Physiologically Based Pharmacokinetic/Pharmacodynamic model of gastrointestinal toxicity induced by 5-fluorouracil in mouse and translation to human

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Background

5-fluorouracil (5-fu) is a chemotherapeutic drug inducing intestinal apoptosis, an acute event in gastrointestinal (GI) toxicity. Pre-clinical studies show that apoptosis can lead to villi atrophy [1]. Clinically, this has been associated with diarrhoea, which can interfere with chemotherapy, cause cardiovascular compromise and, ultimately, death [2]. Understanding drug-induced apoptosis would benefit the detection and prevention of GI toxicity. Physiologically-Based Pharmacokinetic/Pharmacodynamic (PBPK/PD) modelling enables tissue concentrations of drugs to be predicted and linked to models of toxicity. In this work, a PBPK/PD model was built to describe 5-fu induced crypt cell apoptosis in the small intestine of mouse and was extrapolated to the human situation.

Methods

The Simcyp Mouse simulator v17 was used to model the oral PK of 5-fu (260 mg/kg). Absorption was described by first order kinetics and elimination was considered in the liver, intestine and kidney. The unbound intestinal tissue concentration was assumed to drive the cell damage model [3], incorporated using a Lua PD script. In the model, stem cells and Transit Amplifying Daughter Cells (TADCs) divide in the intestinal crypts (Figure 1). TADCs differentiate into enterocytes, which migrate along the villi and slough off at its tip for epithelium turnover. TADC apoptosis induced by 5-fu was modelled using a Sigmoid Emax model parameterized based on published mouse apoptosis data [4]. A PD model with the same structure was assumed for human [3].

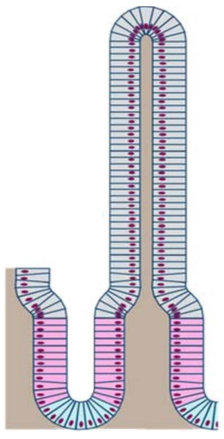


Figure 1. Illustration of the intestinal epithelium adapted from Shankaran et al [3]. Stem cells and Transit Amplifying Daughter Cells (TADCs) occupy the crypts and enterocytes the villi.

The penetration of 5-FU into human enterocytes after intravenous dosing was simulated accounting for passive diffusion across the basolateral membrane [5]. The unbound jejunum enterocyte concentration was used as a surrogate for unbound TADC concentration to drive crypt cell damage in human.

Results

Figure 2. Simulated (black line for 500 mg/m² bolus and orange for 3000 mg/m²) and observed (points, mean ± SD) [5] mean systemic plasma concentration of 5-fu in human (10 trials with 10 subjects each). Dashed lines refer to the 5th and 95th percentile of the virtual population.

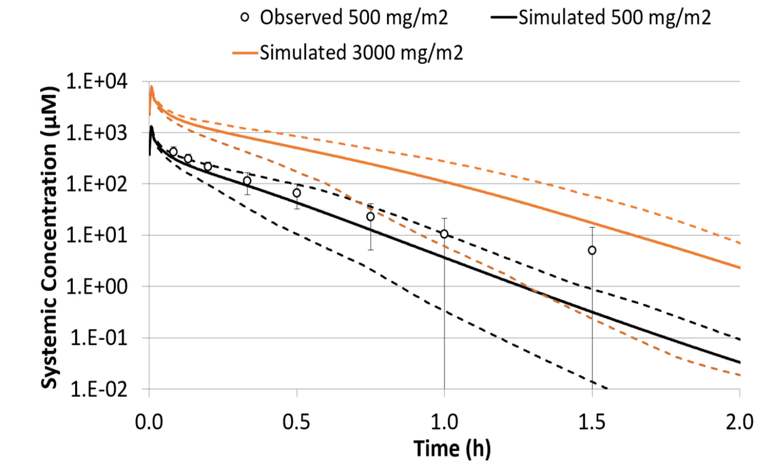
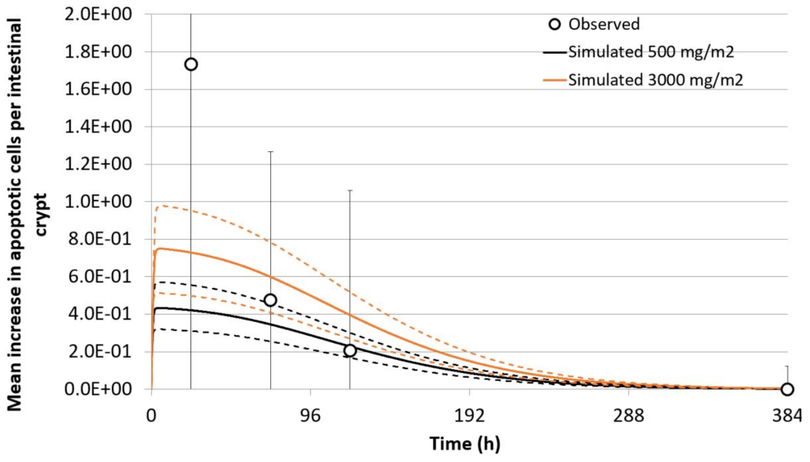


Figure 3. Simulated (black line for 500 mg/m² bolus and orange for 3000 mg/m²) and observed (points, mean ± SD) mean increase in number of apoptotic cells per crypt [6]. Variability in PD prediction is due to subject PK variability, 5th and 95th percentiles as dashed lines.



Results showed that 5-fu systemic concentration was well predicted in mouse – ratio between predicted and measured of 1.12 for Cmax, 0.52 for Tmax and 1.37 for AUC [4]. The evolution of apoptosis was well described, peaking at 10 hrs after dose with a mean number of apoptotic cells per crypt of 1.6, versus the observed 1.9 at 6 hrs [4].

For human, the predicted plasma exposure following a 5-fu bolus of 500 mg/m² reasonably agreed with clinical data (Figure 2) [5]. The predicted mean number of apoptotic cells per intestinal crypt reached a maximum of 0.4 at 5 hrs, had decreased 3% by the end of the dosing day, but recovered at 16 days after dosing (Figure 3). This agrees with histological data showing that apoptosis reaches a maximum of 1.9 cells per crypt on the first day and is recovered 16 days after chemotherapy [6]. In this clinical study, 10 patients out of 23 were in a high dose treatment, while the others were on standard chemotherapy. For this reason, a higher dose of 3000 mg/m² was also modelled. The higher mean number of apoptotic cells per intestinal crypt observed in the clinical study, associated to a high standard deviation, could be explained by the fact that the patients were administered an undefined combination of chemotherapeutic agents and other drugs may also contribute to the GI toxicity [6].

Conclusions

The PBPK/PD model developed worked well to describe the evolution of crypt cell apoptosis induced by 5-fu in mouse, and extrapolate results to human, which can help improve our understanding, as well as prevention and early detection of GI toxicity.

Future work will consider 1) enterocyte and stem cell loss, 2) cell cycle arrest, 3) multicellular events such as changes in villi height and atrophy, and 4) changes in the PK of 5-fu due to chronic GI toxicity, such as changes in intestinal permeability [6].

References

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