Background

Trastuzumab-DM1 (T-DM1) is an antibody-drug conjugate in development for the treatment of human epidermal growth factor receptor 2 (HER2)-positive cancers [1].

T-DM1 is composed of the potent cytotoxic agent DM1 (derivative of maytansine) conjugated to trastuzumab (Herceptin®) via a unique, stable linker.

T-DM1 is designed to target HER2 receptors on tumor cells, and kill tumor cells by releasing DM1 intracellularly and via the anti-tumor activities of trastuzumab.

Thrombocytopenia (TCP) is the dose-limiting toxicity in clinical studies. TCP was generally grade 1 or 2, reversible, and not associated with serious hemorrhage [2, 3]; the mechanism(s) of platelet response to T-DM1 is unclear.

Objectives

A semi-mechanistic population Pharmacokinetic-Pharmacodynamic (PKPD) model was developed in order to:

• describe the time course of patient platelet response to T-DM1;
• support mechanistic hypotheses for platelet response(s);
• to evaluate patient baseline characteristics as covariates on model PD parameters;
• predict patient platelet response and incidence of Grade ≥ 3 TCP in future clinical trials.

Methods

Patients and Data

Women with previously treated MBC were treated with single agent T-DM1.

Model building dataset (n=164 patients; 4340 platelet measurements)

Model evaluation dataset (n=110 patients; 1841 platelet measurements)

Population PKPD Modeling

Data analysis: NONMEM version 7 with FOCE interaction

The final PKPD model (Figure 1) was modified from Friberg et al [4].

• Post-hoc Bayesian estimates of patient PK parameters [5] drove platelet response
• Two primary drug effects (C/Slope, for the first dose and C/Slope, for subsequent doses) were used to describe the low Cycle 1 platelet nadir
• A mixture model quantified a subpopulation of patients with downward platelet drifts

Covariate analysis on drug-related (Kplatelet and Slope) and system-related (BASE, MTT, and GAM) model PD parameters

• Covariates explored were age, weight, race, baseline platelet count, liver function tests, tumor burden, HER2 expression, and prior chemotherapy (i.e. bone marrow suppressive agents).

Model Evaluation (using Phase II dose of 3.6 mg/kg q3w)

• Diagnostic Plots and Visual Predictive Check
• External dataset evaluation

Conclusions

The PK/PD model accurately predicts clinical observations of platelet counts and incidences of Grade ≥ 3 TCP with T-DM1 treatment of 3.6 mg/kg q3w.

Platelet profiles from 25% of patients decline more rapidly than the rest of patients and stabilize within 8 treatment cycles to typically 50% of the original baseline platelet count.

85% of patients demonstrate a pattern of lowest platelet nadir in the first cycle.

Patients with low baseline platelet counts ≤ 200(1000)µL have an increased propensity for grade ≥ 3 TCP with T-DM1 3.6mg/kg q3w.

Baseline covariates were not statistically significant for any PD parameter; platelet response to T-DM1 cannot be predicted a priori.

References