect response mechanism-based PD. We applied our model to experimental data of Gemtuzumab Ozogamycin interaction with leukemic blasts in vitro and in vivo in order to evaluate individual model parameter values in the patient population. Mathematical analysis of model behavior under physiological parameter value ranges allowed for formulation of general principles of treatment by targeted drug delivery, including identification of parameters with highest influence on drug efficacy and optimization of treatment schedule.