A Physiologically-Based Pharmacokinetic and Pharmacodynamic (PBPK/PD) Model for Cisplatin in Humans

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Background

Cisplatin is a potent anticancer drug used for the treatment of epithelial malignancies[1, 2]. The maximum dose of cisplatin that can be administered is limited by its nephrotoxicity which can happen even under therapeutic doses[3, 4]. It is therefore of great importance to understand the pharmacokinetics and pharmacodynamics (PK/PD) of cisplatin in order to optimise therapeutic benefit and mitigate toxicity.

The primary objective of this study was to develop and verify a physiologically-based pharmacokinetic and pharmacodynamic (PBPK/PD) model with the capabilities of predicting the PK of cisplatin under various dose regimens and bridging exposure to PD outcomes such as renal function and tumour response rate.

Methods

The PBPK model of cisplatin was developed with the Simcyp Simulator V16R1. Five clinical PK studies were collated and split into development and verification datasets.

The reported plasma clearance (CL_{IV}) of free cisplatin was assigned to the contributing components[5]. Briefly, covalent binding of free cisplatin to plasma protein was modelled as plasma esterase clearance, which forms the protein bound cisplatin as a metabolite. An additional metabolite with high renal partition coefficient (Kp) was defined to recover the covalently bound cisplatin to kidney[6]. Renal clearance (CL_R) was obtained from clinical data[7]. The remnant of the CL_{IV} was assigned to an undefined additional clearance to reflect covalent binding to tissues except kidney.

Logistic regression between free cisplatin AUC and tumour response rate was carried out using R (V3.4.1.). The relationship between free cisplatin C_{max} and blood urea nitrogen (BUN)/creatinine clearance (CLcr) were reported to follow a linear and simple E_{max} model, respectively[8], and were incorporated in the model. The performance of the model was further checked using the verification dataset[8, 9].

Results

The developed PBPK model of cisplatin successfully captured the observed PK profiles of both free and total cisplatin in the development and verification datasets (**Fig. 1A & 2A, B**). The model also recovered the cumulative urinary excretion of cisplatin (**Fig. 1B**) and the accumulation of cisplatin in kidney as a result of covalent binding to tissue protein (**Fig. 1C**).

When linked to a PD model, the simulated CLcr and BUN levels were in good agreement with the observed data (**Fig. 2C, D**). Logistic regression revealed a highly significant relationship between AUC of free cisplatin and likelihood of a response (**Fig. 3A**). The AUC driven response rate model was further linked to the PBPK model and sensitivity analysis was performed to demonstrate the variation of response rate as a consequence of the interplay between PK components (**Fig. 3B**).

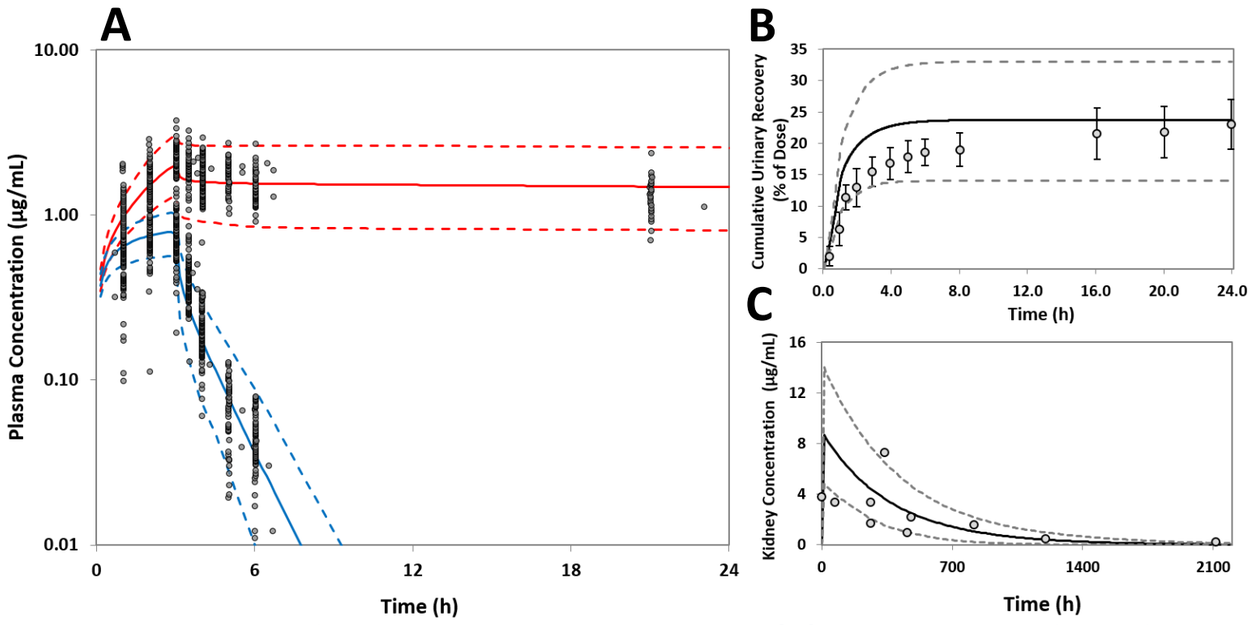

Fig. 1. Simulations for the development dataset. (A) *Plasma PK profiles of total (red lines) and free (blue line) cisplatin at 70 mg/m² over 3-hr IV infusion[5]. **(B)** Cumulative urinary excretion of cisplatin as a percentage of the dose at 70 mg/m² over 1 hr IV infusion[7]. **(C)** Concentration of cisplatin in kidney samples at 90 – 120 mg/m² IV dosing in 10 patients[6]. Solid and dashed lines represent simulated mean values and 5th/95th percentiles in the virtual population. Circles represent observed values.*

Results

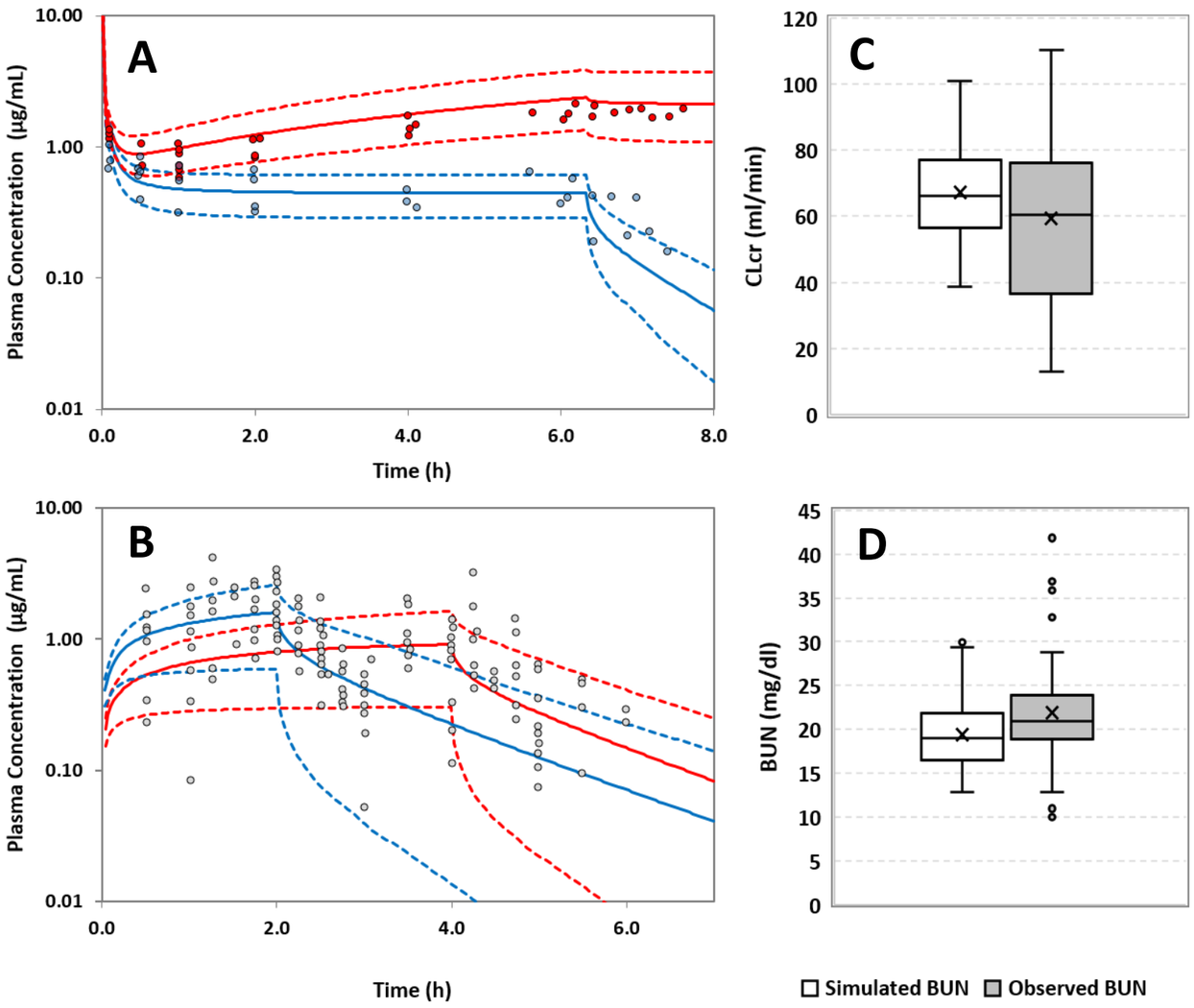

Fig 2. Simulations for the verification dataset. (A) *Plasma PK profiles of total (red lines and circles) and free (blue lines and circles) cisplatin following 100 mg/m² dosing (20% as an IV bolus and 80% IV infusion over 380 min)[9]. **(B)** Plasma PK profiles of free cisplatin at 80 mg/m² over 2-hr (blue lines) or 4-hr (red lines) IV infusion[8]. Solid and dashed lines represent simulated mean values and 5th/95th percentiles in the virtual population. Circles represent observed values. **(C)** Minimum creatinine clearance (CL_{cr}) and **(D)** maximum blood urea nitrogen (BUN) in patients receiving cisplatin treatment[8].*

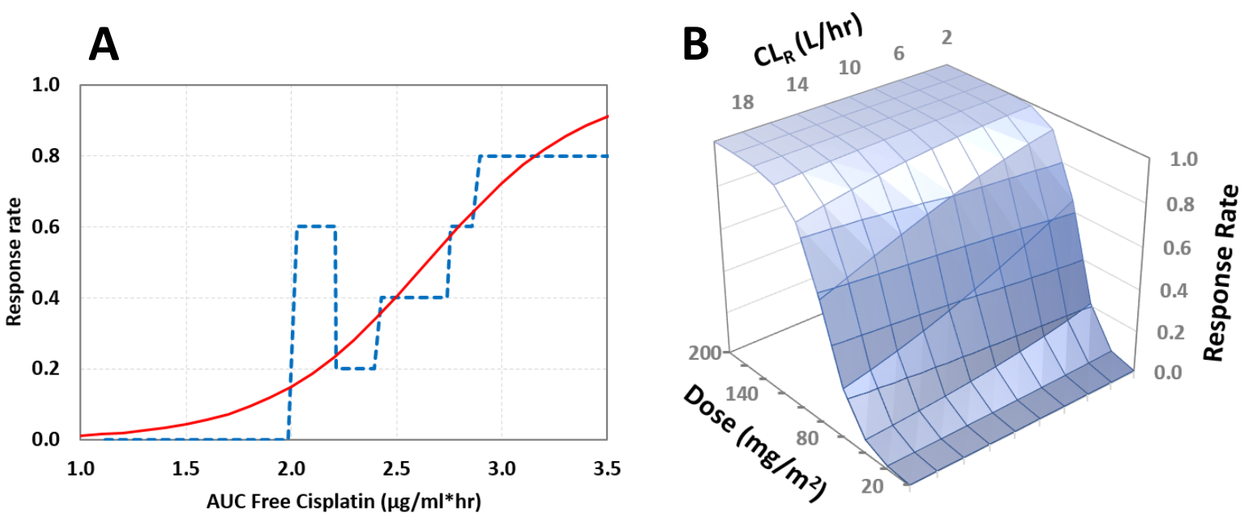

Fig 3. Simulation of tumour response rate. (A) *Logistic regression between free cisplatin AUC and response rate, blue dashed line and red solid line represent observed and simulated response rate versus AUC values, respectively. **(B)** Sensitivity analysis to demonstrate the impact of renal clearance (CL_R) and cisplatin dose on response rate.*

Conclusions

The developed PBPK/PD model of cisplatin exhibits satisfactory predictive performance and provides a better understanding of the PK/PD relationship of cisplatin in humans, which could serve as a promising tool to assist clinical use of cisplatin.

References

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