A Population Pharmacokinetic/Toxicity Model for the Reduction of Platelets during a 48-hr Continuous Intravenous Infusion of the Histone Deacetylase Inhibitor Belinostat

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Objectives: Belinostat is a second-generation histone deacetylase inhibitor (HDI) and is predominantly metabolized by UGT1A1-mediated glucuronidation. There are two common polymorphisms (UGT1A1*28, UGT1A1*60) that were previously shown to impair drug clearance and increase the incidence of thrombocytopenia. This latter phenomenon has been observed with other HDIs such as abexinostat, panobinostat, romidepsin, and vorinostat. The objective of this work was to describe the relationship between belinostat plasma exposure and platelet decreases.

Methods: We expanded a previously developed population pharmacokinetic (PPK) model to include a pharmacodynamic (PD) model describing the change in platelet levels in patients with small cell lung cancer and other advanced carcinomas administered belinostat as a 48-hr continuous intravenous infusion, along with cisplatin and etoposide.

Results: A PPK/PD model was developed, fixing the PPK model previously developed from this same dataset and adapting published thrombocytopenia PD models from literature to fit this dataset. The PD model developed here introduced an additional rate constant to better describe the maturation of megakaryocytes into platelets before degradation and a feedback mechanism. The model employed a proportional error model to describe the observed circulating platelet data. Several covariates were explored, including sex, body weight, UGT1A1 genotype status, liver and kidney function, but none significantly improved the model.

Conclusions: Platelet levels rebounded to baseline within 21 days, just before the next cycle of therapy. This model suggests a q3week schedule allows for sufficient platelet recovery before the next belinostat infusion.