Integrated Pharmacokinetic Model for Antibody-Drug-Conjugate (ADC) in Patients with B-cell Malignancy: Implications for Optimal Sampling

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Objectives: Pinatuzumab vedotin, a MMAE-containing ADC targeting CD22, is in clinical development for treatment of B-cell malignancies. Dense and relatively sparse pharmacokinetic (PK) data for total antibody (tAb), conjugate (antibody-conjugated MMAE [acMMAE]), and unconjugated MMAE (MMAE) from Phase I and II studies following IV administration at doses 0.1-3.2 mg/kg were used to for mechanistic modeling to describe their PK and understand the quantitative relationships among these analytes.

Methods: The ADC model proposed in ref. [1] is simplified from a multi-compartmental model with the assumptions that deconjugation rate is linearly proportional to drug-to-antibody-ratio (DAR) and proteolytic degradation rate is independent of DARs. The model was used to describe tAb and acMMAE data. The model was further expanded to describe unconjugated MMAE PK. Phase I PK data with extensive PK sampling were used for model development (patient number = 89). Phase II PK data with relatively sparse sampling were used to assess the ability of the model to predict tAb PK based on observed acMMAE and unconjugated MMAE data (patient number = 61).

Results: PK of tAb and acMMAE was well described by two 2-compartment models with shared parameters. Unconjugated MMAE generated from deconjugation and proteolytic degradation is input to a delay compartment before appearing in the systemic circulation. Non-linear elimination from the MMAE delay compartment was included in the model. MMAE apparent systemic clearance increased with time with the steady-state value of 3.96 L/hr, initial value of 1.92 L/hr, and the half-life of the increase of 1.97 months. CL and V_1 were 6.61 and 1.47 times higher in CLL patients compared to NHL patients; CL and V_1 were 1.20 and 1.16 times higher in males. CL, Q, V_1, and V_2 increased with weight with the powers of 0.75, 0.75, 0.47, and 1.0, respectively. CL_{MMAE} increased with weight and albumin concentration with the powers of 0.75 and 0.89, respectively. The model accurately predicted the tAb concentrations using the observed acMMAE and unconjugated MMAE data.

Conclusions: The developed model described the observed data in patients with B-cell malignancies. The model predicted tAb PK based on conjugate (acMMAE) and unconjugated MMAE data. Thus, the model developed on tAb, acMMAE, and MMAE data in Phase I and II studies can be used in future studies to potentially eliminate the need to measure tAb in Phase III.

[1]: Gibiansky L., Gibiansky E. Target-Mediated Drug Disposition Model and its Approximations for Antibody-Drug Conjugates, J Pharmacokinet Pharmacodyn. 2014 Feb; 41(1):35-47.