Evaluation of Extrapolation Methods to Predict Trough Concentrations to Guide Therapeutic Drug Monitoring of Oral Anticancer Drugs

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Background: For oral anticancer drugs, trough concentration (C_{min}) is usually used as a target in therapeutic drug monitoring (TDM). Recording of C_{min} is highly challenging in outpatients, in whom there is typically a variability in sample collection time after dosing. Various methods are used to estimate C_{min} from the collected samples. This simulation study aimed to evaluate the performance of 3 different methods in estimating the C_{min} of 4 oral anticancer drugs for which TDM is regularly performed.

Methods: Plasma concentrations of abiraterone, dabrafenib, imatinib, and pazopanib at a random time ($C_{t,sim}$) and at the end of the dosing interval ($C_{min,sim}$) were simulated from population pharmacokinetic models including 1000 patients, and the values were converted into simulated observed concentrations ($C_{t,sim,obs}$ and $C_{min,sim,obs}$) by adding a residual error. From $C_{t,\ sim,obs}$, C_{min} was predicted ($C_{min,pred}$) by the Bayesian estimation (method 1), taking the ratio of the $C_{t,sim,obs}$ and typical population concentration and multiplying this ratio with the typical population value of $C_{min,sim}$ (method 2), and log-linear extrapolation (method 3). Target attainment was assessed by comparing $C_{min,pred}$ with the proposed pharmacokinetic targets related to efficacy and calculating the positive predictive and negative predictive values.

Results: The mean relative prediction error and root mean squared relative prediction error results showed that method 3 was outperformed by method 1 and 2. Target attainment was adequately predicted by all 3 methods (the respective positive predictive value of method 1, 2, and 3 was 92.1%, 92.5%, and 93.1% for abiraterone; 87.3%, 86.9%, and 99.1% for dabrafenib; 79.3%, 79.3%, and 75.9% for imatinib; and 72.5%, 73.5%, and 67.6% for pazopanib), indicating that dose adjustments were correctly predicted.

Conclusions: Both method 1 and 2 provided accurate and precise individual $C_{min,pred}$ values. However, method 2 was easier to implement than method 1 to guide individual dose adjustments in TDM programs.

Key Words: trough concentration extrapolation, oncology, kinase inhibitors

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In recent years, new targeted small-molecule kinase inhibitors (KIs) have become available for the treatment of patients with several types of cancer. These KIs are targeted against specific molecular defects that are expressed by malignant cells. Exposure–efficacy relationships can be expected for these anticancer drugs. It has been shown that exposure may show considerable variability between patients for many of these orally administered drugs owing to both co-administration of other drugs and patient-specific factors, such as genetics, concomitant intake of food, and fixed dosing strategy.[1–3] This may result in treatment failure because of underdosing.[2]

Therapeutic drug monitoring (TDM) is based on the quantification of individual exposure and interpretation of this exposure with respect to the proposed target exposures for any type of treatment response. Subsequently, dose individualizations may be applied to improve target attainment.[4–6] TDM has proven its benefits in treatment optimization in terms of minimal target attainment related to the clinical efficacy of many oral anticancer drugs and indications.[7–10] Target exposure in oncology is most commonly defined by exposure–efficacy analyses using trough concentration (C_{min}) as a pharmacokinetic (PK) parameter for minimal target attainment.

Oral KIs are mostly used by outpatients. Patient blood samples are, therefore, typically collected at any time point within a dosing interval when patients are in the hospital for regular visits. As this is not the exact C_{min}, extrapolation to C_{min} is required. Several methods to extrapolate a single individual plasma concentration at various time points after dosing to C_{min} have been proposed. Model-based methods using population PK models have been suggested.[11–13] These methods should provide good predictive performance and enable the use of an individual plasma concentration sampled at

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This research was performed in accordance with the ethical standard of the institutional review boards and with the 1964 Helsinki declaration and its later amendments or comparable standards.

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various time points after dosing. A method in which the individual C_{min} is derived based on the ratio of the individual plasma concentration at various time points after dosing versus a population mean concentration at that same time point could also be considered. In addition, a log-linear extrapolation approach that uses the typical value of the elimination rate constant has been reported by Wang et al.[14]

The aim of this simulation study is to explore the predictive performance of different extrapolation methods for the determination of C_{min} in individual patients in terms of target attainment, bias, and precision. To this end, the authors applied these extrapolation methods in TDM of 4 oral anticancer drugs (ie, abiraterone, dabrafenib, imatinib, and pazopanib) with varying PK characteristics and for which population PK models are available in the literature.

MATERIALS AND METHODS

Extrapolation Methods

Population PK models for abiraterone, dabrafenib, imatinib, and pazopanib were obtained from the literature (Table 1).[15–18] A densely sampled steady-state concentration–time curve was simulated for 1000 individual patients using these models at the approved dose [1000 mg once daily (OD), 150 mg twice daily, 400 mg OD, and 800 mg OD for abiraterone, dabrafenib, imatinib, and pazopanib, respectively]. Any covariate effects, if reported in the model, were fixed to their reference value. From the individual concentration–time curves, a random time point during a dosing interval and the corresponding concentration were randomly sampled ($C_{t,sim}$). These simulation results were used in the following 3 extrapolation methods.

1. Method 1. Derivation of empirical Bayes PK parameter estimates using NONMEM with MAXEVAL = 0 to obtain an individual predicted C_{min} ($C_{min,pred}$) based on a randomly sampled $C_{t,sim}$.
2. Method 2. Approximation of a $C_{min,pred}$ by taking the ratio of C_{obs} versus the population concentration based on a population PK model and multiplication of this ratio with the simulated population $C_{min,sim}$.
3. Method 3. Log-linear extrapolation using a previously proposed algorithm[14]:

$$C_{min,\,pred} = C_{t,\,sim} \times 0.5^{\left(\frac{\tau - TAD}{t_{1/2}}\right)} \quad (1)$$

where τ is the dosing interval (24 hours for abiraterone, imatinib, and pazopanib; 12 hours for dabrafenib), TAD is the

TABLE 1. Summary of the Identified Population PK Models and Parameter Estimates Used in the Simulations for the Evaluation of the Four Extrapolation Methods

	Base Model Structure	Parameter Estimates	Interindividual Variability (CV%)	Covariate Relationships*	References
Abiraterone	Two-compartment, transit compartments, and sequential zero-order and first-order absorption	K_a = 1.91 h^{-1} D1 = 0.267 h F = 1.24† V_c = 5620 L Q = 1360 L/h V_p = 17,400 L CL = 1550 L/h	K_a = 58.0% D1 = 144% F = 61.1% CL = 28.2%	mCRPC/healthy subjects and food effect	15
Dabrafenib	Two-compartment, first-order absorption, lag time, and dose-dependent clearance	K_a = 1.8 h^{-1} T_{lag} = 0.482 h V_c/F = 69.1 L Q/F = 3.44 L/h V_p/F = 149 L CL/F = 98.8 L/h	K_a = 160% V_c/F = 54.1% Q/F = 102% CL/F = 60.8%	Weight, sex, drug formulation, and last administered dose	16
Imatinib	One-compartment, zero-order absorption, and linear elimination	D1 = 1.7 h V_c/F = 284 L CL/F = 10.2 L/h	V_c/F = 35.8% CL/F = 34.6%	Albumin and WBC	17
Pazopanib	Two-compartment, fast and slow first-order absorption, and dose-dependent bioavailability	$K_{a,fast}$ = 0.40 h^{-1} $K_{a,slow}$ = 0.12 h^{-1} $T_{lag,\,slow}$ = 0.98 h V_c = 2.43 L Q = 0.99 L/h V_p/F = 25.1 L CL/F = 0.27 L/h	K_a = 140% F = 35.6% V_p/F = 98.2% CL/F = 30.9%	Dose	18

*Covariate effects were fixed to the standardized covariate relationship.

†F for modified fasted conditions (ie, fasting 2 hours before to and 1 hour after dosing).

CL, apparent clearance; D1, zero-order absorption duration; F, bioavailability; K_a, first-order absorption rate constant; mCRPC, metastatic castration-resistant prostate cancer; Q, intercompartmental clearance; T_{lag}, lag time; V_c, central volume of distribution; V_p, peripheral volume of distribution; WBC, white blood cell count.

time of $C_{t,sim}$ after the last administered dose, and $t_{1/2}$ is the reported elimination half-life (16 hours for abiraterone, 10 hours for dabrafenib, 18 hours for imatinib, and 31 hours for pazopanib).[15,16,19,20]

All 3 extrapolation methods were explored for 2 scenarios:

1. Timing of $C_{t,sim}$ randomly sampled between T_{max} (2 hours for abiraterone, 2 hours for dabrafenib, 2.5 hours for imatinib, and 4 hours for pazopanib) and the end of the dosing interval (12 hours for dabrafenib; 24 hours for abiraterone, imatinib, and pazopanib).[21–24]
2. Random sampling from 0.5 hours after intake until the end of the dosing interval.

In addition, the true $C_{min,sim,obs}$ at the end of the dosing interval was simulated. Drug concentration in this sample is also expected to be associated with a random residual error[25]; thus, this concentration should also be regarded as a prediction of the true C_{min}.

Evaluation of Predictive Performance

Predictive performance was assessed in terms of the bias relative prediction error (RPE) and mean relative prediction error (MPE) and precision [root mean squared relative prediction error (RMSE)][26]:

$$\mathrm{RPE} = \frac{\left(C_{min,\ pred} - C_{min,\ sim}\right)}{C_{min,sim}} \quad (2)$$

$$\mathrm{RMSE}\ (\%) = \sqrt{\frac{\sum_{i=0}^{n}\left(\frac{C_{min,\ pred} - C_{min,sim}}{C_{min,sim}}\right)}{n}} \times 100\% \quad (3)$$

To determine these measures, the $C_{min,sim}$ was used as the true trough concentration. In addition, the positive predictive value (PPV) was used to evaluate how often the $C_{min,pred}$ is truly above the PK efficacy target. The negative predictive value (NPV) was calculated to evaluate whether $C_{min,pred}$ is truly below the PK efficacy target. The following previously proposed minimal PK targets that were related to improved efficacy of treatment were used: C_{min} >8.4 ng/mL for abiraterone, C_{min} >46.6 ng/mL for dabrafenib, C_{min} >1100 ng/mL for imatinib, and C_{min} >20 mg/L for pazopanib.[5]

Software

Simulation and estimation was performed using NONMEM (version 7.3, ICON Development Solutions, Ellicott City, MD) and Perl-speaks-NONMEM (PsN, version 4.4.8) with the first-order conditional estimation with interaction (FOCE-I) as an estimation method.[27] R (version 3.4.3) was used for data processing, calculations, and graphical diagnostics.[28]

RESULTS

Abiraterone

The population PK model for abiraterone that was used for the simulations was a two-compartment model with absorption through transit compartments and sequential zero-order and first-order absorption processes. Interindividual variability was included for apparent clearance (CL/F), bioavailability (F), first-order absorption rate (ka), and duration of zero-order absorption (D1) (Table 1).[15]

The goodness-of-fit (GOF) plots for abiraterone showed that the log-linear extrapolation method resulted in a structural overprediction of $C_{min,pred}$ for both sampling intervals. For the Bayesian estimation and concentration ratio, an overprediction was present in the lower true $C_{min,sim}$ values (Figs. 1, 2). This overprediction seemed to worsen when the single samples were collected at various time points during the entire dosing intervals (detailed results are presented in Supplementary Material, **Supplemental Digital Content 1**, http://links.lww.com/TDM/A403). In addition, the plots of the RPE showed a trend toward positive outliers, as depicted in Figure 2 and Supplementary Figures, **Supplemental Digital Content 2**, http://links.lww.com/TDM/A402. These plots particularly showed overprediction by log-linear extrapolation.

The predictive performances of the 3 extrapolation methods are presented for sampling scenarios A and B in Table 2 and Supplementary Material, **Supplemental Digital Content 1**, http://links.lww.com/TDM/A403, respectively. Comparison of the 3 methods showed that the Bayesian estimation had similar performance compared with the concentration ratio in terms of both bias (MPE) and precision (RMSE), regardless of the sampling interval. These methods performed slightly worse for samples collected during the dosing interval than for samples collected at C_{min} but clearly outperformed the log-linear extrapolation. These differences in bias and precision in $C_{min,pred}$ did not result in marked differences in PPV between the Bayesian estimation, concentration ratio, and log-linear extrapolation. In addition, sampling at C_{min} resulted in a slightly higher PPV than that with the 3 extrapolation methods. The NPV, however, showed differences between the 3 methods. This indicated that the $C_{min,pred}$ was truly above the PK target to the same extent, but the log-linear extrapolation performed worse compared with the other extrapolation methods in predicting a $C_{min,pred}$ that was truly below the PK target.

Dabrafenib

For dabrafenib, a two-compartment model with first-order absorption after a lag time, dose-dependent clearance and interindividual variability on CL/F, apparent central volume of distribution (Vc/F), apparent intercompartmental clearance (Q/F), and ka was used (Table 1).[16]

Figures 1–3 show a widespread RPE and large overpredictions of the lower $C_{min,sim}$ for dabrafenib with all 3 extrapolation methods. The MPE and RMSE were high for the Bayesian estimation, concentration ratio, and in particular log-linear extrapolation. These results improved only slightly when samples were collected after T_{max} compared with those when samples were collected during the entire dosing interval. Still, the Bayesian estimation showed a higher RMSE than that of concentration ratio and sampling at the end of the dosing interval. Additional simulations with shorter sampling intervals were performed. When samples

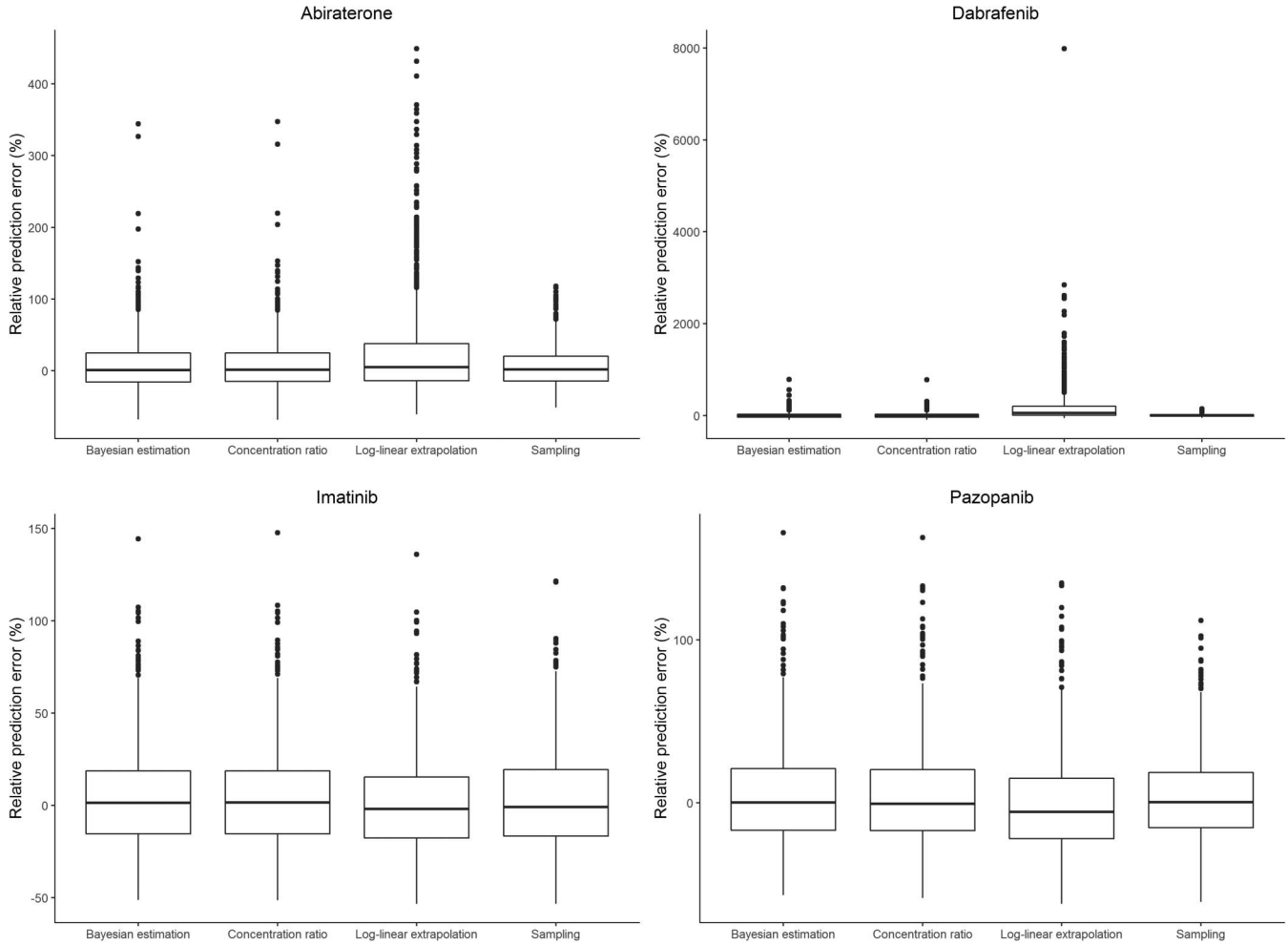

FIGURE 1. RPE of $C_{min,pred}$ of the 3 extrapolation methods for abiraterone, dabrafenib, imatinib, and pazopanib for samples collected after T_{max} compared with that for samples collected at the end of the dosing interval (scenario A).

were collected from 6 to 9 hours after dabrafenib intake until the next intake, predictive performance improved considerably (detailed results are presented in Supplementary Material, **Supplemental Digital Content 1**, http://links.lww.com/TDM/A403). Nevertheless, the log-linear extrapolation still performed worse than the other 2 extrapolation methods and sampling at the end of the dosing interval, whereas the Bayesian estimation and concentration ratio showed similar performance. When the sampling interval was reduced to between 9 and 12 hours after intake, similar results for predictive performance were observed with all 4 methods. The differences in MPE and RMSE did not result in large differences in target attainment between the 3 extrapolation methods. Log-linear extrapolation resulted in the highest PPV and lowest NPV. When samples were collected between 6 and 12 hours after intake, all 4 methods showed similar results in PPV.

Imatinib

The population PK model for imatinib was a one-compartment model with linear elimination from the central compartment. Interindividual variability was included on the parameters for Vc/F and CL/F (Table 1).[17]

For imatinib, both the GOF plots and RPE (Figs. 1–3 and supplementary figures, **Supplemental Digital Content 2**, http://links.lww.com/TDM/A402) showed an adequate prediction of the $C_{min,sim}$ with all 3 extrapolation methods. The 3 extrapolation methods resulted in similar predictive performance, as shown by the MPE and RMSE in Table 2 and Supplementary Material, **Supplemental Digital Content 1**, http://links.lww.com/TDM/A403. Similar performance was observed for the 3 extrapolation methods compared with sampling at the end of the dosing interval. In addition, no noteworthy differences in PPV and NPV were observed between the methods. Sampling at the end of the dosing interval showed the highest PPV and NPV, followed by the Bayesian estimation and concentration ratio. The extrapolation interval did not seem to affect the predictive performance of any of the methods, which suggested that the 3 methods provided good predictions for samples collected at various time points during the entire dosing interval.

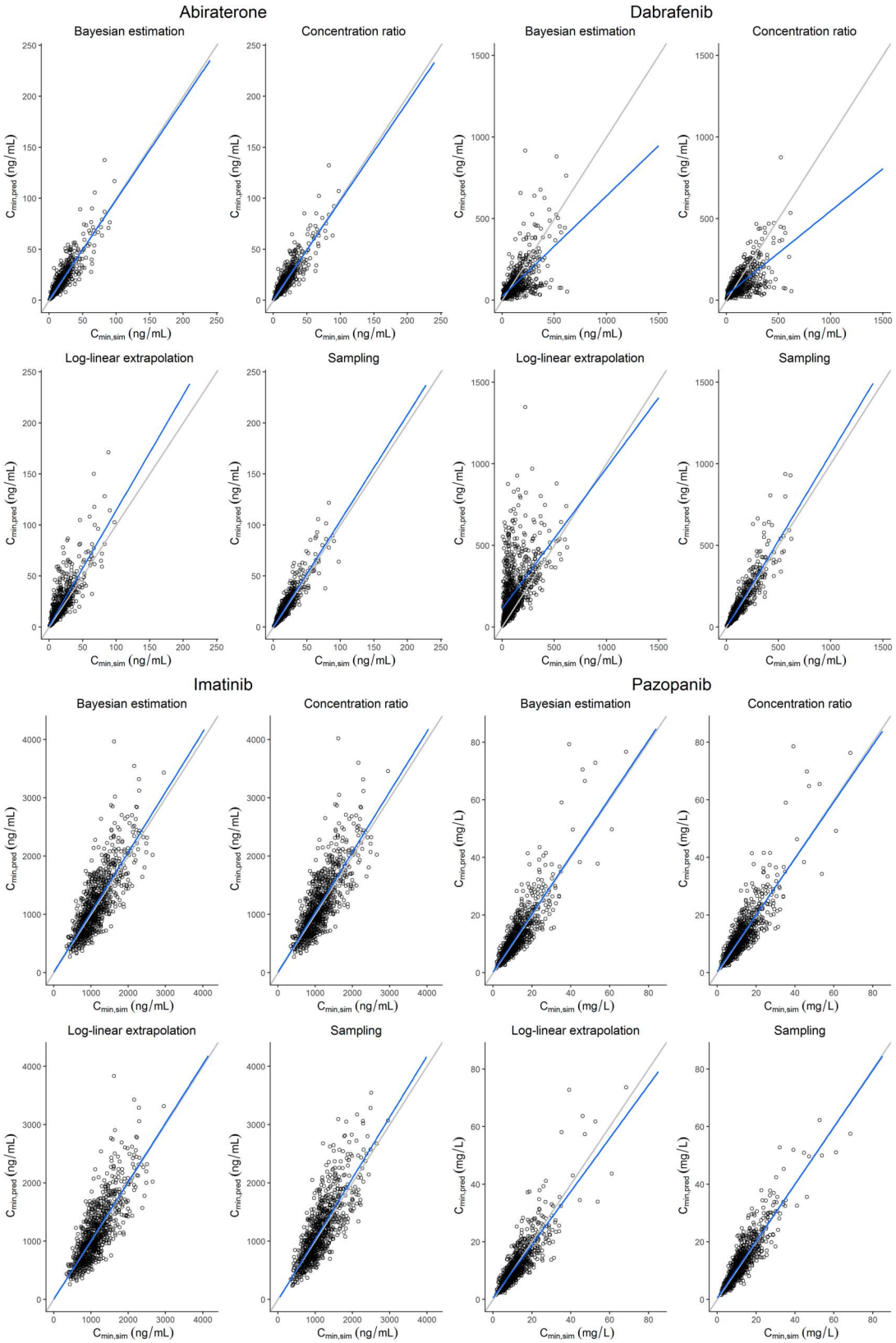

FIGURE 2. GOF plots of $C_{min,pred}$ versus $C_{min,sim}$ of the 3 extrapolation methods for abiraterone, dabrafenib, imatinib, and pazopanib for samples collected after T_{max} (scenario A) compared with that for samples collected at the end of the dosing interval.

TABLE 2. Predictive Performance of the Three Different Extrapolation Methods for Samples Collected After T_{max} Compared With That for Samples Collected at the End of the Dosing Interval (Scenario A)

Parameter	Bayesian Estimation (1)	Concentration Ratio (2)	Log-Linear Extrapolation (3)	Sampling
Abiraterone				
MPE (ng/mL)	7.52	7.89	25.4	5.74
RMSE (%)	37.4	37.3	72.0	28.3
PPV (%)	92.1	92.5	93.1	94.6
NPV (%)	78.5	78.8	71.5	84.8
Dabrafenib				
MPE (ng/mL)	1.05	2.08	177	2.43
RMSE (%)	67.2	61.3	443	27.8
PPV (%)	87.3	86.9	99.1	93.8
NPV (%)	68.1	68.5	33.1	88.5
Imatinib				
MPE (ng/mL)	3.82	3.89	0.976	2.93
RMSE (%)	27.1	27.2	26.1	26.9
PPV (%)	79.3	79.3	75.9	81.5
NPV (%)	80.0	80.0	82.4	82.7
Pazopanib				
MPE (mg/L)	4.73	3.93	−1.05	3.39
RMSE (%)	30.8	30.6	28.8	26.4
PPV (%)	72.5	73.5	67.6	73.5
NPV (%)	95.5	95.7	97.0	93.7

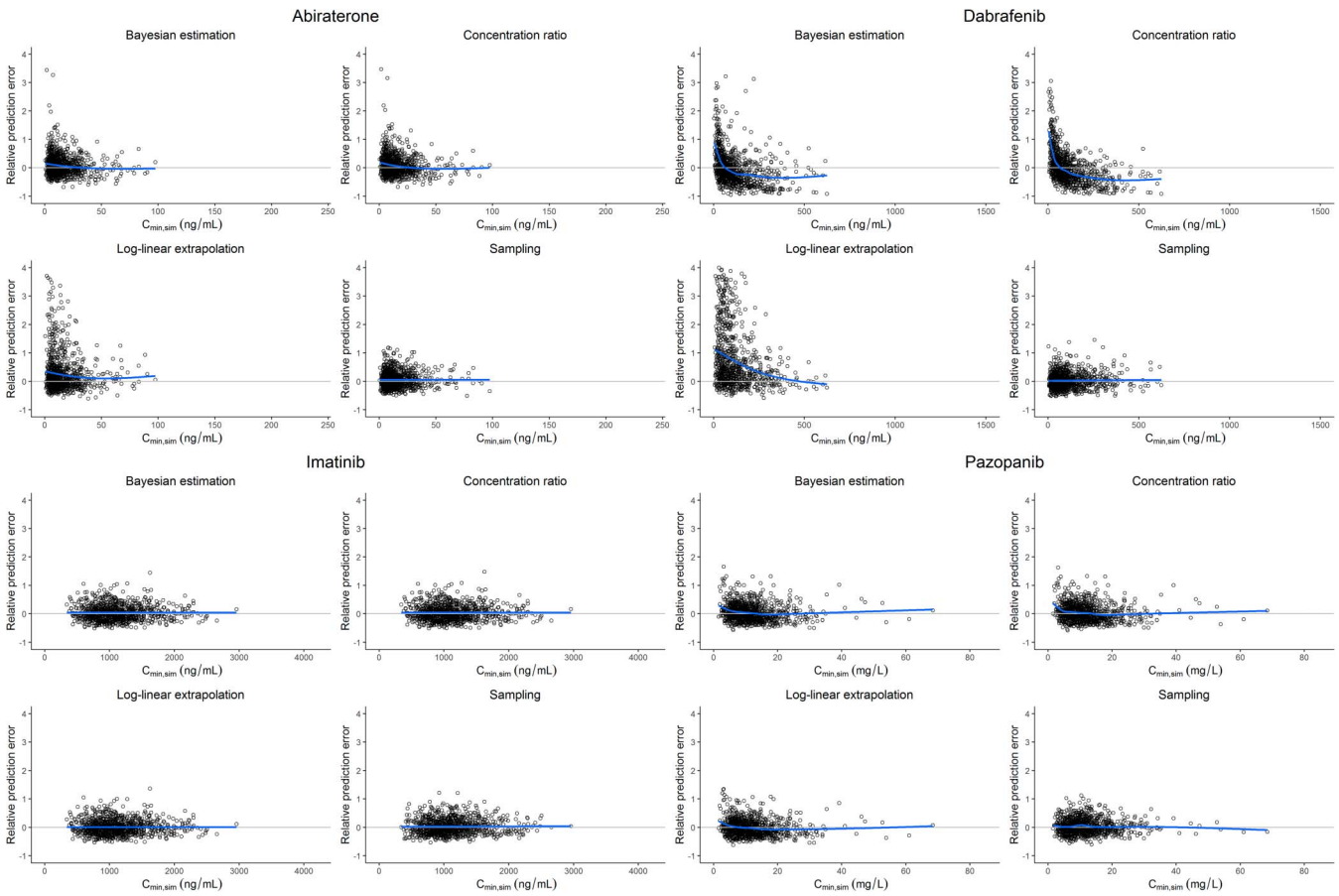

FIGURE 3. RPE of $C_{min,pred}$ versus $C_{min,sim}$ of the 4 extrapolation methods for abiraterone, dabrafenib, imatinib, and pazopanib for samples collected after T_{max} (scenario A).

Pazopanib

A two-compartment model with fast and slow first-order absorption processes, dose-dependent bioavailability, and interindividual variability for ka, CL/F, peripheral volume of distribution (Vp/F), and F was previously published and used for the simulations (Table 1).[18]

The simulation results for pazopanib showed a slight overprediction of the lower $C_{min,sim}$ values for the Bayesian estimation, concentration ratio, and log-linear extrapolation (Figs. 2, 3 and Supplementary Figures, **Supplemental Digital Content 2**, http://links.lww.com/TDM/A402). This overprediction was reduced when samples were only collected after T_{max}. The bias (MPE) and precision (RMSE) were comparable and adequate for all 3 extrapolation methods (Table 2 and Supplementary Material, **Supplemental Digital Content 1**, http://links.lww.com/TDM/A403). Nevertheless, large variability in RPE was observed (Fig. 1 and Supplementary Figures, **Supplemental Digital Content 2**, http://links.lww.com/TDM/A402). The adequate bias and precision resulted in an adequate NPV for all 4 methods; therefore, dose adjustments will be recommended when needed. The PPV showed, however, that the log-linear extrapolation method would result in more $C_{min,pred}$ values falsely classified as above the PK target for efficacy, which would result in a continuation of the dose while a dose increase should have been advised. In additional simulations, the sampling interval was shortened to the last 6 and 3 hours before the next pazopanib intake. These simulations showed a further decrease in overprediction and improved bias, precision, PPV, and NPV (detailed results are presented in Supplementary Material, **Supplemental Digital Content 1**, http://links.lww.com/TDM/A403). In addition, all 3 extrapolation methods showed similar performance when compared with each other and when compared with sampling at the end of the dosing interval.

DISCUSSION

In this study, 3 extrapolation methods were evaluated for the determination of $C_{min,pred}$ based on a single-simulated concentration sampled with different scenarios. This evaluation focused on the quantification of the differences between these extrapolation methods; therefore, the population PK models were simplified by fixing covariates to their reference values. However, the results showed that it was not possible to compare the absolute simulated concentrations to those in real-life patient cohorts. A valid comparison between the extrapolation methods can nevertheless still be made. The 3 extrapolation methods were compared with the best-case scenario, in which a sample was collected at the end of the dosing interval. Although this sample was also associated with a random residual error, it still resulted in an imperfect estimate of the true $C_{min,sim,obs}$.

The Bayesian estimation of individual $C_{min,pred}$ should have several advantages over other simpler extrapolation approaches. It allows handling of deviations from the planned or registered sampling times. In addition, model-informed TDM enables the prediction of expected exposure after dose adjustments.[12,13] These results revealed that the Bayesian estimation did not show superior performance over that of concentration ratio in terms of bias, precision, and target attainment. This method did, however, show a better performance than that of log-linear extrapolation. Even when samples were collected over the entire dosing interval, the Bayesian estimation showed similar performance compared with that of concentration ratio.

The PK of imatinib was characterized by a one-compartment PK model. All 3 extrapolation methods showed similar bias, precision, and target attainment, including log-linear extrapolation. Nevertheless, the log-linear extrapolation method performed worse in terms of bias and precision (MPE and RMSE) for abiraterone, dabrafenib, and pazopanib for which the PK was described by more complex two-compartment models. Specifically, lower $C_{min,sim}$ values were typically overpredicted by the log-linear extrapolation method. The MPE and RMSE were higher for this method than for the other methods, but this did not result in a marked difference in target attainment. The PPV reflects the percentage of $C_{min,pred}$ truly being above the prespecified PK target. A higher PPV thus indicates less false positives for which a dose adjustment is not advised, although this would have been indicated. In clinical practice, this is the most important measure for an adequate extrapolation method.

Bias, precision, and target attainment were similar for all 3 drugs between the Bayesian estimation and concentration ratio. Bayesian estimation did, however, result in an overprediction of low $C_{min,sim}$ values for abiraterone, dabrafenib, and pazopanib. In these PK models, high interindividual variability was present; therefore, individual predictions would shrink toward the typical value because of the extremely sparse sampling. As the lower $C_{min,sim}$ values were extreme values, their Bayesian estimates would be weighted toward the typical concentration. The effect of this shrinkage was shown to decrease when samples were collected closer toward the time of C_{min}. The concentration ratio method used the ratio between the measured patient concentration and the population concentration at the same time point and multiplied this ratio with the population $C_{min,sim}$. Hence, this method did not require estimation by using a nonlinear mixed-effects software and therefore was easier to implement in clinical practice. The mean population concentration–time curve can be extracted graphically from the model that was published in the literature and implemented in commonly used software. In addition, this extrapolation method showed similar performance for all 4 drugs investigated in this study.

A previous report on the development of a Bayesian approach for imatinib TDM showed a wide range of RPE when log-linear extrapolation was used, and it concluded that the Bayesian estimation was a suitable method for the prediction of individual imatinib trough concentrations.[19] This research focused on imatinib alone and did not explore concentration ratio as an extrapolation method. These results showed that all 3 methods provided suitable predictions for imatinib. Taken together, the results of this study showed that the population PK model for imatinib was characterized by moderate interindividual variability and might therefore not reflect most oral anticancer drugs that are currently being used in clinical practice.

CONCLUSIONS

In conclusion, this study showed that using the concentration ratio of a concentration at various time points within the dosing interval versus the population median concentration and multiplying this with the population $C_{min,sim}$ (method 2) provided accurate and precise individual predictions as well as the Bayesian estimation (method 1) for the 4 KIs investigated in this study. The concentration ratio extrapolation method was easier to implement than the other methods. When the PK parameters of a drug were characterized by large interindividual variabilities, it is additionally advised to narrow the sampling window to 3–6 hours before the next drug intake until the end of the dosing interval.

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