Mechanistic projection of bortezomib target-mediated disposition, blood target inhibition and drug-drug interactions using an integrated PBPK/PD approach

Shinji Iwasaki, Andy Zhu, Michael Hanley, Karthik Venkatakrishnan, Cindy Xia

1Drug Metabolism and Pharmacokinetics, 3Quantitative Clinical Pharmacology, Takeda Pharmaceuticals International, Co., Cambridge, MA, USA

Objectives: The objective of this study was to establish a fully mechanistic physiologically-based pharmacokinetic/pharmacodynamic (PBPK/PD) model to project blood target inhibition and drug-drug interactions (DDI) of bortezomib, a 20S proteasome inhibitor approved for the treatment of multiple myeloma.

Methods: A minimal PBPK model consisting of 4 compartments (including plasma, liver, erythrocytes and peripheral organs) was constructed in NONMEM® to describe the pharmacokinetics of bortezomib using in vivo physiological distribution parameters and in vitro metabolism and binding data. Specifically, the fraction metabolized by each CYP isoform (f_m) was estimated from in vitro phenotyping experiments (e.g. f_m,3A4=0.6) and was incorporated into in vivo hepatic intrinsic clearance. The target-mediated drug disposition of bortezomib in erythrocytes, which determines target inhibition in blood, was characterized by incorporating the in vitro K_d value of bortezomib against the 20S proteasome and the 20S proteasome concentration in erythrocytes. The effects of a strong CYP3A inducer (rifampin) and inhibitor (ketoconazole) on bortezomib intrinsic clearance were simulated using the built-in profiles from Simcyp® (V16).

Results: The mechanistic PBPK/PD model was able to describe the multi-exponential and time-dependent pharmacokinetics of bortezomib in humans after both single- and multiple-dose administration. The mechanistic model was also able to adequately describe the 20S proteasome inhibition versus time profiles in blood after multiple dose administration using only in vitro binding parameters. Lastly, the mechanistic PBPK/PD model was able to predict the impact of ketoconazole and rifampin on bortezomib exposure. The simulated AUC ratio was 1.14-1.25 for ketoconazole and 0.56-0.62 for rifampin compared to the observed ratio of 1.35 for ketoconazole and 0.55 for rifampin.

Conclusions: The mechanistic PBPK/PD model was able to adequately capture the complex pharmacokinetics, target inhibition and DDI of bortezomib. This study illustrates the importance of incorporating target biology and in vitro clearance parameters into mechanistic PBPK/PD models and the utility of such models for pharmacokinetic, pharmacodynamic and DDI predictions.