Towards the development of a platform PBPK-QSP model in the Julia programming language for evaluating potential toxicities caused by antibody-drug-conjugate therapies

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Abstract
Antibody-drug-conjugates (ADCs) are a rapidly expanding class of anticancer drugs. They were developed with the aim to expand the therapeutic index of potent cytotoxic agents (i.e., payload) by employing the targeting specificity of monoclonal antibodies (mAbs) to direct the delivery of payload selectively to malignant cells. Although many ADCs have demonstrated efficacy, their clinical use tends to lead to substantial, sometimes dose-limiting toxicities. Moreover, promising candidate ADCs continue to fail late in the development pipeline, after demonstrating activity in preclinical studies, because their toxicity profiles prevent dosing at levels high enough to achieve clinical efficacy.

Here, a physiologically based pharmacokinetics (PBPK) - quantitative systems pharmacology (QSP) model was used to predict the activity of trastuzumab emtansine (TDM1), a widely used ADC to treat HER2 positive breast cancer. It also predicted the low hepatotoxicity of trastuzumab deruxtecan (T-Dxd), another HER-2 targeting ADC, and brentuximab vedotin (BV), an ADC used to treat lymphoma. Furthermore, this model could predict the high hepatotoxicity observed in cantuzumab mertansine (CM), an ADC suspended from development.

The systemic pharmacokinetics (PK) of ADCs were described by a previously published PBPK model [1] (Fig 1A). Plasma ADC could bound to soluble receptor and be degraded (Fig 1C). For the ADC that were not degraded, they could either enter tissue endothelial cells through either FcRII-mediated or FcRn-independent processes before reaching the tissue interstitium (Fig 1B), or into tumor through vascular and surface exchange (Fig 1A). For those removed from tissue interstitium (including tumor interstitium), they could enter cells through receptor-mediated uptake [3] (Fig 1A). ADC inside cells (endothelial cells and tumor cells) could be degraded and released payload, inducing cell killing.

Methods
The systemic pharmacokinetics (PK) of ADCs were described by a previously published PBPK model [1] (Fig 1A). Plasma ADC could bound to soluble receptor and be degraded (Fig 1C). For the ADC that were not degraded, they could either enter tissue endothelial cells through either FcRII-mediated or FcRn-independent processes before reaching the tissue interstitium (Fig 1B), or into tumor through vascular and surface exchange (Fig 1A). For those removed from tissue interstitium (including tumor interstitium), they could enter cells through receptor-mediated uptake [3] (Fig 1A). ADC inside cells (endothelial cells and tumor cells) could be degraded and released payload, inducing cell killing.

Results
ADCs included in this study were listed in Table 1. The model was calibrated using their PK profiles (Fig 2A-D).

The model predicted only 0.001% of the ADC dose reached the tumor, with the rest in organs such as liver (9.4%), skin (3.7%), and lung (3.6%) (Fig 3A). The ADC target receptor’s internalization rate (Fig 3B) and receptor copy number (Fig 3C) were predicted to have limited impact on the amount of ADC destined for the tumor, indicating receptor expression was not the bottleneck. The true predicted bottlenecks were the tumor perfusion (Fig 3D) and the ADC’s diffusivity (Fig 3E), known limitations of ADCs in treating solid tumors [8].

The systemic distribution of ADC in interstitial fluids should be considered a source of potential off-target toxicity. The model predicted ADC concentrations >IC50 in lung, skin, and small intestine interstitia (Fig 4). Given the presence of HER2+ cells in these organs, ADC in tissue interstitium may explain toxicities observed in TDM1 [9].

Free payload could be a source of off-target toxicity. Predicted DM1 concentration >IC50 in liver endothelial cells after a dose of 3.6mg/kg T-DM1, consistent with the hepatic toxicity observed in TDM1 (Fig 5A). Predicted Ddx and MMAE concentrations were lower than their IC50 after a dose of 5.4mg/kg T-Dxd and MMAE (Fig 5B, C), respectively, consistent with the lack of hepatic toxicity observed in T-Dxd and BV [10].

For CM dosed at 235mg/m2, the dose recommended by [7], the model predicted toxicity (caused by DM1) in both liver and skin (Fig 6A). The model predicted hepatic toxicity to be observed starting at 88mg/m2 during dose escalation (Fig 6B), consistent with the adverse events reported in [7].

Conclusion
The PBPK-QSP model was developed to analyze several ADCs’ known toxicities quantitatively: liver and lung toxicity of TDM1, the relatively low hepatotoxicity of T-Dxd and BV, and the high hepatotoxicity of CM.

This model is a step towards a platform PBPK-QSP model that could facilitate ADC design, lead candidate selection, and clinical dose schedule optimization. By enabling early prediction and evaluation of potential toxicities, the model may be used to assess the therapeutic index early and foster understanding of the systemic impacts key design choices have on ADC actions both in and outside of the tumor.

References