Cell-Level Model of Pharmacodynamics-Mediated Drug Disposition: Application to Filgrastim (Neupogen)

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Objectives: To develop a mechanistic model capable of describing pharmacodynamics-mediated drug disposition (PDMDD) which is identifiable from typical in vivo PK/PD data.

Methods: A PDMDD model was developed by combining elements from a cell-level model of target interaction [1] with a traditional model of target-mediated drug disposition (TMDD) [2]. Four different indirect response models (IDRs) [3] were used to identify signature responses of the model. The performance of the model was further evaluated using two previously published filgrastim studies involving single (intravenous and subcutaneous) and multiple subcutaneous doses [6,7] in humans. Data included serum filgrastim concentration and absolute neutrophil counts (ANC).

Results: The cell-level PDMDD model accounted for the linear systemic drug clearance, endocytotic internalization and degradation, and loss due to cell elimination. Comparison of the IDRs with PDMDD versus non-PDMDD scenarios indicates a separation of clearance rates which occurs after a single cycle, but this is not observable in vivo (e.g. free drug observations) until multiple cycles of treatment. The model simultaneously explained the neutrophil-mediated disposition of filgrastim, the kinetics of the endogenous G-CSF (eG-CSF), and ANC dynamics, including the rebound effect in ANC due to accumulation eG-CSF in neutropenic patients, thus eliminating the need for a feedback mechanism [4,5]. Parameter estimates were in the physiological ranges or agreed with similar parameters reported in the literature.

Conclusions: Analysis of the PDMDD model found that multiple dosing data might be required to produce effects in plasma concentration needed to identify model parameters. The PDMDD model reduced to the standard TMDD model in the absence of pharmacological effect on the target. Future applications include chemotherapy induced cytopenias affecting clearance of endogenous hematopoietic growth factors and/or monoclonal antibodies.

References: