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

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Section II

Modeling pharmacokinetics & pharmacodynamics

Chapter 5

Model-informed precision dosing in oncology

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Abstract

In real-world patients, anti-cancer drugs frequently show substantial variability in pharmacokinetics (PK) and pharmacodynamics (PD). Especially for anti-cancer drugs that exhibit a narrow therapeutic window, these characteristics lead to an increased risk of suboptimal therapy and toxicity. This highlights the need for more individualized dosing in cancer patients. Model-informed precision dosing (MIPD) is an advanced quantitative approach which applies pharmacometric models to guide optimal dose selection and enables individualized therapy. This expert opinion article introduces the current application of MIPD in supporting optimal anti-cancer treatment, and discusses the challenges and future perspectives of implementing MIPD in this field.

1. Introduction

Pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of anti-cancer drugs can be highly variable in real-world patients [1, 2]. Due to the correlations between drug exposure and treatment response (efficacy and toxicity), such variability can result in suboptimal treatment outcomes for a considerable part of the patients especially when the therapeutic window is narrow [1, 2]. Moreover, since the dose selection for most oncology drugs is based on the maximum tolerated dose (MTD) or maximal administered dose (MAD) paradigm, the use of standard dosing according to the drug label can result in negative consequences for real-world patients. This leads to a demand for dose modification processes [3]. Therefore, the necessity for dose individualization and optimization in anti-cancer therapies is highlighted, and a useful tool to support the decision making is warranted.

Model-informed precision dosing (MIPD) is a promising tool which adopts pharmacometric models to guide optimal and individualized dose selection, the goal of which is to improve efficacy and reduce the risk of toxicity [2, 4]. Pharmacometric models enable quantitative characterization and prediction of drug PK and PD in target populations under certain dosing regimens [5, 6]. With a mixed-effect modeling (population modeling) approach, variability between and within patients can be quantified and predictive covariates can be identified [5, 6]. Once data of patients are known, the Bayesian framework of the population model would enable more precise description and prediction of individual PK/PD characteristics with individual parameters [2]. Combined with simulations, treatment strategies that are likely to achieve the therapeutic targets and desired clinical outcome can therefore be derived with the model. The value of MIPD in supporting cancer treatment optimization has gained increasing interest in oncology research and clinical practice. However, challenges still remain in the implementation of MIPD.

The current article aims to introduce the application and benefits of MIPD in supporting anti-cancer treatment optimization and individualization, and discuss the challenges and future perspectives of implementing MIPD in cancer therapies.

2. MIPD application

Insight into the correlation between drug or surrogate biomarker concentration and the clinical effect in real-world patients can facilitate determining a therapeutic target or range that is associated with sufficient efficacy and less risk of toxicity. This pre-defined target can then be incorporated in the algorithm of MIPD to derive optimal dosing regimens.

2.1 Starting dose selection

The benefits of MIPD in anti-cancer treatment have been demonstrated in many studies [2, 7]. First of all, MIPD can be applied to guide (starting) dose selection based on identified covariates [7]. Population modeling allows the identification of covariates that influence model parameters and explain the inter- and intra-patient variability in drug PK/PD profiles. Data from various studies can also be pooled in one analysis to facilitate a more in-depth exploration on relevant covariates. Before any data on PK or PD biomarkers are available to inform the individual parameters, the model can guide dose tailoring considering the value of relevant covariates for each individual patient, which would increase the chance to achieve the therapeutic target and reduce inter-individual variability. This can be especially helpful for determining the optimal starting dose.

The current standard practice to individualize the dose of anti-cancer drugs (normally for cytotoxic chemotherapy) is based on body surface area (BSA) [7, 8]. However, BSA may not be a relevant covariate that correlates with the PK variability of these drugs [7, 8]. Dosing based on BSA can thus still lead to substantial PK variability and cause under or over drug exposure, which may lead to less efficacy or a higher risk of toxicity. The model-informed approach allows investigating the impact of a wide range of factors, including patients' characteristics, renal or kidney function, disease related indicators, and co-medications, identifying real covariates that should be accounted for dose adjustment [7]. It also allows taking multiple influential factors into consideration at the same time. The impact of pharmacogenetic variants on drug PK profile can also be investigated and incorporated in MIPD to further refine the dose selection [7].

A clinical trial on busulfan in pediatric hematopoietic cell transplantation (HCT) patients has confirmed the advantage of model-informed dosing in guiding starting dose selection [9]. This trial compared conventional strategies for determining initial busulfan dose (based on weight), calculating AUC following TDM (trapezoidal rule), and determining the following dose (proportional scaling) with the model-informed approach. Their results show that receiving initial doses that were calculated by the PK model enabled more patients to achieve the exposure target at the time of first PK collection, especially in the cohort where the initial dose was guided with an updated PK model (75% vs. 25% in conventional group).

2.2 Adaptive dose selection during treatment

Secondly, MIPD also presents a potential to guide dose selection and adaptation during anti-cancer treatment, which has shown to outperform the conventional therapy in terms of

target attainment and clinical outcome. Such dose selection is typically guided by population PK models that possess sufficient predictive ability. Once measured drug concentrations and individual characteristics of the patient are available, individual parameters can be estimated (empirical Bayesian estimates) which could capture the current and forecast future individual PK time curves, given the applied dosage [2, 10]. Thus, with the aim to achieve the defined exposure target, the optimal dosage for the following treatment can be determined rationally. A recent perspective on MIPD has listed several motivating examples [2]. One study in breast cancer patients performed simulations to compare different dosing strategies of tamoxifen [11]. The results demonstrated that compared with standard dosing (20 mg QD) or CYP2D6-guided dosing, the MIPD strategy (individual maintenance dose was derived with MIPD using three monitored drug concentrations) could reduce the proportion of patients failing to reach the predefined target endoxifen (active metabolite) exposure (22.2% (standard dosing) to 7.19%) and the inter-individual variability.

In addition to drug concentrations, monitoring other biomarkers to inform dose selection can potentially also be accomplished with a model-informed approach.

The benefit of MIPD in guiding anti-cancer treatment dose adaptation has also been confirmed in clinical trials. For instance, Joerger et al. have performed a randomized study in advance non-small cell lung cancer (NSCLC) patients to compare standard paclitaxel dosing (per BSA) and PK-guided paclitaxel dosing which was proposed from their previous simulation-based study (initial paclitaxel dose was adjusted according to patients characteristics and subsequent doses were guided considering previous-cycle paclitaxel exposure estimated with a PK model) [12]. The study demonstrated that that PK-guided dosing can significantly reduce paclitaxel-associated neuropathy while having the similar response rate as standard dosing, thus suggesting an improved benefit-risk profile [12].

2.3 Model-informed TDM

Therapeutic drug monitoring (TDM) is a clinical practice of adjusting drug dosing regimen for an individual patient based on measured drug concentrations in biological fluid (typically plasma, serum, urine, or whole blood) [10]. For anti-cancer therapies, TDM-based dosing has been partially implemented for a small number of agents, including carboplatin, methotrexate, busulfan, and mitotane [13]. The benefits and feasibility of TDM for many other drugs have also been demonstrated in clinical studies, including imatinib, sunitinib, pazopanib, 5-fluorouracil, and tamoxifen [8, 13]. Implementing TDM for other kinase inhibitors, which are typically administrated at fixed doses, has also been recommended due to the high PK variability and clear relationships between exposure and treatment outcomes [1].

MIPD, which is able to guide dose adaptation with population PK models and Bayesian forecasting, can be combined with TDM to ensure optimal dose adjustment. This model-informed TDM has already been implemented in clinical practice, although not yet widely adopted [4]. The exposure metrics that were of interest included trough concentrations, area under the concentration-time curve (AUC), or concentrations at a certain time point. Compared with conventional TDM, the model-informed approach provides the decision support in a quantitative manner and the advantage is multifaceted [2, 8]. First, the individual parameters estimated based on the monitored concentrations (Bayesian estimates) would enable the prediction of whole drug concentration-time curves for each individual patient following the current or subsequent doses. In this way, the concentrations at any time point of interest can be obtained based on the monitored sample. This approach has proved to be able to provide more precise prediction on trough concentrations than normal log extrapolation as is used in conventional TDM [14]. In addition, this approach also allows more accurate estimation of AUC, and flexible limited sampling strategies can be applied. Second, MIPD provides the ability to account for non-linear PK behavior and guide dose adjustment when steady state is not yet reached. This is because MIPD supports the dose adaptation based on the forecasting of drug exposure after dose adjustment. In conventional TDM, the decision on dose adjustment is simply made by scaling the previous dose with the ratio of the observed and target exposures, assuming a linear PK profile [7, 10]. This requires the concentration profile to be at steady state [10]. Finally, with the help of the pharmacometric models and simulations, different TDM strategies can be explored and the most optimal strategy can be identified for further exploration and/or clinical implementation [8].

The clinical trial on busulfan in pediatric HCT patients has strengthened the clinical utility of model-informed dosing and TDM for supporting personalized busulfan dosing and target exposure attainment [9]. In addition to the benefit of selecting the initial dose using the PK model, in the cohort where busulfan AUC and subsequent doses were estimated with the MIPD platform during TDM, the achievement of the goal exposure (cumulated AUC) has shown to be significantly improved (100% vs. 66% in conventional group) and the variability among patients was reduced (from 14.8% to 4.1%), which is expected to improve clinical outcomes [9].

3. Challenges and perspectives

Challenges still have to be overcome to implement MIPD of cancer therapies in clinical practice. A previous perspective has provided a comprehensive overview on the chal-

lenges that hinder the implementation of MIPD in clinical practice in general, as well as corresponding recommendations and future opportunities, from multiple aspects [2]. Here, we highlight a few challenges and provide future perspectives specifically for anti-cancer therapies.

3.1 Therapeutic target identification

A pre-defined therapeutic target of drug or biomarker exposure that is associated with optimal treatment outcome is fundamental for MIPD to estimate optimal dosing regimens. A therapeutic target can be determined based on the PK/PD study outcomes in registration files or clinical studies. Developing a PK-PD model on exposure-response relationship based on retrospective data can also facilitate the identification of an optimal therapeutic target for real-world cancer patients. The therapeutic target can be an exposure range, as is traditionally aimed at during drug TDM, or a specific exposure value which can relate to a specific PD target [10]. For anti-cancer drugs, the potential PD target of interest can relate to the change in tumor burden or PD biomarkers. Typically, one therapeutic target is being used for one whole patient population. For future studies and practices, personalizing dosage based on an individual target determined with the help of population PK/PD modeling and Bayesian forecasting would be of interest.

3.2 Model selection

In order to implement MIPD, selecting a suitable model that presents sufficient predictive ability to the target patient population is essential. Whether a model matches the target patient population, regarding e.g. age (adult or pediatric), body composition (normal or obese), indications (cancer types and drugs), or dose levels, need to be considered when selecting the model [15]. The intention to use the model should also be taken into account. For example, if a population PK model was developed based on trough concentrations, it may not be able to adequately capture the drug absorption and distribution phase, thus may be suboptimal to support AUC estimation [8].

At times, identifying one model that already has sufficient predictive ability to the target population is difficult. This can be due to the sample size of the study population, or the lack of ability to cover all potential influential factors (e.g. different genotypes or the use of co-medications) in one study [8, 10]. In this case, pooling data of the same drug and cancer type to develop a model, or updating the model (structure or parameters) with newly collected data during TDM allows to derive a model that can better fit the target population [2, 15]. The clinical study on MIPD application in busulfan treatment has proved

that a model updated with additional patient data can improve the performance of MIPD on therapeutic target attainment [9]. A recent study also proposed a continued learning framework which uses a sequential hierarchical Bayesian framework to update the model during MIPD. With this method, the prior model used within MIPD is improved as new data from the target patient population are integrated [16].

Nowadays advanced approaches such as machine learning (ML) approaches have also shown to be able to assist with model selection for MIPD [17].

Model evaluation is also essential for selecting a model that is most suitable. This can be done using the historical data considering the intention to use the model (TDM or starting dose) [15]. In the case where inter-occasion variability (IOV, which represents intra-patient variability) is considered, the predictive value of the historical data (covariate value, data points from much earlier) to subsequent treatment courses needs to be evaluated [15].

3.3 User-friendly MIPD program

To motivate clinicians and clinical pharmacists to implement MIPD and remove the barrier due to the lack of knowledge in quantitative pharmacology, translating the research findings into user-friendly MIPD software would be beneficial and can also be challenging [2]. Luckily, there are already multiple programs available and some are already integrated with local electronic health records [2, 18]. The user-friendliness of 3 Bayesian forecasting programs (TDMx, InsightRx and DoseMe) in a clinical setting has also been evaluated and confirmed [19]. Moreover, many of the available programs also allow including new PK models and adjust PK/PD targets [18]. In order to guide anti-cancer treatment, a program that already has a validated model available for the intention drugs in the intention patient population, or allows including such a new model would be ideal to be selected. Developing a program for local use could also be an option, which can be facilitated by the increasingly available program packages. In addition, training and education are still needed to increase the uptake of MIPD into routine clinical practice [2].

3.4 Prospective clinical trials

To promote the implementation of MIPD in clinical practice, a necessity for prospective clinical trials comparing standard dosing strategies versus MIPD has been highlighted [4]. It is pointed out that the clinical evidence supporting the benefit of the MIPD tools in improving patient outcomes is crucial for the integration of MIPD into clinical care [4]. Although clinical trials will continue to take an important role, given the repeatedly occurring evidence on the advantage of MIPD tools in cancer treatment from clinical trials

and the ability of pharmacometric methods to provide the most likely beneficial strategy, the requirement for largescale trials can decrease [8].

4. Conclusion

Substantial PK/PD variability and suboptimal dosing of anti-cancer drugs highlight the need for precision dosing in real-world cancer patients. MIPD is a promising tool which adopts pharmacometric models to guide precision dose selection aiming for improved therapeutic target attainment and optimal treatment outcome. Many research and clinical trials have demonstrated the benefits of applying MIPD in anti-cancer treatment, including guiding dose selection and adaptation, as well as TDM. To promote the implementation of MIPD in clinal cancer treatment, challenges regarding optimal target identification, suitable model selection, available programs, and the necessity of prospective clinical trials need to be addressed.

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