Summary

Peritoneal carcinomatosis (PC) from ovarian cancer is characterized by poor prognosis with current standard of care: cytoreductive surgery (CRS) plus intravenous (IV) chemotherapy. The poor outcome is thought to be due to the insufficient killing of IV chemotherapy for the peritoneal residual microscopic disease left by CRS. Encouraging results have been reported with use of intraperitoneal chemotherapy (IPC) as a local-regional treatment strategy for enhancing drug delivery at the peritoneal surface, thereby may improve the treatment outcome (see details in Chapter 1). The main objective of this thesis was to evaluate the benefits and risks of the intraoperative (hyperthermic) intraperitoneal chemoperfusion ((H)IPEC) and prolonged IPC for treating residual microscopic disease at clinical and preclinical levels, respectively (see details in Chapter 2). Cisplatin was selected as the model drug for the evaluation of (H)IPEC treatment regimens in patients with advanced ovarian cancer (Chapter 6), while in-house developed paclitaxel-loaded genipin-crosslinked gelatin microspheres (PTX-GP-MS) were used to test the efficacy of prolonged IPC in a microscopic peritoneal carcinomatosis mouse model (Chapter 7).

In an attempt to answer our research questions, a multi-disciplinary strategy was followed: First, we developed bioanalytical methods serving as the tools for obtaining the time-course information of the plasma / blood concentration of the analyte of interest; Second, experimental work either through a clinical trial or through preclinical experiments was set up to collect the required data; Third, the experimental results were integrated and interpreted using pharmacokinetic-pharmacodynamic (PKPD) modelling and simulation approach.

Chapters 3-5 show the efforts for the development of state-of-the-art (bio)-analytical methods in support of the preclinical and clinical trials. In Chapter 3, we described the experimental work on cisplatin’s hydrolysis—a activation process for its mode of action and toxicity—using electrospray ionization mass spectrometry. The results revealed a complicated hydrolysis process of cisplatin, and based on the found degradation pathways a renewed mechanistic equilibrium system of cisplatin was proposed. The hydrolysis information of cisplatin served as a basis for the subsequent bioanalytical method development for intact cisplatin. Chapter 4 outlines the development of a selective, sensitive, and high throughput assay for the quantification of intact cisplatin in human plasma, based on HybridSPE-precipitation coupled to UPLC-MS/MS. Throughout the method development, we overcome the prime challenges encountered with cisplatin: the chromatographic separation of the poorly retained cisplatin and the required high sensitivity, with respect to its high polarity and weak MS signal response. Extensive validation of the developed method showed that we succeeded in developing a reliable bioanalytical method free of relative matrix effects and with good accuracy and...
precision. In Chapter 5, we described a dried blood spots (DBS)-based assay for paclitaxel and its metabolites in support of efficient blood sampling and measurement in mice. This developed method demonstrated several advantages, including the use of tiny blood sample volume, simple sample processing procedure, short elution time, and excellent sensitivity. The use of DBS method offers the opportunity for serial PK microsampling in mice thus reduces the number of study animals, promoting an animal-friendly preclinical investigation.

Using the developed bioanalytical method of cisplatin (Chapter 4), the clinical plasma and perfusate samples from ovarian cancer patients treated with cisplatin-based (H)IPEC were analyzed. In Chapter 6, we showed how these drug concentration measurements were interpreted using population modelling approach in order to elucidate the influences of different doses and hyperthermic administration in the PK properties of cisplatin. Afterwards, we demonstrated how to quantitatively bridge the PK knowledge to drug-induced continuous hematoxicity data (leukocyte-based measurements) as well as frequently collected ordered categorical nephrotoxicity data (serum creatinine-measurements). Lastly, using the developed PKPD models, we prospectively evaluated the safety of new (H)IPEC treatment regimens through simulations in order to find the optimal treatment protocol with minimal toxicities.

In Chapter 7, by pooling the measured DBS data of PTX-GP-MS in mice, we showed how to use the population approach to maximize the utility of these sparse data in order to inform the local and systemic PK behaviors of PTX-GP-MS. Subsequently, by combining the PK information with the survival outcome, we developed a PKPD model capable of simultaneously describing the competing effects of treatment efficacy and toxicity of PTX on the survival. The model was then used to learn the interplay between positive treatment effects and toxicity on survival outcome. Based on the simulations, we concluded that low-dosed PTX-GP-MS is the way forward to achieve the optimal net benefit.

Chapter 8 presents the discussion and conclusions of this thesis. The findings of bioanalysis and PKPD modelling in preclinical and clinical studies were combined to describe the lessons learned. Throughout the thesis, it was shown that the development and use of suitable bio-analytical methods to quantify the target analytes in biological samples are the crucial element to obtain valuable PK data, which are the driving force for the PKPD modelling. Also, PKPD modelling was demonstrated powerful to leverage the collected data to inform optimal treatment regimens, especially dealing with the common but intractable PD categorical data such as survival and repeatedly measured graded data.

Finally, in Chapter 9, we showed the broader international context, relevance and future perspectives of this work. We outlined the international efforts and controversies in the IPC treatment of PC and pointed out the international need to further validate and improve IPC treatment of PC. Furthermore,
future directions and novel strategies were highlighted to answer the unsolved questions (such as the role of hyperthermia) and to improve the IPC treatment of PC.