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THE EFFICACY OF PHARMACOKINETIC MODELING IN DRUG DOSAGE OPTIMIZATION

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Abstract

Precision dosage in cancer has significant appeal for several reasons. A significant number of anticancer medications have a limited range of effectiveness, such that inadequate treatment might result in serious consequences for the patient. Recruitment of clinical research participants is seldom expanded outside the target patient group, resulting in challenges in enrolling patients for specific clinical studies. Given the significant number of individuals who do not react to cancer therapy and the expensive nature of such treatments, it is necessary to explore new approaches that might enhance clinical efficacy and cost-benefit. Pharmacokinetic (PK) modeling and model-informed precision dosing (MIPD) provide potential solutions to optimize these outcomes. Pharmacokinetic (PK) modeling offers a precise method to measure and analyze the differences in drug exposure across individuals, taking into consideration factors such as confounders and the effects of drug interactions. This is achieved via the use of physiologically-based PK (PBPK) modeling, which allows for accurate predictions in particular populations and the extrapolation of data. This article provides an overview of the current status of pharmacokinetic (PK) modeling in precision dosing of anticancer medications. The information is derived from a thorough assessment of the literature and includes several case studies from both the pharmaceutical business and healthcare research. Although significant advancements have been achieved in incorporating model-informed dose recommendations into prescription labels and much research has been conducted to address dosing concerns that are important in clinical settings, the use of MIPD in healthcare has been limited. The efficacy of pharmacokinetic (PK) modeling in the industrial sector has been facilitated by cooperative efforts among regulatory bodies, the private sector, and educational institutions. In order to promote the broader use of PK modeling in precision dosing of anticancer medications, it is crucial to establish collaboration between academia, healthcare, and industry. Additionally, financial support for studies on patient benefit, cost-benefit analysis, and clinical success of these techniques is essential.

Keywords: Population pharmacokinetics (PK); physiologically-based pharmacokinetics (PBPK); modeling; customized dose; cancer.

1. Introduction

During medication development, late phase clinical studies often seek to determine consistent dosing that balances effectiveness and toxicity among the patient population using a restricted range of potential dose plans.Jeny (1). Traditionally, the administration of anticancer medications has been determined by considering the body surface area (BSA) since it is believed to be correlated with clearance (CL) or volume of distribution (Vd). Nevertheless, this connection often lacks effectiveness and may not precisely represent the change in drug exposure seen in the general population (2-5), resulting in a significant level of variability in drug exposure at the prescribed dose regimen (5). This is especially accurate when administering the medicine to a broader range of patients in clinical settings, including those with complicated drug-drug interactions (DDIs), pediatric patients, and those with poor kidney or liver function or other specific groups (6).

Detailed dose instructions are often lacking in the medicine label for the majority of specific groups upon approval (7). These aspects contribute to the variability of clinical practices, where physicians face the problem of making judgments based on their expertise and sometimes inadequate knowledge. Patients who have several comorbidities or are taking many medications are consequently at risk of receiving suboptimal pharmacotherapy, which may result in excessive levels of toxicity or diminished effectiveness (6,8,9). Model-informed precision dosing (MIPD) is a method that uses statistical and mathematical modeling, such as pharmacokinetic (PK) modeling, to determine the optimal dose for each individual patient. It takes into account factors like inter-individual variability (IIV) and other factors that can cause differences in drug exposure and pharmacodynamic (PD) response.

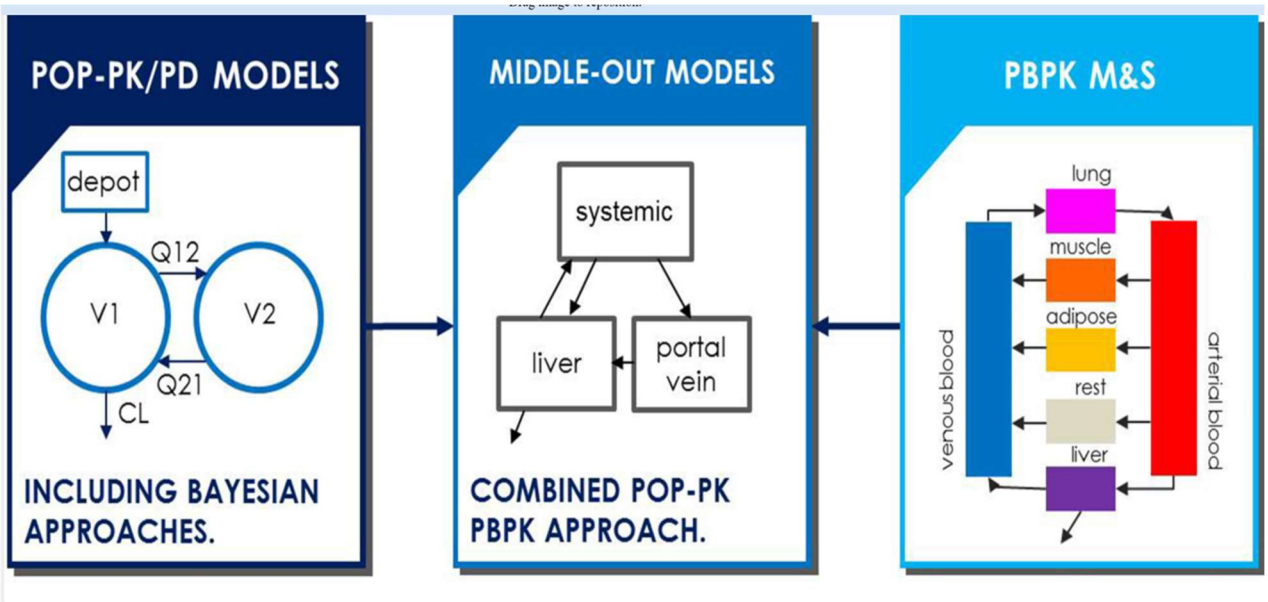
In this analysis, we investigate the present condition of pharmacokinetic (PK) modeling in the process of customizing the dosage of anticancer medications for specific patients. The comparative analysis conducted in this study used a sample of 393 peer-reviewed papers on pharmacokinetic (PK) modeling in the field of cancer. The details of the sample can be found in Table S1, which is provided in the supplemental appendix accessible online. The dataset should not be regarded as a comprehensive compilation of the extensive literature on pharmacokinetic modeling in the field of cancer. The arguments provided here about precision dosage are a subset of a larger debate on model-informed precision dosing (MIPD) across several therapeutic domains (7,10-12).

2. Oncology's rationale for MIPD

A common approach to address the issue of optimizing medication dosage in unique groups and drug-drug interactions is to conduct specific clinical trials. However, in the field of cancer, it is often not possible to carry out this approach owing to challenges in recruiting patients who are

susceptible or do not fit into the specified therapy group (13). Statistical nonlinear-mixed effects (NLME) modeling, also known as population-PK/PD modeling or pop-PK/PD, is used to characterize the inter-individual variability (IIV) in pharmacokinetic (PK) parameters. This is achieved by using compartmental and progressively more mechanistic models. Physiologically-based pharmacokinetic (PBPK) modeling and simulation (M&S) assign physiological significance to pharmacokinetic (PK) models by replicating physiology (inter-compartmental clearance rates informed by blood flows, volumes based on organ/tissue volumes, etc.) in an effort to gain a deeper understanding of the processes that govern drug absorption, distribution, metabolism, and excretion (ADME). The integrated method, known as "middle-out," takes into consideration physiological models in which model parameters might explain the observed inter-individual variability (IIV) in the population sample. Please refer to Figure 1 for more details (14).

Pharmacokinetic/pharmacodynamic (PK/PD) and physiologically-based pharmacokinetic (PBPK) modeling and simulation (M&S) have become more widely accepted in pharmaceutical research and development (R&D) and by regulatory agencies in recent decades. These models can now be used to replace or supplement dedicated clinical trials, particularly when assessing the impact of drug-drug interactions on metabolism (15). It is expected that M&S will become more useful in the future as trust grows in its use in many sectors such as pharmaceutical



research and development, regulatory filing, and clinical practice for personalized dosing.

Figure 1. Several methods of pharmacokinetic modeling used to accurately determine the appropriate dosage of cancer medications. The bars represent the characteristics of both the individual procedures and the combined techniques.

Individualizing doses, often known as customized dosing or precision dosing, is a recognized aspect of precision medicine. Precision medicine aims to customize the prevention, diagnosis, and treatment of diseases by taking into account specific patient features, such as genotyping, renal function, and other biomarkers (16). Similarly, precision dosing aims to consider the differences in medication exposure and reaction amongst patients in order to adjust the dosage for each person. Carboplatin is well recognized as a prominent example in the field of oncology. It has been early adopted for renal function guided dose, using the Calvert et al. formula, to minimize the likelihood of hematological toxicity (17). Furthermore, a study shown that adjusting the dosage of 5-fluorouracil (5-FU) based on pharmacokinetics (PK) and employing therapeutic drug monitoring (TDM) resulted in better treatment response and less toxicity compared to relying only on body surface area (BSA) for dosing in patients with metastatic colorectal cancer (18).

The concept of precision dosage in cancer treatment is appealing for several reasons. A significant number of anticancer medications have narrow therapeutic indices, meaning that inadequate treatment might result in serious consequences for the patient. The challenges in recruiting clinical study participants highlight the difficulties in recruiting patients for specialized clinical trials involving specific populations. This, along with expedited approvals, may explain why there has been a higher-than-average use of PBPK M&S (Physiologically Based Pharmacokinetic Modeling and Simulation) in new drug applications (NDAs) for oncology drugs submitted to the U.S. Food and Drug Administration (FDA) (19). The prevalence of non-responders in cancer treatment, along with the expensive nature of cancer therapies, necessitates the exploration of alternative methods to enhance patient outcomes and cost-effectiveness. This may involve optimizing treatment outcomes through the utilization of PK modeling and MIPD (20,21).

3. Utilization of pharmacokinetic (PK) modeling in oncology

Model-informed drug discovery and development has been a standard practice in the pharmaceutical industry in recent decades. It is now widely used throughout the drug development process to provide information for internal and regulatory decision-making (15,22). During the first stages of discovery and pre-clinical development, modeling is used to guide the selection of potential candidates, characterize their absorption, distribution, metabolism, and excretion (ADME), translate their exposure and effects, and utilize various methodologies such as population pharmacokinetics/pharmacodynamics (pop-PK/PD), physiologically-based pharmacokinetics (PBPK), and mechanistic systems pharmacology/biology. Pop-PK/PD is often used in clinical development to examine effectiveness, determine appropriate dosage, and establish dosage continuity. Physiologically-based pharmacokinetic (PBPK) modeling and simulation is used in clinical settings to forecast the occurrence of drug-drug interactions (DDIs), evaluate the influence of genetic variations, assess biopharmaceutical effects, and make predictions for specific patient groups (22).

An examination of peer-reviewed publications utilizing pharmacokinetic (PK) modeling in the field of oncology, as indicated by the modeling approach illustrated in Figure 2, revealed that the majority of studies (75%) utilized population-based methods in their data analysis. Within this subset, traditional population PK (45%), population PK/pharmacodynamics (PK/PD) (14%), Bayesian population PK (10%), and semi-mechanistic population PK/PD (6%) approaches were employed. Pharmacokinetic-pharmacodynamic modeling and simulation (PBPK M&S) was used in 8% of the research that were found. Regarding the domains where PK modeling is used, the most significant application is the examination of variables (49%) to include inter-individual variability in PK.

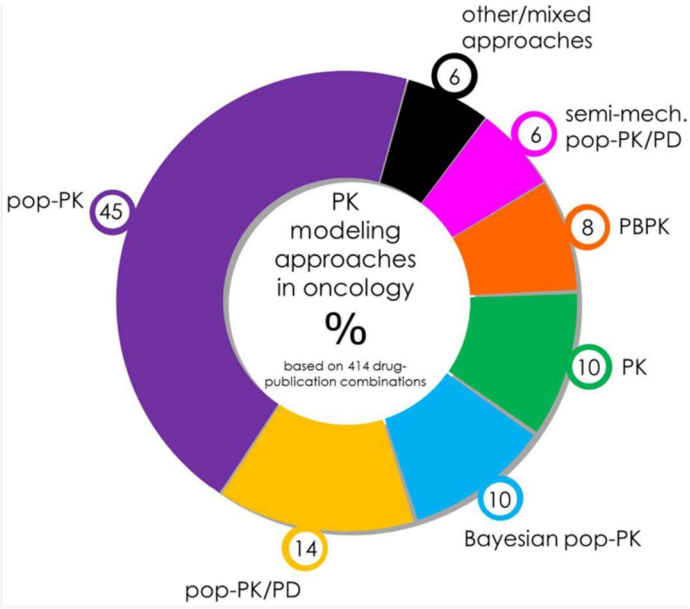


Figure 2. Peer-reviewed publications on pharmacokinetic modeling of oncology drugs categorized based on method of approach

Subsequently, research was conducted to examine dosing matters (22%), including the determination of appropriate dosage and practical considerations related to dosage. The particular groups that received the greatest attention in studies were pediatric patients (13%), those with hepatic impairment (3%), and those with renal impairment (2%). Additional specific groups that were examined include: pregnant individuals, the elderly, and others. Additional areas of research included toxicity (18%), studies on dose/pharmacokinetics and effectiveness (response: 8%), kinetics of metabolites (8%), genotype/phenotype of metabolic/transporter systems (6%), drug-drug interactions (5%), techniques for restricted sampling (5%), and others.

4. Utilizing PBPK modeling for personalized dosage of anticancer medications

PBPK M&S provides a means of quantitatively extrapolating drug exposure from in vitro to in vivo (IVIVE), across different species, populations, and for metabolic/transporter drug-drug

interactions (DDIs) by attributing physiological significance to model parameters. Within the field of cancer, the use of physiologically-based pharmacokinetic modeling and simulation (PBPK M&S) has been widely utilized for the purpose of forecasting drug-drug interactions (DDIs), evaluating the impact of specific patient populations (such as those with renal or hepatic impairment, as well as pediatric patients), and assessing the impacts of biopharmaceutical factors (including drug absorption, formulation, and food interactions). Indeed, the use of Physiologically-Based Pharmacokinetic (PBPK) Modeling and Simulation (M&S) in the field of oncology can be dated back to the 1970s, when it was first used to estimate the effects of chemotherapeutic drugs (23).

Multiple reasons contribute to the extensive use of PBPK in the field of oncology: Due to ethical and safety concerns, certain oncology drugs have a narrow range of effective doses and can cause severe toxicity. Therefore, precision dosing should be carefully considered for these drugs. Additionally, many anticancer drugs are approved for use quickly through accelerated regulatory processes. This means that if studies on these drugs are not conducted in a timely manner, they may be replaced by pharmacokinetic and pharmacodynamic modeling and simulation (PBPK M&S). There are many instances of pharmacokinetic-pharmacodynamic modeling and simulation (PBPK M&S) of cancer drugs in scientific literature. These include studies on the use of PBPK M&S in pediatrics (24-26), the effects of drug formulation on drug absorption and distribution (27), the impact of kidney dysfunction on drug metabolism (28-30), the influence of liver dysfunction on drug clearance (31), the relationship between metabolic phenotypes/genotypes and drug response (32,33), the effect of patient adherence on drug efficacy, and the interactions between drugs and metabolic/transporter systems (34-38). Additional examples can be found in the drug labels provided by the FDA (39). The FDA's current perspective on PBPK-informed dosing is that there is enough data to use validated models to anticipate metabolic drug-drug interactions (DDIs) when the drug is the one being affected (39). The capacity to forecast particular populations and biopharmaceutics effects in a prospective and quantitative manner is still uncertain due to the lack of sufficient data. Here, we provide specific case studies to demonstrate the practicality of PBPK M&S in customizing the dosage of anticancer medications.

5. Pharmacokinetic modeling of anticancer medicines in the healthcare field

Recently, there has been much discussion on the use of PK modeling in assisting with precise dosage in clinical settings (10,11,40). In a previous scholarly article, we put out a classification system to explain the use of MIPD (Model-Informed Precision Dosing) in healthcare. This classification consisted of three categories: real-time implementation in healthcare systems, mechanistic modeling and extrapolation, and model-derived dosage banding (10).

Real-time implementation in healthcare systems refers to the immediate integration of modeling and simulation (M&S) into healthcare processes, such as the use of software tools and their integration into electronic health records (EHR). This strategy is especially suitable for

therapies that need regular and ongoing monitoring, such as Therapeutic Drug Monitoring (TDM), throughout the therapy. Bayesian modeling systems are very suitable for this task, since they allow for the use of feedback-control to update prior parameter estimates and improve individual patient forecasts as more data is obtained (10,11). Mechanistic or physiologically-based pharmacokinetic (PBPK) models are a potent tool for enabling extrapolation, such as in the case of drug-drug interactions (DDIs) or specific populations. While there have been several instances of using dosage strategies for particular groups, there is a scarcity of evaluations of this strategy in actual clinical practice. This might be attributed, in part, to the fact that PBPK relies on drug-specific and physiological data and has a lesser capacity to explain inter-individual variability (IIV) compared to population pharmacokinetics (pop-PK). However, it is possible that this situation may change in the future.

The collection of fresh proteome data (41), the development of "middle-out" modeling (14), and the use of Bayesian PBPK M&S (42) are all factors that contribute to making PBPK a more feasible strategy in precision dosing. Model-derived dosage banding involves using pharmacokinetic (PK) models to create dosing plans that are determined by clinically significant factors discovered during data analysis. This strategy is considered the most practical, however it may have limited potential for individualizing doses compared to other model-based approaches (43-45). Previous experiences have provided the basis for proposing work streams that outline the process of developing model-based methods, from their initial conception to their application in clinical practice.

6. Summary

In this study, we provide an overview of the current status of pharmacokinetic (PK) modeling in the context of precision dosage for anticancer medications. We have demonstrated, through the use of documented instances, some of the possible advantages that this approach can offer in terms of providing guidance on appropriate dosages for drug-drug interactions (DDIs) and in specific populations. These benefits include better achievement of desired drug levels, decreased likelihood of harmful effects, reduced resource wastage, and potential for enhanced patient outcomes and cost-effectiveness. Although there has been significant advancement in the incorporation of model-informed dose recommendations in medication labeling, the adoption of this approach in healthcare has been limited despite the joint efforts of regulators, industry, and academics. There is a need for collaboration between academia, healthcare, and industry, as well as increased financial support for applied research on the patient benefits, cost-benefits, and clinical efficacy of model-based dosing techniques. This is necessary for these approaches to be more widely used in healthcare.

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