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The Application of Virtual Therapeutic Drug Monitoring to Assess the Pharmacokinetics of Imatinib in a Chinese Cancer Population Group

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ABSTRACT

Purpose: Imatinib is used in gastrointestinal stromal tumours (GIST) and chronic myeloid leukaemia (CML). Oncology patients demonstrate altered physiology compared to healthy adults, e.g. reduced haematocrit, increased α-1 acid glycoprotein, decreased albumin and reduced glomerular filtration rate (GFR), which may influence imatinib pharmacokinetics. Given that Chinese cancer patients often report raised imatinib plasma concentrations and wider inter-individual variability reported in trough concentration when compared to Caucasian cancer patients, therapeutic drug monitoring (TDM) has been advocated.
Method: This study utilised a previously validated a Chinese cancer population and assessed the impact of imatinib virtual-TDM in Chinese and Caucasian cancer populations across a dosing range from 200-800 mg daily.
Results: Staged dose titration to 800 mg daily, resulted in recapitulation to within the target therapeutic range for 50 % (Chinese) and 42.1% (Caucasian) subjects possessing plasma concentration < 550 ng/mL when dosed at 400 mg daily. For subjects with plasma concentrations >1500 ng/mL when dosed at 400 mg daily, a dose reduction to 200 mg once daily was able to recover 67 % (Chinese) and 87.4 % (Caucasian) patients to the target therapeutic range.
Conclusion: Virtual TDM highlights the benefit of pharmacokinetic modelling to optimising treatments in challenging oncology population groups.

Introduction

Tyrosine kinase inhibitors (TKIs) have revolutionised the treatment of several cancers,[1] but there still remains a need to consider optimising dosing to ensure personalised anticancer treatment in a range of patient groups.[2] Imatinib, which inhibits BCR-ABL activity, has gained attention as one candidate which would benefit from TDM approaches,[3-5] particularly in gastrointestinal stromal tumours (GIST) and chronic myeloid leukaemia (CML).

Gastrointestinal stromal tumours (GIST) are one of the commonest types of mesenchymal tumour localised to the gastrointestinal tract, affecting approximately 7 people per million per year in Western countries,[6] 16 people per million per year in Korea[7,8] and approximately 4 people per million per year in China.[9] Whilst surgical resection is the mainstay treatment, only 70 % of patients attain a 5-year post-operative survival[10] and the economic burden of therapeutic interventions is high, at over $100,000 per patient per year.[11] Furthermore, a large study in Chinese patients identified a steep rise in cases after 50 years old, with males being more predisposed than females.[9] Chronic myeloid leukaemia (CML) accounts for approximately 20 % of all cases on leukaemia within adults.[12] Approximately 33 % of patients with CML treated with imatinib demonstrate a lack of complete cytogenetic response (CCyR) or present with drug resistance/toxicity.[13-15]

In both cases, a key in the paradigm of treatment is imatinib, which has revolutionised treatment outcomes and improved survival times.[16,17] Imatinib is well absorbed with an absolute bioavailability of > 98 %,[18,19] which is not dose/dosage form[20,21] dependant nor food/fed-state dependant.[22,23] Its' half-life is approximately 18 hours, and multiple dosing often leads to target plasma concentrations in-excess of the 0.5 μM (~ 250 ng/mL) required for tyrosine kinase inhibition in-vitro.[20,24] Furthermore, it is highly protein bound (>95 %)[25]

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and has a large volume of distribution (Vd) > 400 L.[19] The elimination of imatinib is governed by CYP 2C8 (primary role)[26] and 3A4,[27-29] with other CYP isozymes (CYP1A2, CYP2D6, CYP2C9 and CYP2C19) playing a minor role (< 3 % contribution in total).[27-30] Furthermore, being a low extraction drug, the elimination of imatinib is highly sensitive to protein binding and intrinsic clearance. Confounding the pharmacokinetics of imatinib, is its wide inter-individual variability with steady-state trough concentrations varying by over 20-fold in CML patients.[31,32] Furthermore, the intrinsic variability of CYP 3A4 is thought to also contribute to this inter-individual variability.[33,34]

Oncology patients tend to demonstrate altered physiology which may influence a drugs pharmacokinetics, with key changes including reduced haematocrit, increased α-1 acid glycoprotein and decreased albumin and reduced glomerular filtration rate (GFR).[35,36] Furthermore, racial and weight differences between Chinese and Caucasian patient demographics have a direct role in current Chinese guidelines for treatment. Furthermore, the tolerance of Chinese patients to higher doses (> 400 mg/day) is often lower than that of Caucasian patients, with the (United States) National Comprehensive Cancer Network (NCCN) guidelines recommending 800 mg/day[37-39] for those who show limited improvement at the standard dose (400mg/daily) (originating from Caucasian studies), whereas in Chinese studies doses are recommended at 600 mg/day.[40,41]

Given the long-term use of imatinib, appropriate steady-state levels are critical in limited side effects and toxicity such as myelosuppression, nausea, diarrhoea, hypophosphatemia, musculoskeletal symptoms, rash, fatigue, and headaches.[42] For both CML and GIST, a target trough concentration of 1000 ng/mL and 1100 ng/mL has been suggested, respectively.[43,44] Whilst these are often drive around pharmacodynamic endpoints (e.g. hematologic, cytogenetic and molecular responses), some groups have advocated the use of such concentrations as pharmacokinetic predictors of response.[45,46] Furthermore, given the wide inter-individual variability reported in trough concentration (50-100 %)[47] likely a result of the intrinsic variability in CYP 3A4 activity,[33,34] sub- or supra- therapeutic dosing is possible.[47,48]

In order to address the clinical consequences of this variability, Gotta *et al* (2014) coined the term "rescue TDM" to refer to 'corrective' dosing based on therapeutic drug monitoring (TDM) for specific cases to support optimal imatinib plasma concentrations.[5] Recently, Buclin *et al* (2020)[3] utilised the work by Gotta *et al*[5] to reiterate the need for TDM for imatinib, providing a structured approach to accomplish this. In the approach originally developed by Gotta *et al* (2014),[5] dose adjustments were support for subtherapeutic patients (500-800 mg once daily) and supratherapeutic patients (200-400 mg once daily), to target an "acceptable" target concentration range (750-1500 ng/mL) surrounding the target trough concentration of 1000-1100 ng/mL.[3]

Higher plasma concentrations have been reported in Chinese cancer patients when compared to Caucasian cancer patients.[49,50] Given the physiological difference between Chinese and Caucasian cancer patients, particularly changes in alpha-1-acid glycoprotein, the assessment of optimal doses to attain targeted plasma concentrations is warranted and can be pragmatically achieved through the use of mechanistic physiologically-based pharmacokinetic modelling approaches.[51]

In this study, we utilise previous work conducted by our group to assess the requirements and approaches towards dose titrations in Chinese cancer patients, with explicit account of the physiological differences encountered in Chinese cancer patients compared to Caucasian cancer patients.

Methods

In order to conduct virtual clinical trials simulations in subjects, the physiologically-based pharmacokinetic (PBPK) modelling tool Simcyp (Simcyp Ltd, a Certara company, Sheffield, UK, Version 19) was utilised. The algorithms and ordinary differential equation describing elements of the Simulator have been previously described.[52,53] Furthermore, the concept of virtual populations incorporates subjects forming representatives from a specific population group and incorporates appropriate physiological and biochemical variances defined for each population.[54] Unless otherwise stated, all simulations utilised mixed genders (50:50). Further, we adopted a workflow model with four stages (Fig. 1).

Validation of Imatinib in Caucasian Subjects

We utilised a previously developed and validated model of imatinib,[55] with some modifications. The validation dataset utilised included 4 studies within Caucasian populations: (i) 12 healthy Caucasian volunteers (2 female) (40-58 years old) who received a single

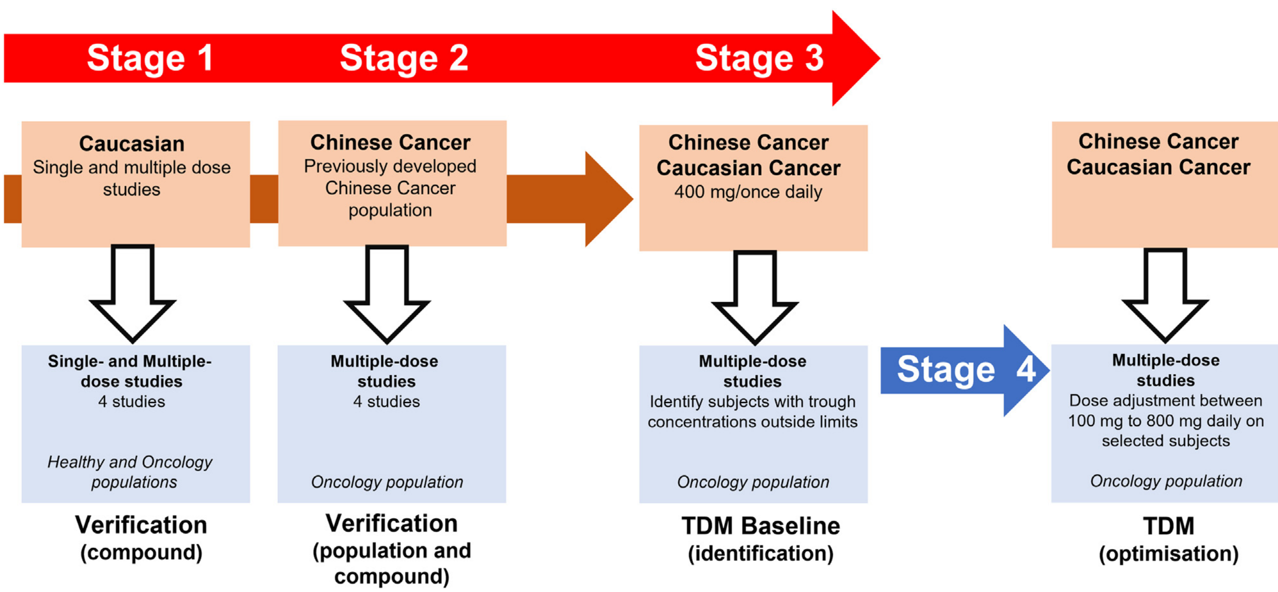

Fig. 1. The workflow model for model verification and TDM.

dose administration of imatinib 400 mg;[19] (ii) 34 cancer patients (6 female) (28-84 years old) who received multiple doses of imatinib 400 mg with sampling on days 1 and 15;[56] (iii) 50 cancer patients (21 female) (39-82 years old) who received multiple doses of imatinib 400 mg/day for 15 days;[57] (iv) 103 patient (83 female) (18-77 years old) who received multiple doses of imatinib 400mg/day for 15 days.[58] The Simcyp Healthy Volunteer population[54] or Cancer populations[59] were utilised in trials.

Validation of Imatinib in a Virtual Chinese Cancer Population

In order to assess differences in pharmacokinetics of imatinib in Chinese and Caucasian cancer subjects, we utilised a previously developed virtual Chinese cancer population group[60] in a virtual trial to compare predicted trough imatinib plasma concentration to those reported at steady state for doses of (i) 100, 200, 250, 300, 400, 600 and 800 mg once daily (36 subjects aged 17-79 years);[61] (ii) 190 GIST subjects dosed at 400 mg once daily (31-85 years) demarked for age/weight in addition to trough concentrations reported at doses of 300, 400, 500 and 600 mg once daily;[62] (iii) 84 CML subjects dosed 300-600 mg once daily (18-76 years);[63] (iv) 129 GIST subjects dosed 200-600 mg once daily (29-75 years).[64] This virtual Chinese cancer population group incorporates physiological alterations previously reported[35] to occur within oncology populations includes reductions in haematocrit, increases α-1 acid glycoprotein and decreases in both albumin and GFR.[36]

Imatinib TDM in a Virtual Chinese Cancer Population

Although there is no definitive guidance on the need for TDM for imatinib, previous studies have examined approaches to implementing TDM in clinical practice.[3-5,65-68] Utilising the “rescue TDM” approach coined by Gotta *et al* (2014), we implemented the subsequent structured approach to TDM suggested by Buclin *et al* (2020)[3] (Fig. 2), in order to assess the need for imatinib TDM in a virtual Chinese cancer population group.

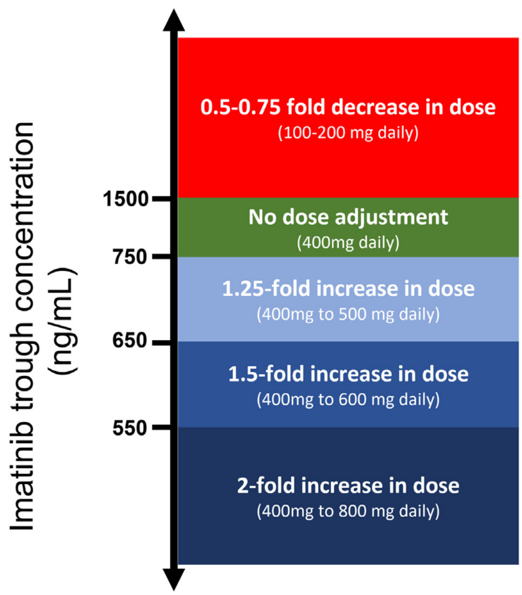

Fig. 2. TDM-guided dose titrations. Dose titrations were conducted based on approaches previously described[3]. Subjects with imatinib trough plasma concentration outside of the prescribed target trough window (750-1500 ng/mL), following a 400 mg once daily (to steady-state) dosing schedule, were identified and subjected to dose adjustment based on either a dose increase or decrease, dependent upon their trough plasma concentration.

A 10 × 10 trial design (100 subjects) was implemented (20-50 year olds, 50 % female) with a dose of 400 mg once daily for 28 days, followed by dose adjustments in 100 mg daily increments to the target dose and maintained for a further 28 days at each specific target dose. At day 28 (before adjustment) and day 56 (after adjustment), subjects were identified who demonstrated trough plasma concentrations below or above the target thresholds, and the impact of the dose adjustment was quantified in relation to ability to target the therapeutic concentration range (750-1500 ng/mL) identified by Buclin *et al* (2020).[3] Subjects’ demographics were maintained for the TDM-applicable cohorts.

As a comparison, an identical trial design was implemented for the Simcyp Cancer (Caucasian) population group.

Predictive Performance

For the validation steps 1-3, predictive performance was determined within a 2−fold (0.5−2.0−fold) range of reported pharmacokinetic parameters.[69-71] A visual predictive checking (VPC) strategy (U. S. Food and Drug Administration, 2012)[72-74] was also adopted for predicting plasma concentration-time profiles. This checking strategy was performed visually when the predicted plasma-concentration profiles, including the predicted mean and 5th and 95th percentiles, was compared with the observed data which should overlap with the predicted data sets. Furthermore, the prediction accuracy of the simulation profiles was evaluated using average fold error (AFE) (Eq. (1)) and absolute average fold error (AAFE) (Eq. (2))[75-77] were calculated to further validate provide a measure of precision and bias, as follows:

$$AFE = 10^{\frac{1}{n} \cdot \sum \log\left(\frac{pred_t}{obs_t}\right)} \quad (1)$$

$$AAFE = 10^{\frac{1}{n} \cdot \sum \left|\log\left(\frac{pred_t}{obs_t}\right)\right|} \quad (2)$$

where n represents the number of observations, $pred_t$ and obs_t are the predicted and observed concentrations at time t. Deviations from unity refer to over-prediction (AFE > 1) or under-prediction (AFE < 1) of the observed data. AAFE measures the absolute error from the true value and inherent determined bias of the profile. AAFE values of ≤2 were considered appropriate.[78]

Mean predicted values (e.g. C_{max} or C_{min}) were compared with observed values and the standard deviation ratio (SDratio) calculated (Eq. (3))[51] as follows:

$$\text{SDratio} = \sqrt{\left(\frac{\text{SD observed}}{\text{Mean observed}}\right)^2 + \left(\frac{\text{SD predicted}}{\text{Mean predicted}}\right)^2} \times \frac{\text{Mean predicted}}{\text{Mean observed}} \quad (3)$$

where SD observed and SD predicted are the SD of observed and predicted values; Mean observed and Mean predicted are the arithmetic mean of observed and predicted values. A criterion of < 2-fold was deemed an acceptable prediction of values.[69-71]

The observed clinical data used in verification studies were extract using WebPlotDigitizer v. 3.10 (https://automeris.io/WebPlotDigitizer/). Statistical significance was confirmed as $p < 0.05$.

Results

Validation

The model was successfully validated against 5 adult imatinib single- and multiple-dosing regimen studies, with the majority of plasma concentrations falling within the 5th and 95th percentiles of the predicted concentrations (Supplementary Materials Fig. S1). Further, in all cases the AFE and AAFE were between 0.85-1.21 and 0.98-1.14, indicating successful model predictions (Supplementary Materials Table S1).

Validation of Imatinib in a Virtual Chinese Cancer Population

Simulated median steady-state trough and peak imatinib plasma concentrations in Chinese cancer populations were broadly within 1.5-fold of those reported for a variety of doses from 100 mg − 800 mg (Fig. 3) with mean prediction ratio and SD-ratio within the 2-fold boundary (Table 1).

Imatinib TDM in a Virtual Chinese Cancer Population

In order to examine the requirement for TDM-based dose adjustment, simulations in Chinese and Caucasian cancer populations assessed the changes in trough imatinib plasma concentrations following dose adjustment from a baseline of 400 mg once daily across a range of 200-800 mg once daily. Trough plasma concentrations were higher for Chinese than Caucasian subjects (Fig. 4A) (Table 2) with a standard dose resulting in trough levels of 1816.2 ng/mL (52.85-8257.29 ng/mL) and 1216.6 ng/mL (121.23-4464.89 ng/mL) respectively (Table 2) (Fig. 4B).

In order to engage in virtual-TDM, we considered each simulated subject and sampled the steady-state trough plasma concentration (following 400 mg once daily dosing), prior to dose-titrations. At a 400 mg dose, fewer Chinese subjects possessed trough concentrations within the target range (750-1500 ng/mL) when compared to Caucasian subjects, 26 % and 43 % respectively (Table 3). However, a greater number of Chinese subjects possessed trough concentrations in excess of the upper limit of the target range (>1500 ng/mL), 51 %, when compared to Caucasian subjects, 25 % (Table 3).

In Chinese and Caucasian populations, 9 % and 13 % of subjects, respectively, possessed sub-therapeutic concentration in the range of 550-750 ng/mL, of which all were recapitulated to the target range, upon the application of the appropriate TMD method (Fig. 2) (Table 3). However, for those with a plasma concentration < 550 ng/mL, a dose increase to 800 mg was only able to recover 50 % (Chinese) and 42.1% (Caucasian) of those subject to within the target therapeutic range (Table 3). For subjects with plasma concentration >1500 ng/mL, a dose reduction to 200 mg once daily was able to recover 67 % (Chinese) and 84 % (Caucasian) of those patients of within the target therapeutic range (Table 3).

Discussion

The management and treatment of patients with CML and GIST have significantly improved since the first TKI, imatinib, was introduced, with similar survival rates to that of control subjects.[79] As a selective inhibitor of the protein tyrosine kinase Bcr-Abl, platelet-derived growth factor receptors (PDGFRα and PDGFRβ) and KIT, imatinib has been demonstrated as part of the treatment of CML and GIST.[80,81]

Monitoring the plasma concentration of imatinib may be beneficial in optimising treatment strategies,[82] particularly given that all tyrosine kinase inhibitors are administered orally and, usually, as fixed doses regardless of the patient's weight, age, or gender, leading to inconsistent bioavailability and individual differences in plasma levels across a population.[83]

For adult CML/GIST patients (irrespective of ethnicity), the current recommended dose is 400 or 600 mg once daily,[84] resulting in quite diverse plasma concentrations in different ethnic groups, with the average plasma imatinib concentration in 10 countries (Asia (China, South Korea, Japan, and India), Europe (France, Norway, the Netherlands, Belgium, and Italy), and North America (United States)) ranging from 800-1500 ng/mL.[85]

In this study, we utilised virtual-TDM to optimise imatinib therapy in virtual Chinese and Caucasian cancer subjects. The imatinib model was adapted and validated in single and multiple dose studies in Caucasian subjects[19,56-58] in addition to a being validated using a previously developed virtual Chinese cancer population group[60] with CML/GIST multiple dose studies.[61-64] In these validation studies, the predicted imatinib plasma concentrations were within the range reported in clinical studies (Fig. S1 and Fig. 3) and mean predicted pharmacokinetics parameters were all within 2-fold of those reported (Table 1). Some level of under/over-prediction was evident in Fig. 3F and G, when predicting trough (Fig. 3F) and peak (Fig. 3G) plasma concentrations with observed data from 129 GIST subjects dosed 200-600 mg once daily (29-75 years).[64] However, the observed data recruited a total of 129 patients in an observational phase 4 trial, with patients demarked for imatinib daily dose and hence the observed data for each dose reflect a smaller subset of the total patient number, and this may have contributed to the under/over-prediction at the higher doses. Nonetheless, median predictions were within 2-fold of those reported.

Failures in imatinib treatment can be attributed to the resistance mutations of imatinib in the kinase domain of BCRABL1.[86] In these cases, therapeutic drug monitoring (TDM) may provide clinicians with opportunities for informed dosage decisions. The European CML Treatment and Outcome Study (EUTOS),[87] offered guidance on approaches for TDM with imatinib in addition to identify the relationship between imatinib plasma concentration and response. Using centralised TDM and clinical outcome data including cytogenetic response (CyR) and molecular response (MR), the imatinib plasma concentrations of thousands of CML patients were collected in the registry, and the population PK modelling was used to analyse the data. This model describes pharmacokinetic parameters of imatinib in specific populations, quantifies the impact of patient characteristics on the behaviour of imatinib, and provides an individual estimate of Cmin. Additionally, the observations suggest that due to the lower concentration of imatinib and the slower response rate, early dose optimisation of TDM may benefit some patients.[87] This study exemplifies the potential of TDM for different populations and provides theoretical evidence for individual variations. Critically, this study suggested at a defined therapeutic target concentration which was utilise as the basis for this work.

Having confirmed the ability of the model to recapitulate plasma concentrations within both Caucasian cancer and Chinese cancer populations, we subsequently applied TDM-based dose adjustment, using the approach developed by EUTOS,[5] in simulations by assessing the changes in trough imatinib plasma concentrations following dose adjustment from a baseline of 400 mg once daily across a range of 200-800 mg once daily (Fig. 4).

For all doses studied, the trough imatinib plasma concentration was higher than that predicted within Caucasian Cancer subjects, concurring with previous reports which have highlighted that broadly lower doses may be required in Asian versus Caucasian subjects.[49,88-93]

Notability, there was a wide interpatient variability in predicted plasma concentrations in both population groups (Fig. 4), a feature also reported by others.[32,43,94] The cause of this may be attributed to both variability in the abundance of CYP metabolic pathways or transporter expression/function pathways. However, in the context of comparing Chinese and Caucasian cancer population, the differences in both body weight and body surface area may also contribute to this, with our virtual Chinese and Caucasian cancer populations possessed body weights of 62.21 kg $\pm$ 9.45 kg and 74.3 kg $\pm$ 14.8 kg and BSA of 1.69 m^2 $\pm$ 0.16 m^2 1.85 m^2 $\pm$ 0.21 m^2. This difference is the often quoted reason for Chinese cancer population required lower

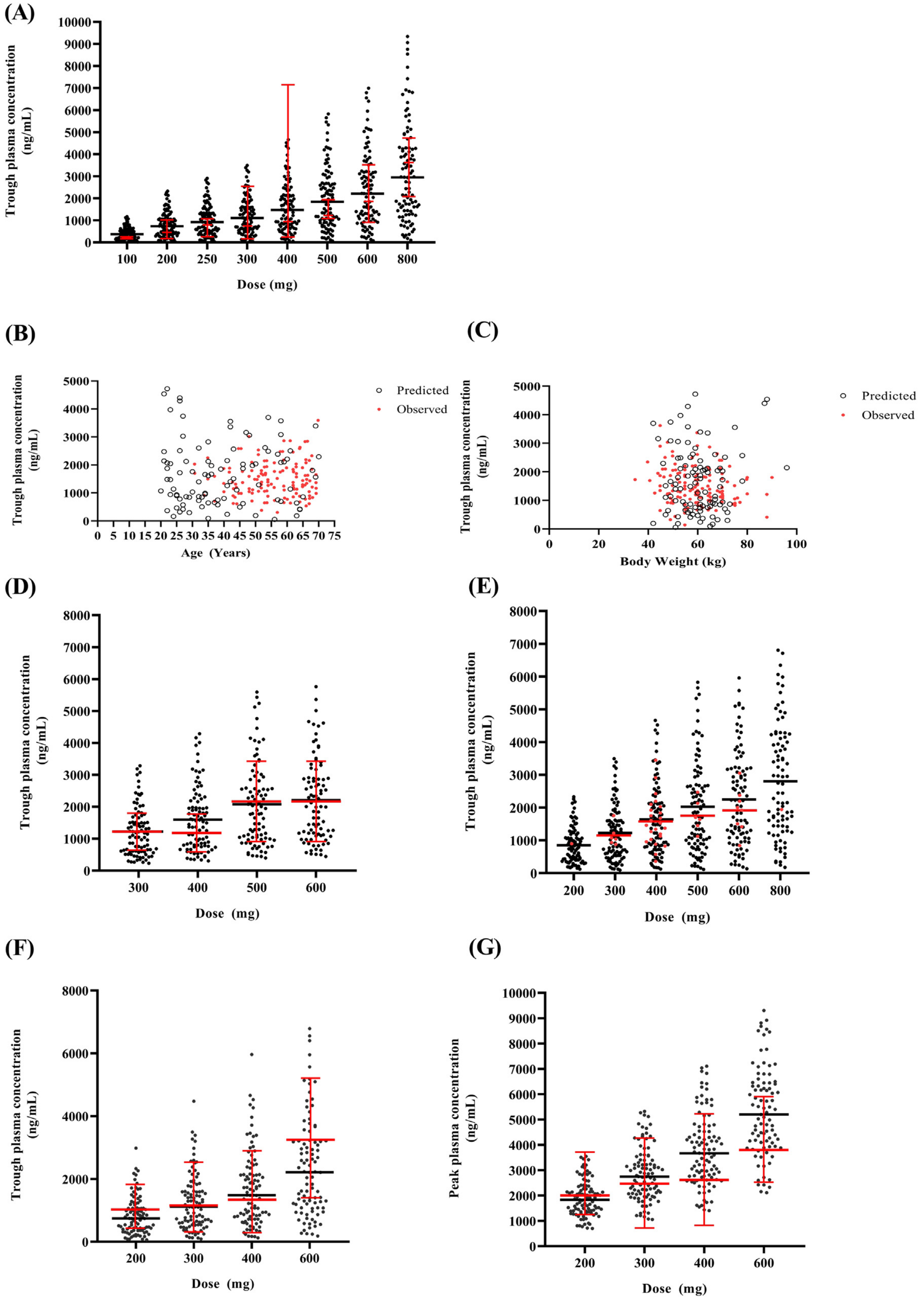

Fig. 3. Imatinib plasma concentration following oral dose administration in Chinese cancer subjects. Steady-state trough plasma concentration reported following (A) 100, 200, 250, 300, 400, 600, 600 and 800 mg once daily doses (36 subjects aged 17-79 years)[61]; 190 GIST subjects (31-85 years) demarked for age with a 400 mg once daily dose (**B**), body weight with a 400 mg once daily dose(**C**)[62], trough plasma concentration dosed at 300, 400, 500 and 600 mg once daily (D)[62]; (**E**) 84 CML subjects dosed 300-600 mg once daily (18-76 years)[63]; (**F** and **G**) 129 GIST subjects dosed 200-600 mg once daily (29-75 years)[64]. Circles indicate the predicted (black) or observed (red) individual data. Where individual concentration observed data was not reported, the reported observed mean and range were used and is represented by red horizontal lines (mean) and range (upper and lower horizontal lines). Predicted mean is represented by the horizontal black lines.

Table 1
Predicted and observed imatinib trough or peak plasma concentrations at in the Chinese cancer population group

		C_{min} (ng/mL)		Comparison	
	Dose (mg)	**Predicted**	**Observed**	**Mean ratio**	**SD Ratio**[a]
Xia et al (2020)	100	369.11 (82.74-1162.87)	378 (140-334)	0.98	1.08
	200	738.015 (85.46-2327.15)	640 (346-1222)	1.15	1.12
	250	922.41 (111.8-2909.74)	986 (440-1265)	0.94	1.02
	300	1106.8 (138.2-3492.63)	940 (337-2781)	1.18	1.24
	400	1475.37 (150.8-4659.26)	1139 (421-7493)	1.32	1.42
	500	1843.795 (320.49-5827.25)	1422 (1283-2155)	1.31	1.38
	600	2212.075 (76.14-6996.38)	2076 (1103-3775)	1.07	1.08
	800	2948.395 (101.38-9336.94)	3879 (2303-5017)	0.76	1.05
Wu *et al* (2018)	300	1221.7 (756.7)	1564.65 (596.2)	0.80	1.24
	400	1593.4 (987.2)	1521.3 (610.3)	1.07	1.42
	500	2078.9 (1289.9)	2540.3 (1298.1)[#]	0.82	1.38
	600	2208 (1291.3)		0.87	1.08
Zhong *et al* (2012)	200	849.7 (541.2)	732.6	1.16	nd
	300	1227.2 (828.1)	996 (337.7)	1.23	1.45
	400	1635.8 (1105.6)	1446.2 (757.3)	1.13	1.52
	500	2024.5 (1388.5)	1631.9 (507.1)	1.23	1.24
	600	2246.9 (1440.2)	1802.3 (709.1)	1.24	1.13
	800	2802.7 (1724.1)	1832.7	1.56	nd
Zhang *et al* (2018)	200	738.3 (78.2-2981.1)	960.1 (367.2-1751.2)	0.73	1.26
	300	1107.6 (102.15-4471.9)	1087.5 (253.2-2452.1)	1.02	1.11
	400	1484.3 (143.2-5963.2)	1270.9 (224.7-2809.3)	1.17	1.23
	600	2215.3 (192.4-6788.9)	3162.6 (1327-5112.8)	0.73	1.42
		C_{max} (ng/mL)			
	200	1832.2 (701.6-3548.2)	1988.5 (1232.2-3699.3)	0.93	1.23
	300	2748.3 (1053.6-5342.6)	2456.3 (701.8-4256.7)	1.11	1.15
	400	3665.7 (1406.2-7102.1)	2604.8 (802.6-5211.9)	1.43	1.33
	600	5205.7 (2113.6-9303.4)	3785.6 (2516.5-5897.3)	1.39	1.23

Data represents mean (range) or mean (SD). C_{min}: trough plasma concentration; C_{max}: peak plasma concentration; Mean ratio: ratio of predicted to observed concentration; nd: not determined.

[a] SD ratio: ratio of predicted to observed SD ratio. Observed SD was obtained or calculated from original reference source.

[#] Observed data for 500 mg and 600 mg doses were reported as a single value.

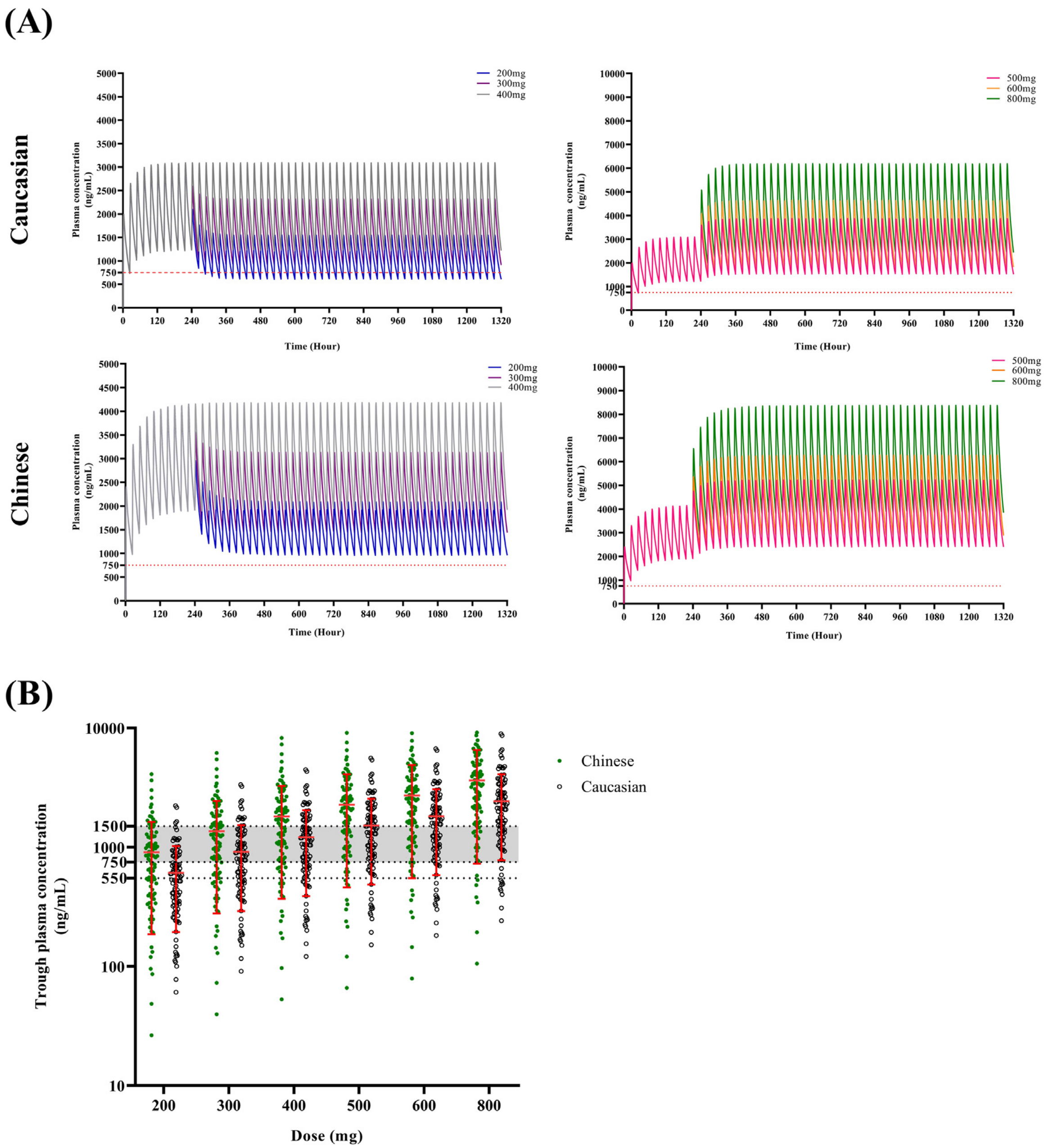

Fig. 4. Simulated imatinib plasma concentrations in Chinese and Caucasian cancer subjects at different doses. (A) Simulated plasma concentration in 100 Caucasian (upper panels) or Chinese (lower panels) cancer subjects (20-50 year olds) following an initial dose of 400 mg once daily to steady-state (10 days) and thereafter dose titrations to between 200-400 mg once daily (left panels) or 500-800 mg once daily (right panels). Horizontal dashed line indicates lower target trough plasma concentration (750 ng/mL). (B) Simulated plasma concentration in 100 Caucasian (open circles) or Chinese (solid green circles) cancer subjects (20-50 year olds) at steady-state doses of between 200-800 mg once daily Horizontal shaded regions represents target trough plasma concentration (750-1500 ng/mL). Red lines indicate median and 5th- and 95th percentiles.

doses to support treatment outcomes broadly lower doses are required in Chinese versus Caucasian subjects.[49,88-93]

For Chinese cancer subjects, at the standard dose of 400 mg once daily, only 26 % of subjects possessed trough concentrations within the expected therapeutic range, with 51 % exceeding 1500 ng/mL (Table 3). In applying TDM approaches, whilst a doubling of dose to 800 mg was only able to recapitulate 50 % (n=7) of the subtherapeutic subjects at 400 mg below 550 ng/mL, the equivalent 1.25-fold (500 mg) and 1.5-fold (600 mg) increase in dose was able to recover all subtherapeutic subjects between 550-750 ng/mL into the target range. For trough levels above 1500 ng/mL, a 50 % reduction in dose was able to recover 66% of subtherapeutic subjects into the target window. Similar trends were identified for Caucasian cancer subjects, albeit with dose adjustment for subjects with trough levels above 1500 ng/mL resulting in an increase in the recovery to target concentrations. Drug included adverse effects are likely with high imatinib plasma concentrations, and include, nausea, vomiting, oedema and cutaneous reactions.[95] The latter occurs often at higher doses (400-800 mg/day), although most are mild in nature.[96] Although our study was limited to 200 mg/day as the lowest dose, case reports of 100-200 mg/day have demonstrated to result in improve clinical outcomes.[97,98]

The case for TDM for imatinib has been widely made by many,[2,3,5] and clear cost-effectiveness with TDM-guided therapy versus fixed

Table 2
Predicted imatinib trough plasma concentrations at difference doses in Chinese and Caucasian cancer subjects

Dose	Trough plasma concentration (ng/mL)							
	Chinese				Caucasian			
(mg)	Mean	Median	Range	SD	Mean	Median	Range	SD
200	907.79	772.01	26.46-4095.64	721.56	608.28	531.78	60.66-2231.98	413.81
300	1361.92	1157.52	39.66-6168.77	1083.7	912.44	797.51	90.96-3348.33	620.79
400	1816.2	1542.73	52.85-8257.29	1446.7	1216.6	1063.155	121.23-4464.89	827.82
500	2270.62	1927.69	66.02-10360.15	1810.49	1520.77	1328.77	151.48-5581.64	1034.9
600	2725.17	2312.42	79.17-12476.44	2175.04	1824.95	1594.335	181.71-6698.57	1242.03
800	3634.66	3081.33	105.42-16745.82	2906.26	2433.36	2125.32	242.1-8933.03	1656.426

n=100 subjects. Data represents arithmetic mean. SD: standard deviation.

Table 3
Predicted imatinib trough plasma concentrations at difference doses in cancer subjects following the application of TDM

Population	Trough level[a]	Mean trough concentration (ng/mL)	SD (ng/mL)	Subjects within trough range[b]	Dose Adjustment[c]	Adjusted Dose (mg)	Mean trough concentration (ng/mL)	SD (ng/mL)	Pre-adjustment subjects within target therapeutic range post-adjustment[d]
		Pre-Adjustment				Adjustment			
Chinese	**<550**	320.99	156.12	14	x2	800	640.61	311.36	50 % (n=7)
	550-650	611.67	16.77	3	x1.5	600	916.79	24.5	100 % (n=3)
	650-750	695.22	30.57	6	x1.25	500	868.64	38.15	100 % (n=6)
	750-1500	1102.7	216.96	26	None	400	1102.7	216.96	na
	>1500	2995.07	1909.81	51	x0.5	200	1496.31	950.81	66.7 % (n=34)
					x0.75	300	2245.4	1429.34	29.4 % (n=15)
Caucasian	**<550**	336.97	136.91	19	x2	800	673.34	273.68	42.1 % (n=8)
	550-650	593.7	30.84	6	x1.5	600	890.39	46.66	100 % (n=6)
	650-750	683.21	25.01	7	x1.25	500	853.89	31.13	100 % (n=7)
	750-1500	1126.77	223.42	43	None	400	1126.77	223.42	na
	>1500	2338.47	779.16	25	x0.5	200	1169.04	389.53	84 % (n=21)
					x0.75	300	1753.71	584.33	44 % (n=11)

100 subjects (20-50 year olds) were initiated on an initial dose of 400 mg once daily to steady-state (10 days) ('Pre-Adjustment') and thereafter dose titrated to between 200-800 mg once daily ('Adjustment').
[a] Trough levels were demarked for therapeutic range (750-1500 ng/mL) and regions above and below this.
[b] Represents the percentage of subjects (n=100 in total) with trough levels within the range indicated.
[c] Represents the adjustment made to the initial steady-state dose (400 mg once daily) and below this.
[d] Represents the number of pre-adjustment subjects who have a concentration, following the revised dose adjustment, within the target trough range (750-1500 ng/mL). na: not applicable.

dose therapy has been demonstrated with improved in 'cost per quality-adjusted life year'.[4,99] TDM has been applied with imatinib in a number of approaches. Lamkheet *et al* (2017),[66] demonstrated that under standard imatinib dosing, < 40 % of subjects had trough levels within the target range (calculated per individual) which with dose adjustment (400 mg to 800 mg) leading to > 90 % of subjects with adequate trough levels. Similarly, Yoon *et al* (2013),[98] considered dose titrations in toxicity cases in two GIST patients and demonstrated reduced intolerable adverse events through dose reductions to 100 mg/daily.

However, challenges remain, ranging from throughput limitations of current analytic methods for the detection of imatinib, lack of specific anticancer TDM cost-effectiveness studies to support implementation, constrains of precise trough sampling, and ultimately the unwillingness of prescribers to modify established dosing approaches[3]. Furthermore, although the impact of intra-subject variability in imatinib pharmacokinetics is low (~30 % on key pharmacokinetic metrics)[100,101] virtual-TDM approaches should further consider addressing approaches to model this to fully capture the range of inter- and intra- subject variability associated with imatinib therapy.

In addition, our dose recommendations within other Asian populations, e.g. Japanese or Korean, may applicable but would require further validation with appropriate clinical studies, given the known interethnic differences in Asian populations for CYP 2C8 polymorphisms[102] and CYP abundance.[103]

Conclusion

This study demonstrates the application of physiologically-based pharmacokinetic modelling and virtual clinical trials, to engage in virtual-TDM of imatinib in a specific Chinese cancer population. Clear differences are evident between Caucasian and Chinese cancer patients, and this warrants further analysis to fully implement TDM in multiple ethnic groups.

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Author Contributions

RB and HE devised the study; HE generated and analysed results; HE wrote the manuscript; RB reviewed the manuscript.

Data Availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Declaration of Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary Materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.xphs.2022.09.028.

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