Population Pharmacokinetic-Pharmacodynamic Modeling and Simulation of Neutropenia in Patients With Advanced Cancer Treated With Palbociclib

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Objectives: Neutropenia is the most common hematologic toxicity following treatment with palbociclib, a cyclin-dependent kinase (CDK) 4/6 inhibitor approved for metastatic breast cancer. There is a paucity of pharmacokinetic (PK)-pharmacodynamic (PD) modeling studies of neutropenia associated with targeted anticancer drugs, such as CDK4/6 inhibitors. A PK-PD model was developed to describe the time course of absolute neutrophil count (ANC), quantify the exposure-response relationship for neutropenia, and characterize neutropenia associated with palbociclib treatment.

Methods: A semi-mechanistic PK-PD analysis was performed using data from 185 advanced cancer patients receiving palbociclib in 3 clinical trials (NCT00141297; NCT00420056; NCT00721409). A population PK model was developed first to obtain the individual PK parameters that were sequentially used in the PD portion of the model. Plasma concentration was related to the anti-proliferative effect of palbociclib on stem cells through drug-related parameters; maturation of neutrophil in bone marrow was mimicked through a proliferation compartment, 3 transit compartments, and blood circulation compartment using system-related parameters. The effects of covariates including demographic factors and laboratory test variables were evaluated. Different approaches were used to assess model adequacy and predictive capability; model-based simulations were conducted.

Results: The final model adequately described longitudinal ANC with good predictive capability across dose levels and regimens. Gender and baseline albumin level were significant covariates on baseline ANC value. The model suggested correlation of higher palbociclib dose levels associated with lower ANC time profiles; ANC nadir was reached approximately 21 days after initiation of palbociclib treatment (both schedules: 3 weeks on/1 week off [3/1]; 2/1). Model-predicted ANC time profiles suggested that neutropenia associated with palbociclib is rapidly reversible rather than cumulative, with no trend of worsening ANC level observed over multiple cycles (Figure).

Conclusions: PK-PD modeling analyses support the approved palbociclib dosing and management strategies for the breast cancer indication and aid in predicting ANC and neutropenia incidence in future palbociclib trials with different dosing regimens/combinations and optimizing dosing schedules for future indications.
Figure. Observed and model-simulated ANC time profile for patients treated with a starting dose of palbociclib 125 mg (3/1 schedule), with simulation alone for ANC values after discontinuation of dosing.

Black dashed lines are reference lines for ANC=1.0 × 10^9/L and ANC=0.5 × 10^9/L; ANC=absolute neutrophil count.