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

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# Chapter 1

## General introduction

## Importance of optimizing anti-cancer treatment

Worldwide, cancer is a leading cause of death and the incidence of cancer is rapidly increasing, reflecting both the aging of the population and the prevalence of main risk factors such as unhealthy lifestyle [1, 2]. Continuous efforts have been made to meet the medical needs of cancer patients and numerous options are currently available. A conventional treatment option for cancer patients is cytotoxic chemotherapy, which aims to inhibit tumor cell multiplication by affecting the synthesis or function of macromolecular [3]. In recent decades, targeted therapies, which act on specific oncogenic proteins that drive tumor growth or progression, have also become a standard type of anti-cancer treatment [4, 5]. Due to the increasing knowledge of molecular alterations in tumor cells, appropriate drug targets can be identified and specific targeted treatment options can be selected [6]. These targeted therapies have significantly improved the survival of cancer patients, and more than eighty targeted drugs have been brought to the market over the past decades [4, 7].

However, obstacles to accomplishing successful anti-cancer treatment still exist. First, for both conventional chemotherapies and targeted therapies, one important reason for patients experiencing treatment failure is drug resistance [8, 9]. The occurrence of drug resistance is mediated by a range of mechanisms, including physical barriers and impact of the tumor microenvironment [4, 9]. Evolutionary mechanisms are also increasingly acknowledged as key factors that contribute to the development of drug resistance. It is driven by inter- and intra-tumor heterogeneity, i.e. distinct cells exist in different or same tumors which show different susceptibility to treatments, and the evolving adaptation of tumor cells to the selection pressure of anti-cancer drug treatment, i.e. resistance subclones are acquired or are adaptively selected from pre-existing subclones during treatment [9-12]. To increase the chance to suppress the development of drug resistance, a better characterization and understanding of evolutionary tumor progression, and subsequent use of this knowledge to design new adaptive treatment regimens are desired.

Another important factor that challenges successful treatment is the substantial variability in pharmacokinetics (PK) and pharmacodynamics (PD) of anti-cancer drugs, which is especially frequently observed in real-world patients. Due to the existing correlations between drug exposure and treatment response (efficacy and toxicity) for many oncologic drugs, such variability can result in suboptimal treatment outcomes for part of the patients especially when the therapeutic window is narrow [13, 14]. Thus, the need for precision dosing in cancer therapy instead of a 'one-dose-fits-all-approach' is emerging [14]. In addition, the dosages of most oncology drugs are selected according to the maximum tolerated dose (MTD) paradigm [15]. This can lead to a demand for dose modification

in real-world patients due to the risk of toxicity [15]. Therefore, optimizing dosage of anti-cancer drugs to ensure efficacy while minimizing toxicity is essential. To achieve this goal, it would be beneficial to better understand and predict PK/PD profiles and exposure-response relationships of anti-cancer drugs, and identify factors that explain PK/PD variability (between and within patients) in real-world populations. In addition, a useful tool to support optimal and personalized dose and regimen selection based on the therapeutic target is warranted. This knowledge can also contribute to a better implementation of therapeutic drug monitoring (TDM) in cancer patients.

## Longitudinal (bio)markers

Monitoring longitudinal (bio)markers during anti-cancer therapies enables assessment of cancer progression and treatment response. Tumor burden is a commonly used indicator of anti-cancer treatment effect and is routinely monitored in clinical practice. In solid tumors, tumor burden is typically quantified with the sum of the longest diameters (SLD) of target lesions, which also forms several clinical endpoints defined by Response Evaluation Criteria in Solid Tumours (RECIST version 1.1) [16]. The longitudinal tumor size measurements can reflect the dynamics of treatment effect and tumor progression. SLD related metrics, such as relative or absolute changes from baseline, have also showed to be predictive to the overall survival of cancer patients [17]. In addition to tumor diameters, soluble tumor markers have also been used to measure total tumor burden in clinical practice. These include prostate-specific antigen (PSA) in prostate cancer, CA125 in ovarian cancer, M-protein in multiple myeloma, and carcinoembryonic antigen (CEA) in colorectal cancer [17, 18].

Circulating biomarkers, including soluble drug targets, inflammatory biomarkers, and circulating genetic biomarkers, can also be assessed to monitor treatment response and guide treatment modification. Circulating tumor DNA (ctDNA) is an emerging genetic biomarker which refers to cell-free DNA (cfDNA) fragments that are released into the circulation from primary tumor or metastatic cells [6]. It can be detected from liquid biopsies which allows real-time monitoring with limited patient burden. From serial ctDNA analysis, cancer-related genetic alternations can be detected and quantified, which can reveal the mechanisms of resistance to targeted therapies, and provide important insights into tumor heterogeneity and drug resistance evolution during treatment [6, 9, 19-21]. With relevant genetic alternations detected, ctDNA monitoring can potentially guide early adjustment of treatment to target newly developed actionable mutations, thereby suppressing the proliferation of tumor subclones [9, 19, 22]. In addition, the quantified

ctDNA measurements have also shown to correlate with tumor burden and stage, and ctDNA dynamics has been demonstrated to correlate with therapeutic response in various kinds of cancers [19, 20, 23-25].

Therefore, data on longitudinal (bio)markers demonstrate great value in supporting the investigation of evolutionary tumor dynamics and resistance development and PK/PD relationships of oncologic drugs. Biomarker monitoring also holds the potential to guide better treatment design aiming for improved cancer treatment outcomes.

## Pharmacometric modeling

Pharmacometric modeling has been increasingly applied in pharmaceutical research to support decision making in drug development and treatment optimization. Computational models allows quantitative characterization and prediction of the time courses of drug exposure (PK), treatment response (PD), and disease progression, as well as their relationships following drug administration [26, 27]. Mixed-effect modeling (population modeling) approach is commonly applied which allows the description of population level trends (i.e. fixed effects) and quantify random inter- and intra-individual variability (i.e. random effects) simultaneously [26, 27]. Covariates that explain the variability can also be explored.

In oncology research, the model-based approach is a helpful tool to make use of longitudinal data to gain knowledge about the interaction between drug treatment, the human body and disease. This knowledge can subsequently be used to advance treatment optimization and rationalize individualized therapy [14, 27, 28].

Models that characterize the dynamics of tumor size measurements represent one key class of PD models in cancer research. To better interpret the emergence of drug resistance, the importance of accounting for tumor heterogeneity and drug resistance evolution in tumor dynamics modeling has been pointed out before [29]. Up until now, various model structures have been proposed to characterize the tumor dynamics and drug resistance evolution in solid tumors, which can serve as references for future studies [10, 17, 30, 31]. Moreover, PK metrics and genetic biomarkers as well as their relation with tumor size dynamics can also be investigated and incorporated in the model, which would further benefit the understanding of PK/PD relationships and evolutionary tumor progression. In conjunction with simulations, the model could be used to explore optimal adaptive treatment strategies that can better prevent or delay anti-cancer treatment resistance.

Computational models that characterize the PK/PD profiles and variability of anti-cancer drugs can also guide optimal dose selection and enable individualized therapy (model-informed precision dosing (MIPD)) [14]. With the PK-PD behavior and covariates identified by the model, the optimal treatment regimen that ensures balance between efficacy and toxicity for individual patients can be identified. This can be especially helpful to guide the selection of the initial dose and schedule aiming at the target exposure. Other approaches that support precision dosing, such as pharmacogenomics, can also be integrated with MIPD [14]. Moreover, with the Bayesian framework of the developed model, individual parameters can be estimated once patient characteristics and data are known [14]. This enables more precise capture and prediction of individual PK/PD profiles, which could guide the selection of the next dose rationally. Compared with conventional TDM, MIPD provides the decision support in a quantitative manner.

## Aim and outline of this thesis

With the studies in this thesis, we aim to proceed toward better treatment for oncology patients with model-based approach.

In **section I**, we aim to quantitatively characterize and understand the evolutionary tumor dynamics and resistance development during treatment, and to identify treatment schedules that can better suppress the occurrence of resistance.

In **chapter 2**, we perform a systematic literature search and comprehensively summarize the mathematical models that have been used to describe and predict tumor growth (inhibition) dynamics and evolutionary resistance development. The focus of this review lies particularly on models that are applicable for clinical data.

In **chapter 3**, a mathematical model incorporating various tumor clonal populations and evolving cancer resistance is developed to characterize tumor size dynamics and resistance development under treatment, as well as and ctDNA dynamics based on data from metastatic colorectal cancer (mCRC) patients. Subsequently, we evaluate adaptive and intermittent treatment schedules and demonstrate the use of ctDNA as a marker to guide adaptive treatment.

In **chapter 4**, we further characterize the tumor dynamics and development of drug resistance in NSCLC patients treated with erlotinib with a model considering tumor heterogeneity. A population PK model of erlotinib is also developed and subsequently used to facilitate the investigation on the exposure-tumor dynamics relationship of erlotinib.

Additionally, the potential correlation between ctDNA measurements and tumor dynamics in NSCLC patients is explored to further understand the value of monitoring ctDNA.

In **section II**, we aim to characterize the PK/PD profiles and variabilities of anti-cancer drugs in real-world patients to facilitate treatment optimization, and to demonstrate the use of pharmacometric models in guiding individualized treatment.

In **chapter 5**, we introduce the application and benefits of model-informed precision dosing in supporting anti-cancer treatment optimization and individualization, and discuss the challenges and future perspectives of implementing MIPD in cancer therapies.

In **chapter 6**, a population PK analysis is performed for mitotane in patients with adrenocortical carcinoma (ACC). The effect of pharmacogenetic variations on mitotane PK are investigated to better explain mitotane PK variability. Simulations are subsequently performed to investigate optimal treatment regimens and facilitate treatment individualization for patients with ACC.

In **chapter 7**, we perform a population PK analysis on high-dose methotrexate (HD-MTX) in patients with central nervous system lymphoma. Additionally, a (exposure-)toxicity analysis is performed to identify baseline and exposure-related predictive factors for the acute renal and hepatotoxicity.

Finally, in **chapter 8** we conclude this thesis with a general discussion and future perspectives in data collection, model development, and results implementation regarding the suggested regimens and developed models. English and Dutch summaries are presented in **chapter 9**.

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