Model-based Meta-analysis of Bortezomib Exposure–Response Relationships in Multiple Myeloma Patients

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Objectives: Multiple myeloma (MM) is an incurable bone marrow plasma cell malignancy that accounts for 20% of hematological malignancy related deaths in the United States. Bortezomib, a reversible proteasome inhibitor, shows potent antineoplastic activity by inhibiting the constitutively elevated proteasome activity in myeloma cells and is approved as a first-line therapy for MM. Although clinically successful, drug resistance and dose limiting toxicities (e.g., thrombocytopenia) remain unmet challenges for the clinical use of bortezomib. This study aims to develop a quantitative and predictive pharmacodynamic model to investigate bortezomib dosing-regimens.

Methods: Mean temporal profiles of bortezomib pharmacokinetics, proteasome activity, M-protein concentrations, and platelet counts following bortezomib monotherapy were extracted from published clinical studies. A model–based meta-analysis of bortezomib anti-myeloma activity and thrombocytopenia was conducted sequentially with the Stochastic Approximation Expectation Maximization algorithm in Monolix. The final model was further used to simulate the clinical response and risk of thrombocytopenia during bortezomib monotherapy in myeloma patients under several regimen scenarios.

Results: A small systems model linking drug exposure to response was developed by integrating major regulatory mechanisms, including: target-mediated disposition of bortezomib, proteasome inhibition, modulation of apoptotic intracellular signaling, and subsequent regulation of myeloma progression with proteasome-mediated platelet turnover. Bortezomib pharmacokinetics, myeloma progression, and platelet dynamic profiles were well characterized in myeloma patients. Local sensitivity analysis suggested that increased target density may alter bortezomib PK and attenuate cytotoxic effects, with decreased bortezomib exposure leading to the rapid recovery of proteasome activity, diminished apoptosis signal activation, and accelerated disease relapse and progression (Figure 1). In addition, model simulations indicate that a once-weekly dosing schedule represents an optimal therapeutic regimen with comparable antineoplastic activity but reduced risk of thrombocytopenia.

Conclusions: A pharmacodynamic model was successfully developed, which provides a quantitative, mechanism-based platform for exploring bortezomib dosing-regimens. Further research is needed to apply this model to maximize antineoplastic efficacy and minimize thrombocytopenia for individual MM patients.

Figure 1: Model simulated profiles of bortezomib plasma exposure, proteasome activity (%), apoptosis signals (NFκB, Bcl-xL, and cPARP), and myeloma tumor burden or M-protein (%) in MM patients with varying basal proteasome density ($R_{\text{tot}}$) values after bortezomib multiple-dosing (1.3 mg/m$^2$ IV administration on Days 1, 4, 8, and 11 for up to eight 21-day cycles). $IC_{50}$ represents the model estimated bortezomib potency of proteasome inhibition. Lines represent model-simulated mean profiles and arrows indicate the direction of increasing $R_{\text{tot}}$ values.