Assessment of Combination Therapy Effects on Tumor Growth Using PBPK/PD Modeling

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Objectives: Current treatment regimens for cancer patients tackle tumor growth using combination therapies to increase efficacy and reduce adverse effects [1]. A major challenge remains the decision for the most efficacious dosing regimen of a combination therapy taking into account tumor properties, PK properties, and mode of action. This applies for combination therapies of small molecules and biologics [2]. The objective of this approach is to assess the usability of PBPK/PD combination models for these questions.

Methods: PBPK/PD models of bevacizumab and imatinib were established using PK-Sim® and MoBi®. The generic PBPK model was extended by a physiological representation of the tumor. Relevant biological processes integrated comprise target expression, binding, and dynamics. A PD model was integrated to represent tumor growth of the physiological tumor as well as the effect of the combination therapy. Impact of dosing schedule for combinations of bevacizumab and imatinib was investigated on a population scale.

Results: The established PBPK/PD model structure is able to describe the impact of a combination therapy of bevacizumab and imatinib on tumor growth on a population scale. The combined PBPK/PD model of bevacizumab and imatinib predicts a median stable disease according to the RECIST criteria in a patient population which is well in line with published data [3].

Conclusions: PBPK/PD models of combination therapies can improve decision making in the clinic. The integration of relevant biological processes driving PK and PD of small molecules and biologics in one model structure allows for assessment of a combination therapy in the example. Further assessments of combination therapies by such models are required to further evaluate the potential to improve decision making in the clinic.

References: