

A model-based analysis of the kinetics of leukocytes in stage III ovarian cancer patients treated with neo-adjuvant chemotherapy, cytoreductive surgery and cisplatin-based intraperitoneal chemoperfusion

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Background and Objectives

One of the well-known side effects of cisplatin, a chemotherapeutic agent used since the 1970s, is haematological toxicity. However, little is known on the quantitative relationship between the pharmacokinetics and the haematological toxicity.

The goal of this study is to develop a pharmacokinetic-pharmacodynamic (PKPD) model that explains the time course of leukocytes in stage III ovarian cancer patients. Ideally, this model should account for the residual myelosuppressive effects of prior doses of neo-adjuvant systemic chemotherapy (carboplatin and paclitaxel), the transient leucocytosis induced by cytoreductive surgery (CRS), and the myelosuppressive effect of cisplatin-based intraperitoneal chemoperfusion.

Material and Methods

Study flowchart and data

- 24 patients with stage III ovarian cancer
- 144 measurements of intact cisplatin concentrations in plasma
- 236 observations of leukocytes

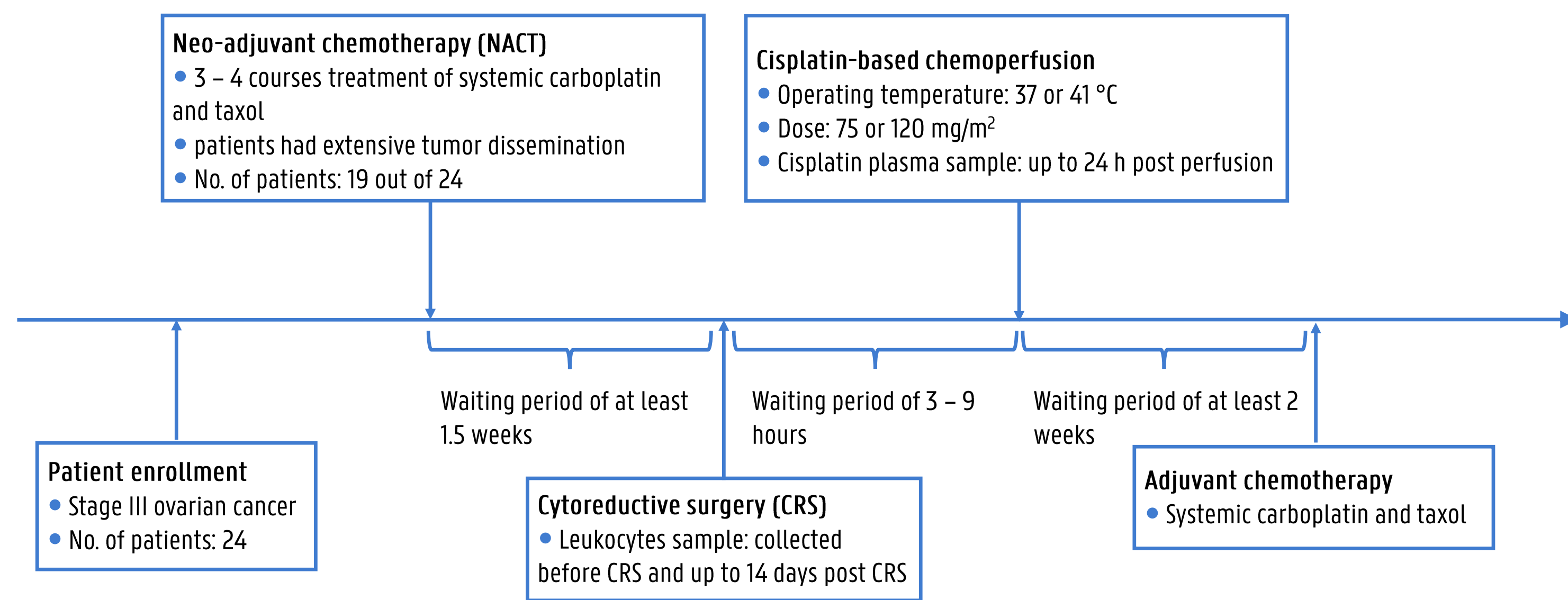


Figure 1. The treatment flowchart for the ovarian cancer patients

PKPD modelling

- Data analysis: FOCE method with interaction implemented in NONMEM®.
- Individual pharmacokinetic profiles of intact cisplatin were predicted from a newly developed population pharmacokinetic model.
- The resulting individual predicted concentrations were used as a driving force for the leukocyte counts.

Final PKPD model

- PK model: two-compartment model with first-order absorption and elimination.
- PD model: The semi-mechanistic myelosuppression model [1] was extended by adding a deposit compartment representing the stored mature leukocytes within the bone marrow sinusoids.
- The model incorporates residual myelosuppressive effects of neo-adjuvant chemotherapy, the CRS stimulatory effect and the myelosuppressive effect of cisplatin-based chemoperfusion.

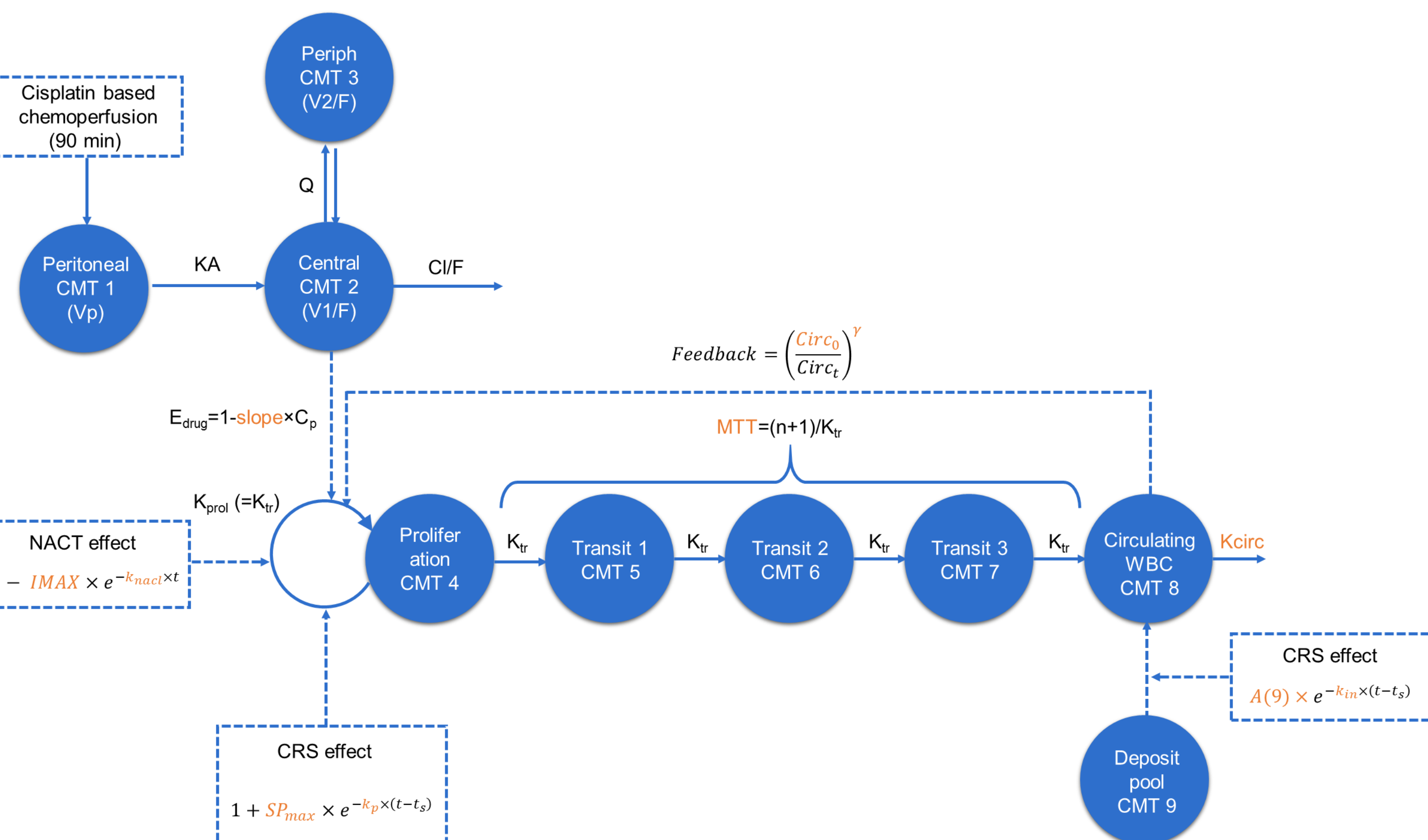


Figure 2. The extended semi-mechanistic myelosuppression model. The model consists of a proliferating cell pool connected to three transit compartments describing the maturation of the non-proliferative cells, a blood circulation compartment for the observed leukocytes, and a deposit compartment representing the stored mature leukocytes within the bone marrow sinusoids. A feedback loop on the proliferation from the circulating leukocytes was incorporated. CRS was assumed to initialize the mobilization of leukocytes from the deposit compartment to the circulating compartment and increased the mitosis rate of proliferative cells[2-3]. The residual myelosuppressive effect of the neo-adjuvant chemotherapy was modeled using an inhibitory function on proliferation rate. The estimated parameters are in yellow. NACT: Neoadjuvant chemotherapy.

Results

Model graphical evaluation

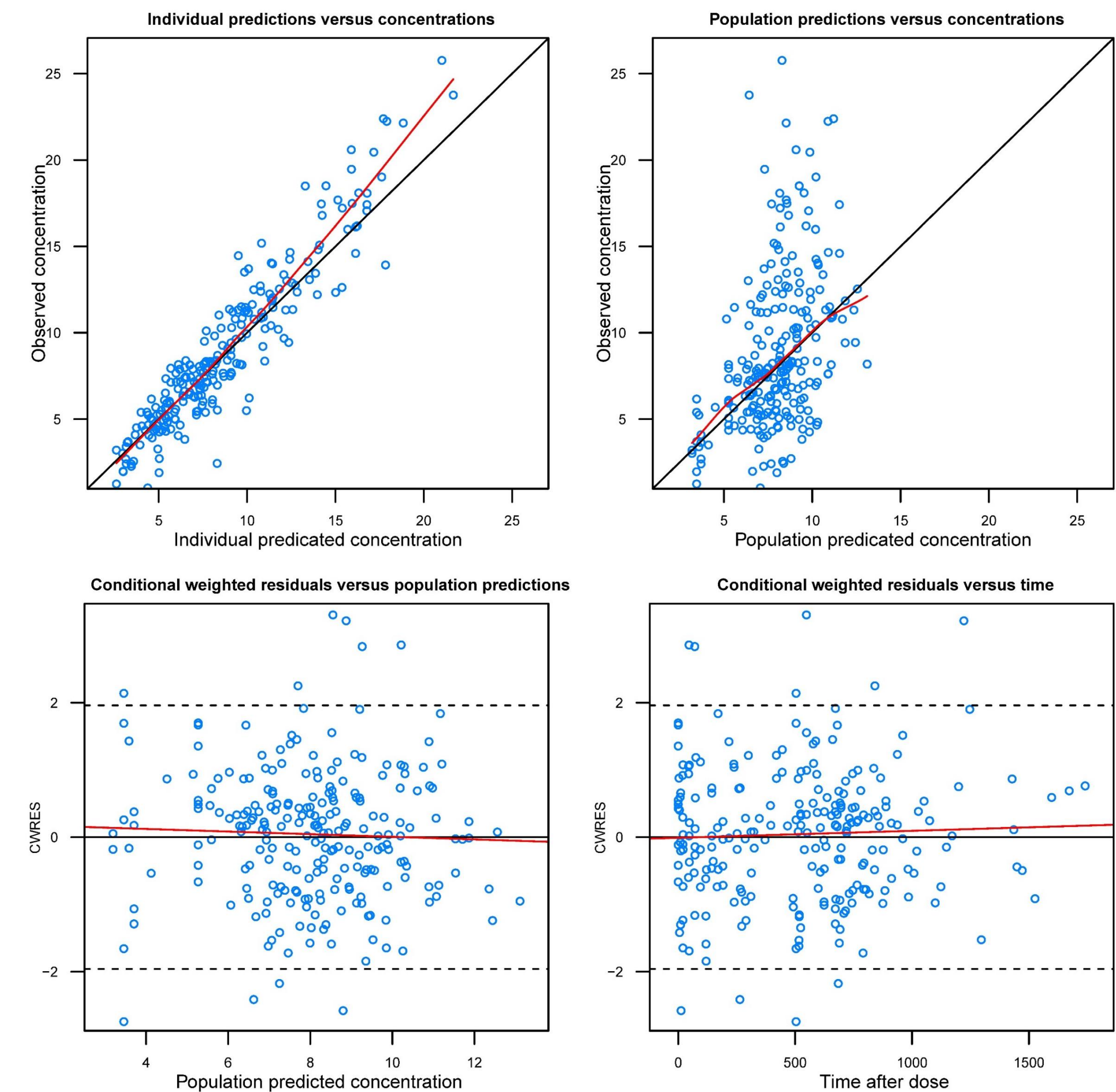


Figure 3. Goodness-of-fit plots for the leukocyte model

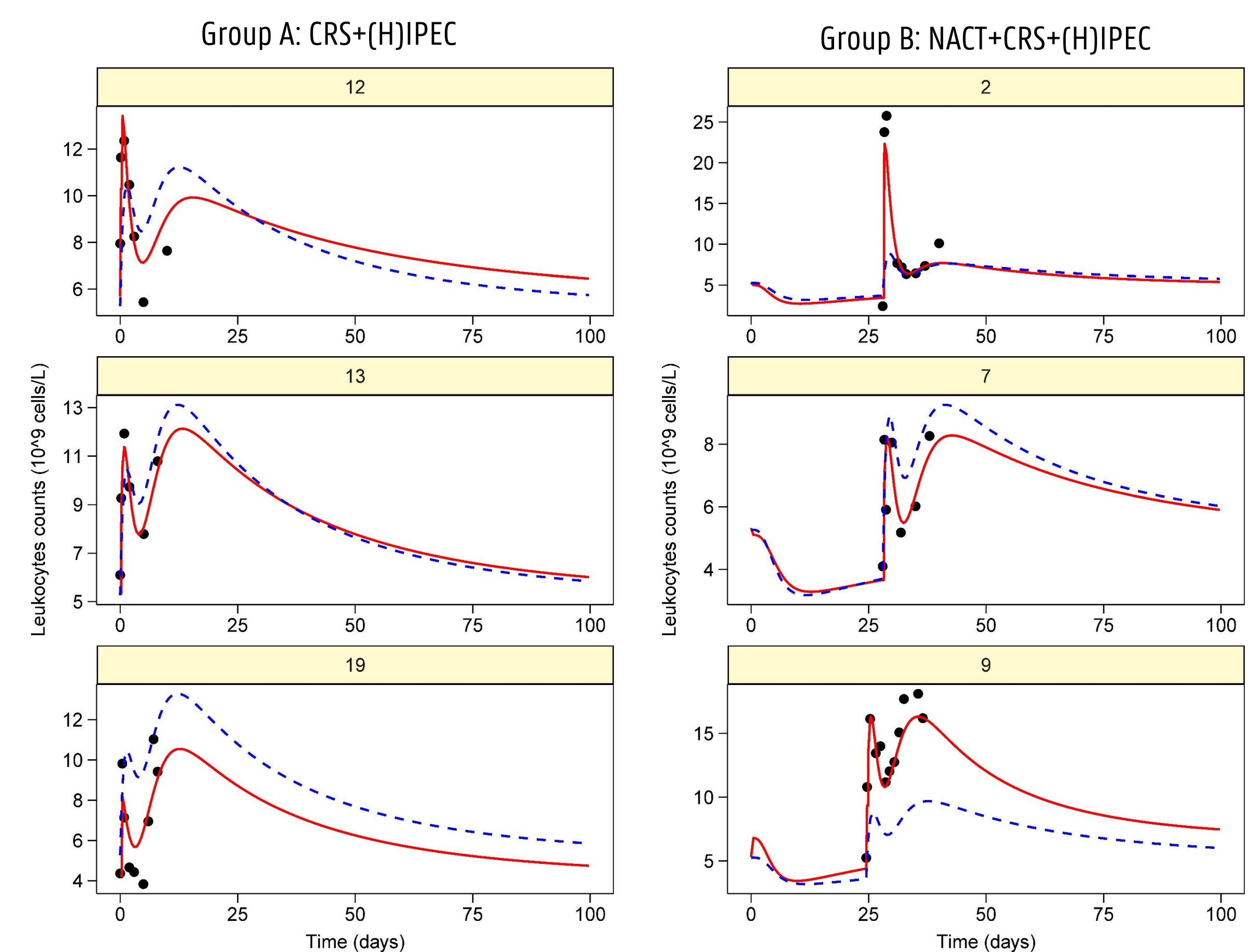


Figure 4. Representative individual time-course of leukocytes and the model population (blue line) and individual predictions (red line) for group A and B. NACT: Neoadjuvant chemotherapy, (H)IPEC: normothermic (37°C) or hyperthermic (41°C) intraperitoneal chemoperfusion.

Simulation of typical population response

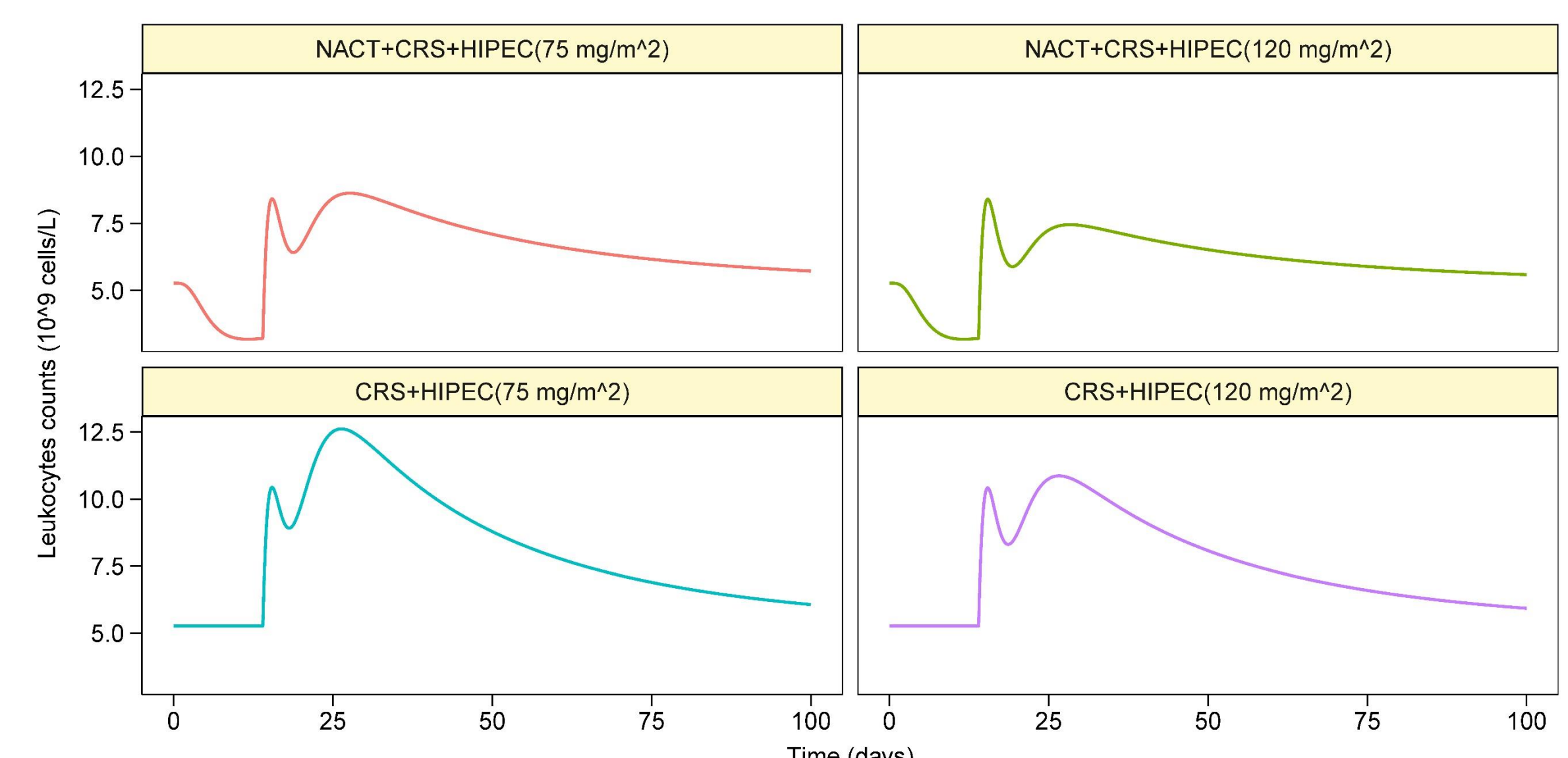


Figure 5. Typical population response in various scenarios. NACT: Neoadjuvant chemotherapy, HIPEC: hyperthermic (41°C) intraperitoneal chemoperfusion.

Conclusions

A leukocyte model was developed to simultaneously account for the residual myelosuppressive effect of neo-adjuvant chemotherapy, the transient leucocytosis response induced by CRS, and the myelosuppressive effect of cisplatin-based (H)IPEC. The PKPD model demonstrates that leucocytosis and leucopenia were reversible and short-lasting following CRS and cisplatin based (H)IPEC. In the absence of other cisplatin-induced side effects, higher cisplatin (H)IPEC doses could be considered without significantly raising the risk of major haematological toxicities.

References

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