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Mechanisms of hematological toxicity of antibody drug conjugates: Role of drug-load release

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Purpose: To develop a unified pharmacokinetic (PK)/pharmacodynamic (PD) model that describes the concentrations time profiles of the only two FDA-approved antibody-drug conjugates (ADCs) which are trastuzumab emtansine (TDM1) and Brenduximab Vedutin (SGN35) and their induced myelosuppression including thrombocytopenia for TDM1 and neutropenia for SGN35 in normal and human cancer xenograft mice.

Methods: Balbc mice, normal or nude xenografted with human Her2-positive breast cancer for the TDM1 treatment arm or Hodgkin lymphoma for the SGN35 treatment arm, were intravenously injected with either a large single does (SD) or multiple medium doses (MD) every week for two weeks. The investigated doses were 120 mg/kg (SD), 10 and 30 mg/kg (MD) for TDM1 and 15 and 45 mg/kg (MD) for SGN35. For each treatment arm group a control subgroup of normal mice were injected with saline. The hematological toxicity induced by both agents was followed by whole blood sampling every 2 days for platelets (PLT) and neutrophils (ANC) measurements using a hematology analyzer. Few blood samples were collected for total trastuzumab concentration measurements performed with a commercially available ELISA kit with a limit of quantification of 2 ng per mL. The plasma concentrations for SGN35, the payloads (DM1 for TDM1 and MMAE for SGN35) as well as the antibodies, trastuzumab (TDM1) and anti-CD30 (SGN35) were extracted from the literature. A non-linear mixed-effect modeling approach was performed using MONOLIX software. Model simulations were performed using Berkeley Madonna. Internal model evaluation was performed using a visual predictive check and the precision of the parameter estimates was assessed by the percent of relative standard errors (%RSE).

Results: A two compartment model with linear elimination described the PK of both ADCs. Similarly, the PK of the payloads DM1 from TDM1 and MMAE from SGN35 as well as the monoclonal antibodies, trastuzumab from TDM1 and anti-CD30 from SGN35, were described with two compartment models and linear eliminations after deconjugations (kdec) from their corresponding ADCs. The thrombocytopenia induced by TDM1 and neutropenia induced by SGN35 were captured with a series of five transit compartments representing proliferative and maturing cells in the bone marrow and the differentiated cells (PLT or ANC) in the blood circulation. A negative feedback loop was used to account for the observed tolerance phenomenon. The half-lives for TDM1 and SGN35 were estimated at 4.8 (32%) and 4.6 (21%) days and the kdec were 0.46 (18%) and 0.12 (13%) h-1. The lifespan for PLT under TDM1 and ANC under SGN35 were 3.73 (12%) and 4.72 (9%) days. Comparison of performance between alternative models suggests that TDM1 and SGN35 myelosuppressions are caused by different mechanisms: ADC binding to FcgR for TDM1 and payload-driven toxicity for SGN35 due to high lipophilicity of MMAE. Model based-simulations suggest that a 6-fold increase and 70% decrease in kdec of TDM1 and SGN35 would improve myelosuppression.

Conclusions: The developed unified PK/PD model well captured TDM1 and SGN35 PK as well as their corresponding payloads DM1 and MMAE and monoclonal antibodies trastuzumab and anti-CD30 plasma concentration profiles. The thrombocytopenia induced by TDM1 and neutropenia induced by SGN35 were also well captured with the suggested unified PD model for myelosuppression. The proposed unified PK/PD model could serve as a general platform for the investigation and prediction of PK and hematological toxicities to other ADCs.

Biography

Sihem Bihorel utilizes quantitative systems pharmacology approaches to guide the development of new therapies and the identification of promising combination therapies as well as of novel biomarkers in oncology. She integrates quantitative systems pharmacology with PK/PD modeling and simulation to advance drug discovery and development and leverage the understanding of drugs action which holds great promise to facilitate translational research. Her research is also focused on investigating how priming solid tumors with a pro-apoptotic agent then combining a subsequent large protein therapeutic and an antiangiogenic agent can defeat drug resistance and treatment failure in cancer and further enhance the efficacy of targeted anticancer agents and translating these findings toward clinical settings. Earlier she has held the position of Research Assistant Professor at the State University of New York at Buffalo where she was also trained as a Post doctorate and received her PhD from the same.

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