Computational modeling of pharmacokinetics and tumor dynamics to guide anti-cancer treatment

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Chapter 9

Summary
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Quantitative modeling with mixed-effect models has been increasingly applied in pharmaceutical research. It allows quantitative description and prediction of pharmacokinetics (PK) and pharmacodynamics (PD) of therapeutic agents, as well as to quantify and explain inter- and intra- individual variability. In oncology research, the model-based approach can be applied to make use of longitudinal data to learn about the interaction between drug treatment and the human body, as well as cancer progression. The developed model can subsequently support the identification of the optimal regimen and facilitate individualized treatment.

In cancer treatment, the occurrence of treatment resistance is one of the major causes of treatment failure in patients. An insight into the inter- and intra-tumor heterogeneity and evolutionary dynamics of tumors, and subsequent use of this knowledge for designing treatment strategies would be beneficial for optimizing targeted anti-cancer treatment. In **Section I** of this thesis, we applied the model-based approach to specifically interpret tumor size dynamics and evolutionary resistance development during treatment, and explored optimal regimens that can better suppress the development of resistance.

In order to identify opportunities and challenges of quantitatively characterizing anti-cancer treatment response accounting for tumor dynamics and evolutionary resistance development, an overview of currently available model structures is needed. In **chapter 2**, we performed a systematic search and comprehensively summarized the mathematical models that have been used to describe and predict tumor growth (inhibition) dynamics and evolutionary resistance development. We particularly focused on models that are applicable to clinical data. In this review, tumor dynamic models displayed by ordinary differential equations, algebraic equations, and partial differential equations were identified and summarized. Tumor proliferation, regression due to treatment, tumor heterogeneity and treatment resistance are key elements that are commonly considered in those models. The dynamics of biomarkers can also be incorporated which enables better understanding and prediction of tumor progression. As for models for evolutionary tumor resistance, stochastic and deterministic models were identified and summarized. The required data and knowledge as well as the applicability of the models to different cancer types and treatment options were also summarized. The results of this review may facilitate a novel model-based analysis of anti-cancer treatment response and the occurrence of resistance, which incorporates both tumor dynamics and evolutionary resistance development.

Among the studies included in this review, detailed data regarding evolutionary resistance has not yet been incorporated in tumor size-based modeling of anti-cancer treatment

response. Given that genetic biomarkers, such as circulating tumor DNA (ctDNA), become increasingly available, there is an opportunity to make use of such data to support the development of a tumor dynamics model that accounts for evolutionary resistance for cancer patients. The developed model could subsequently support the optimization and personalization of anti-cancer therapy with simulations.

In order to test this concept, in **chapter 3**, a mathematical model incorporating various clonal populations and evolving cancer resistance was developed to characterize tumor size dynamics and resistance development under treatment. With parameter values fitted to the data or informed by literature data, the model well captured previously reported tumor sizes and mutant *KRAS* levels in ctDNA of patients with metastatic colorectal cancer (mCRC) treated with panitumumab. Subsequently, we evaluated anti-cancer treatment schedules the design of which considered the evolving progression of tumor and demonstrated the use of ctDNA as a marker to guide adaptive treatment. The simulation results indicated that compared with a conventional continuous treatment schedule, intermittent schedules with treatment holidays and adaptive schedules guided by ctDNA could better suppress the evolving cancer resistance. Intermittent and adaptive schedules were also predicted to result in improved clinical outcomes, i.e. the predicted median progression-free survival (PFS) and time period in which the tumor size stayed below the baseline level were prolonged. With the sensitivity analysis, we identified parameters of which the accurate estimation is important for the model to capture the observed dynamics of tumor sizes and mutation concentrations. Nevertheless, the intermittent and adaptive treatment still provided better treatment outcomes when parameter values varied.

In **chapter 4**, we further characterized the tumor dynamics considering intra-tumor heterogeneity and explored the correlation between ctDNA measurements and tumor dynamics parameters based on data from non-small cell lung cancer (NSCLC) patients treated with erlotinib. The study included intensively sampled erlotinib PK curves from 29 patients, and tumor sizes, ctDNA measurements, and sparsely sampled erlotinib concentrations from 18 patients from the START-TKI study. A population PK model of erlotinib was first developed and subsequently applied to investigate the exposure-tumor dynamics relationship. To characterize the tumor dynamics, models accounting for intra-tumor heterogeneity and acquired resistance with or without a pre-existing resistance component were investigated. Eventually, a model with acquired resistance only resulted in an adequate fit to the data. Additionally, no significant exposure-response relationship for erlotinib was identified within the observed exposure range. Subsequently, the correlation of baseline ctDNA measurements on *EGFR* and *TP53* variants with tumor dynamics parameters was explored. The analysis indicated that higher baseline plasma *EGFR* mutation levels correlated with

increased tumor growth rates, and the inclusion of ctDNA data improved model fit. This result suggests that quantitative ctDNA measurements have the potential to be a predictor of anti-cancer treatment response, which encouraged to use ctDNA as an early biomarker.

Since high PK/PD variabilities of anti-cancer drugs are present in real-world patients which may result in unfavorable treatment outcomes, a better understanding of such variabilities would be beneficial to improve anti-cancer therapy for individual patients. In **Section II** of this thesis, we demonstrated the application of pharmacometric modeling in characterizing the PK/PD profiles and variabilities of anti-cancer drugs, and in supporting precision treatment for real-world patients. We first introduced model-informed precision dosing (MIPD) and the current application and benefit of MIPD in supporting optimal and precision anti-cancer treatment in **chapter 5**. MIPD adopts pharmacometric models to guide precision dose selection aiming for improved therapeutic target attainment and optimal treatment outcome. MIPD can be applied to rationally guide initial dose selection and dose adaptation during anti-cancer treatment, as well as therapeutic drug monitoring (TDM). The advantage of MIPD over conventional strategies in cancer treatment has been demonstrated in many research and clinical trials. However, challenges still have to be overcome to implement MIPD of cancer therapies in clinical practice. We highlighted a few challenges and provided future perspectives regarding optimal target identification, suitable model selection, available programs, and the necessity of prospective clinical trials.

In **chapter 6**, we performed a population PK analysis to characterize and predict mitotane PK in patients with adrenocortical carcinoma (ACC). Additionally, we explored and quantified the potential effect of pharmacogenetic variations on mitotane clearance for the first time to better explain the PK variability of mitotane. A two-compartment PK model was developed based on retrospectively collected data from 48 patients. For each patient, the genotyping results of 172 SNPs from the DMET™ platform were included in the analysis. The exploratory analysis identified 11 SNPs that were potentially related to mitotane clearance. The final stepwise covariate analysis identified the lean body weight (LBW), genotypes of *CYP2C19*2* (rs4244285), *SLCO1B3* 699A>G (rs7311358), and *SLCO1B1* 571T>C (rs4149057) as significant covariates on mitotane clearance (CL/F). This suggests that enzyme CYP2C19 and transporter SLCO1B1 and SLCO1B3 may play roles in mitotane disposition but further external or in vitro evaluation is warranted to confirm the results. Based on the developed model, various dosing regimens and the TDM process were simulated to investigate optimal and individualized mitotane regimens for patients with ACC. The results indicated that determining the starting dose individually with the developed model is beneficial to shorten the period for mitotane to reach the therapeutic target and limit the risk of toxicity. Regimens that can effectively maintain

mitotane concentration within its therapeutic range, i.e., 14–20 mg/L, were established. One optimal regimen was then built in a Shiny app to elucidate an option of providing treatment advice for a new patient based on the model.

In **chapter 7**, we performed a population PK analysis on high-dose methotrexate (HD-MTX) in patients with central nervous system (CNS) lymphoma. Data from 110 patients from 3 medical centers were available in this study. A two-compartment population PK model was developed and shown to adequately describe the PK data. Estimated glomerular filtration rate (eGFR), treatment schedule, albumin, alkaline phosphatase, and body weight were identified as significant covariates. The results suggest that adjusting the HD-MTX dose with a model-based approach may be more rational to further reduce PK variability than dosing only based on body surface area (BSA). Subsequently, a (exposure-)toxicity analysis was performed to identify predictive factors for acute renal and liver toxicity. eGFR and sex were identified to be significant baseline predictors for renal toxicity, and HD-MTX dose (mg/m^2) was the strongest baseline predictor of liver toxicity. Simulation results suggest that starting HD-MTX when eGFR > 66.6 $mL/min/1.73m^2$ is recommended for patients with CNS lymphoma, and a dose higher than 3500 mg/m^2 predicted a high risk of liver toxicity. The exposure metrics of methotrexate (MTX) including the area under the concentration-time curve ($AUC_{24-\infty}$) and concentration at 24 hours (C_{24h}) were identified to correlate with renal toxicity but not with liver toxicity. $AUC_{24-\infty}$ > 109.5 μmol/L*h and C_{24h} > 8.64 μmol/L were suggested to be potential exposure thresholds that predict a high risk of toxicity. These findings would be beneficial for further individualizing HD-MTX dosage and preventing acute organ toxicity, which can improve HD-MTX therapy in CNS lymphoma patients.

Finally, in **chapter 8**, we discussed the results of this thesis and potential challenges and perspectives for future studies. We have shown that with the quantitative models, the evolutionary progression of tumor can be characterized and predicted, accounting for interactions among heterogeneous tumor cells and supported by mutant gene variants detected in ctDNA. In addition, population PK/PD modeling allows for a quantitative description of the PK and PD of anti-cancer drugs at both population and individual levels. The developed model can further facilitate the identification of optimal treatment designs and guide individualized treatment rationally for oncology patients. However, challenges still remain for data collection (especially for ctDNA data), model development and validation, and results implementation (including suggested regimens and the models). Further research is warranted to validate the findings and support better practice of personalized treatment.