Pharmacokinetically guided dosing of oral sorafenib in pediatric hepatocellular carcinoma: A simulation study

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Abstract

Sorafenib improves outcomes in adult hepatocellular carcinoma; however, hand foot skin reaction (HFSR) is a dose limiting toxicity of sorafenib that limits its use. HFSR has been associated with sorafenib systemic exposure. The objective of this study was to use modeling and simulation to determine whether using pharmacokinetically guided dosing to achieve a predefined sorafenib target range could reduce the rate of HFSR. Sorafenib steady-state exposures (area under the concentration curve from 0 to 12-h [$AUC_{0->12\,h}$]) were simulated using published sorafenib pharmacokinetics at either a fixed dosage (90 mg/m^2/dose) or a pharmacokinetically guided dose targeting an $AUC_{0->12\,h}$ between 20 and 55 h μg/ml. Dosages were either rounded to the nearest quarter of a tablet (50 mg) or capsule (10 mg). A Cox proportional hazard model from a previously published study was used to quantify HFSR toxicity. Simulations showed that in-target studies increased from 50% using fixed doses with tablets to 74% using pharmacokinetically guided dosing with capsules. The power to observe at least 4 of 6 patients in the target range increased from 33% using fixed dosing with tablets to 80% using pharmacokinetically guided with capsules. The expected HFSR toxicity rate decreased from 22% using fixed doses with tablets to 16% using pharmacokinetically guided dosing with capsules. The power to observe less than 6 of 24 studies with HFSR toxicity increased from 51% using fixed dosing with tablets to 88% using pharmacokinetically guided with capsules. Our simulations provide the rationale to use pharmacokinetically guided sorafenib dosing to maintain effective exposures that potentially improve tolerability in pediatric clinical trials.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
Sorafenib pharmacokinetics (PKs) show large interindividual variability given fixed doses (90 mg/m^2/dose twice daily). This leads to a wide exposure range, particularly higher exposures, which can lead to hand foot skin reaction (HFSR), withheld doses, and therefore a possible lower antitumor efficacy.

WHAT QUESTION DID THIS STUDY ADDRESS?
Can PK and pharmacodynamic modeling and simulation approaches provide the rationale to use pharmacokinetically guided sorafenib dosing to maintain effective exposures that potentially improve tolerability in pediatric clinical trials?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
This study provides evidence, through PK and pharmacodynamic simulations, that it is possible to decrease the variability of sorafenib exposure, increase the percentages of studies in a target range, and reduce the occurrence of HFSR.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?
This study provides the rationale to use pharmacokinetically guided sorafenib dosing to maintain effective exposures that potentially improve tolerability in pediatric clinical trials, including our prospective protocol in children with rare solid malignancies.

INTRODUCTION

Hepatocellular carcinoma (HCC) is rare in children, accounting for about 0.5% of all pediatric malignancies. Cure is only possible with complete surgical resection, which only occurs in approximately a third of patients and survival rates remain poor (<30% 5-year survival) for those with unresectable disease.[1–4] Sorafenib, a tyrosine kinase inhibitor (TKI), has shown clinical activity in both adults and children with unresectable HCC. We recently completed a phase I study in children with refractory or recurrent solid tumors, including HCC, using a combination of sorafenib, bevacizumab, and low-dose oral cyclophosphamide.[5] This combination was well-tolerated and 17.6% of the patients experienced a partial response. To further build on the efficacy of the combination, we are developing a prospective protocol in children with rare solid malignancies, including HCC, that evaluates the safety and efficacy of the addition of the immunotherapeutic agent atezolizumab to the previous combination regimen. As part of the primary objectives of this protocol, we have proposed to evaluate the feasibility of using a pharmacokinetically guided dosing approach for sorafenib.

Using pharmacokinetically guided dosing to individualize sorafenib doses to a desired systemic exposure instead of a fixed sorafenib dosage, which has been previously used,[5] has been motivated by several reasons. These include the pharmacokinetics (PKs) of sorafenib have large interindividual variability and relatively smaller interoccasion variability[5–13]; sorafenib systemic exposure decreases over time[14]; the dose limiting toxicity hand foot skin reaction (HFSR) is sorafenib exposure dependent[13,15–21]; and, longer continuous exposure to sorafenib, even at lower doses can manage toxicities and lead to improved outcomes.[22,23]

Designing clinical studies to evaluate whether pharmacokinetically guided dosing can improve therapy is challenging for TKIs due to the large number of individuals needed to sufficiently power the analysis. For example, it has been shown that in the case of sunitinib, many individuals (>1000) would be required to appropriately power a study to show a significant exposure-response relationship.[24] Due to this intractable sample size, this study used Monte Carlo simulations based on clinically observed exposure-response data (time to tumor progression) to simulate the benefits of PK-guided dosing. These simulations showed that pharmacokinetically guided dosing could potentially increase the time to tumor progression by about 1 to 2 months.

Therefore, in the current study, we used PK and pharmacodynamic modeling and simulation approaches to support the rationale for including pharmacokinetically guided dosing of sorafenib in our prospective protocol. The objectives of this study were to use modeling and simulation approaches to evaluate the likelihood of achieving our desired sorafenib target range and to determine whether by achieving the target range we would reduce the rate of HFSR.

METHODS

Definition of exposure target range

The sorafenib mean (range) target steady-state exposure, defined as the area under the concentration curve from 0 to 12-h ($AUC_{0-12\,h}$) that will be used in the proposed clinical study and evaluated in this simulation study was 42.5 (20 to 55) h μg/ml. The rationale for the mean and upper limit of the range were based on the exposure versus HFSR toxicity relationships observed in our previous study.[13] The target steady-state $AUC_{0-12\,h}$ of 42.5 h μg/ml was chosen as this was the median sorafenib $AUC_{0-12\,h}$ in the group with HFSR grade less than 2, whereas the upper limit of the range of 55 was chosen as this was the upper quartile for individuals with HFSR grade less than 2. Additionally, the median sorafenib $AUC_{0-12\,h}$ in the group with HFSR grade greater than or equal to 2 was 60 h μg/ml.

The rationale for the lower limit of the sorafenib $AUC_{0-12\,h}$ range was related to previously reported sorafenib exposure versus efficacy relationships, which have shown trends to increased efficacy with sorafenib steady-state $AUC_{0-12\,h}$ exposures ranging from ~ 17 to 54 h µg/ml.[20,21,25] However, these studies were in adults with a variety of diseases (HCC, renal cell carcinoma, and sarcoma), differing demographics (both from Japan and the United States), and underpowered and not statistically significant most likely due to their small sample sizes. Other studies have suggested that sorafenib exposures that cause adverse effects, along with continuous exposure even with lower doses (which can provide higher overall exposure compared to higher doses that are intermittent due to dose limiting toxicities), may be more efficacious.[22,23] Therefore, we chose to focus on reducing the probability of toxicity and thus maximize the likelihood a patient will continue sorafenib treatment and chose the lower limit of 20 h µg/ml.

Sorafenib formulation

For our proposed clinical trial, sorafenib will be available either as tablets (Nexavar; Bayer HealthCare) or capsules, which are formulated from tablets.[26] The tablets are 200 mg and can be quartered allowing for dosing increments of 50 mg, and the lowest dosage available for the capsules is 10 mg. All dosages are normalized to body surface area (BSA) and the capsules allow for a dosage closer to the BSA normalized dose. In addition, the capsules could be sprinkled on food making them practical for younger individuals who cannot swallow tablets. Furthermore, we have previously shown that sorafenib PK parameters in patients receiving capsules or cut tablets were consistent with those reported previously in adults and children receiving intact tablets.[26]

Pharmacokinetic simulation methods

For our first objective, we used previously published pharmacokinetic data from 35 patients to simulate the likelihood of achieving our desired sorafenib target exposure range using pharmacokinetically guided dosing.[5,13] We first estimated the individual PKs on day 1 alone and then on both days 1 and 7 accounting for interoccasion variability. Specifically, using nonlinear mixed-effects modeling (Monolix, version 5.1.0) with a one-compartment PK model with zero-order absorption and first-order elimination[13] (Supplementary Figure S1), we estimated the population PKs and generated the conditional mode (empirical Bayesian estimates) and random samples from the conditional distribution ($n = 10$ per individual).[27] These individual PK parameters sampled from

the conditional distribution were used for all the simulations in this study.

Fixed dosing pharmacokinetic simulations

The sorafenib steady-state exposure ($AUC_{0-12\,h}$) given a fixed 90 mg/m^2/dose twice-daily dose (rounded to the nearest 50 mg for tablets or 10 mg for capsules) was simulated as described above using the day 7 individual PK parameters.

Pharmacokinetically guided dosing simulations

The sorafenib steady-state exposure ($AUC_{0-12\,h}$) from a pharmacokinetically guided dose adjusted to target a steady-state exposure between 20 and 55 µg h/ml was simulated as follows. (1) Use the individual PK parameters from the day 1 PK study to predict the steady-state exposure on day 7, and the dose (given twice daily) needed to obtain a steady-state $AUC_{0-12\,h}$ of 42.5 h µg/ml on day 7. (2) If the steady-state exposure on day 7 is predicted to be outside the exposure range of 20 and 55 h µg/ml based on day 1 PKs, then adjust the dose by the first dose on day 4 to target 42.5 h µg/ml on day 7. Doses were rounded to the nearest 50 mg for tablets or 10 mg for capsules and the maximum change in the dose relative to the fixed dose of 90 mg/m^2 was 2-fold. (3) Using the dose that was selected (adjusted or not), simulate the steady-state exposure using the day 7 individual PK parameters obtained from the PK analysis of the combined day 1 and day 7 PK studies. This simulated exposure based on the day 7 individual PK parameters was compared to the predicted exposure based only on the day 1 PK parameters to assess our ability to target a steady-state exposure between 20 and 55 µg h/ml.

Assessment of pharmacokinetically guided dosing success

We evaluated the number of individuals with a steady-state $AUC_{0-12\,h}$ in the target range of 20 to 55 h µg/ml along with the 95% confidence interval (CI; based on a bootstrap, $n = 1000$) of the estimate for both fixed and pharmacokinetically guided dosing. To assess our ability to perform pharmacokinetically guided sorafenib dosing, we used 6, 12, or 24 individuals as potential study subjects and defined the study to be a success if at least 4 of 6, 7 of 12, or 14 of 24 individuals (at least 60% of patients, i.e., greater than the expected percentage of studies within the target range given a fixed sorafenib dose—55%) had results in the target exposure range. The probability of success was determined by resampling with replacement ($n = 1000$) from the simulated results (either fixed and pharmacokinetically guided dosing).

Exposure versus toxicity simulations

To address our second objective, we evaluated the probability of HFSR toxicity relative to the simulated sorafenib steady-state exposure ($AUC_{0-12\,h}$) using the Cox proportional hazard model we previously developed[13] (Supplementary Figure S2). In this previous study, 10 of 45 individuals (22.2%) had grade 2/3 HFSR toxicity and each 1000 ng/ml increase in sorafenib steady-state trough concentration was associated with a 1.45-fold increase in the HFSR rate (95% CI = 1.18–1.78, $p = 0.0004$). Using this model, we simulated the probability of grade greater than or equal to 2 HFSR toxicity along with the 95% CI (based on a bootstrap, $n = 1000$) of the estimate for both fixed and pharmacokinetically guided sorafenib dosing. In addition, we determined the probability of a successful study with $n = 24$ or 36 individuals as this was considered the second part of the clinical trial. A success was defined as less than 6 of 24 or 9 of 36 individuals (<25% of patients, i.e., the upper bound of the 95% CI for the rate of HFSR given a fixed dose of sorafenib) results with grade greater than or equal to 2 HFSR toxicity. The probability of success was determined using resampling with replacement ($n = 1000$) from the simulated results (either fixed and pharmacokinetically guided dosing).

RESULTS

The sorafenib PK and HFSR toxicity data from a previously published study[5] were used for all the simulations in this analysis. The sorafenib PKs along with its exposure versus HFSR toxicity relationship in this study has been previously described.[13] The demographics for the pediatric population in that study included children as young as 1.1 years old and BSA as low as 0.4 m² (Table 1). The population PKs of this study used for all the simulations are summarized in Table 2.

By considering capsule formulations of sorafenib we were able to obtain more accurate sorafenib dosages in our pediatric populations. Specifically, using tablets with a minimum dosage increment of 50 mg, the actual BSA normalized dose received compared to the fixed dosage of 90 mg/m² varied due to dosage rounding by a median (range) of 4.8% (−26% to 39%). However, using capsules with a minimum dosage increment of 10 mg, the variance due to dosage rounding compared to the fixed dosage of 90 mg/m² was reduced to a median (range) of 1.0% (−9.3% to 11%).

Pharmacokinetically guided dosing

Based on the day 1 sorafenib PKs and a fixed dosage of 90 mg/m², 55% of the studies were predicted to be outside the target

TABLE 1 Demographics of the ANGIO1 simulation population

	Median (minimum, maximum)
N	35
Age (years)	12.4 (1.1, 22.5)
BSA (m²)	1.41 (0.40, 2.81)
Weight (kg)	46.7 (7.5, 149.2)
Sex	Male: 20 Female: 15
Race	White: 25 African American: 9 Hispanic: 1

Abbreviation: BSA, body surface area.

steady-state $AUC_{0-12\,h}$ range of 20 to 55 h µg/ml on day 7 and thus required a dose adjustment. Pharmacokinetically guided dosing using the tablet formulation decreased the interindividual variability of the day 7 steady-state $AUC_{0-12\,h}$ compared to fixed dosages (51% vs. 42%; $p = 2.1 \cdot 10^{-4}$; Figure 1) and increased the percentage of studies in-target from 50% (95% CI = 45%–55%) using a fixed dosage of 90 mg/m² to 67% (95% CI = 62%–72%; Figure 2). Furthermore, the median targeted dosage was 18% lower than the median fixed dose (76.9 mg/m² vs. 94.3 mg/m²; $p = 9.4 \cdot 10^{-18}$). This reduced variability and increased percentage of studies in-target was mostly a result of fewer studies with very high sorafenib steady-state exposure—the number of studies with a steady-state $AUC_{0-12\,h}$ greater than the upper limit of the target range (i.e., 55 h µg/ml) decreased between fixed versus pharmacokinetically guided dosing by 16% (47% vs. 31%; $p = 2.3 \cdot 10^{-32}$; Figure 1).

Using the capsule formulation, pharmacokinetically guided dosing further decreased the interindividual variability of the day 7 steady-state $AUC_{0-12\,h}$ compared to fixed dosages (49% vs. 40%; $p = 1.1 \cdot 10^{-4}$; Figure 1) and increased the percentage of studies in-target from 56% (95% CI = 51%–62%) using a fixed dosage of 90 mg/m² to 74% (95% CI = 69%–78%) when using the pharmacokinetically guided dosing approach (Figure 2). We observed the most improvement in targeting success in the younger individuals (<5 years old). In that subset of individuals, the percent of courses within the steady-state $AUC_{0-12\,h}$ target range increased from 52% (95% CI = 40%–63%) using the tablet formulation to 80% (95% CI = 68%–88%) using the capsule formulation. However, the advantage of using capsules was not as large with the older individuals (>5 years old) where the percent of courses within the steady-state $AUC_{0-12\,h}$ target range was similar; 70% (95% CI = 65%–76%) using the tablet formulation compared to 72% (95% CI = 67%–78%) using the capsule formulation.

TABLE 2 ANGIO1 population pharmacokinetics

Population Estimate	Day 1			Day 1 + day 7		
	Estimate	RSE (%)	Shrinkage (%)	Estimate	RSE (%)	Shrinkage (%)
T_{lag} (h)	0.54	11.3	5.7	0.54	0.6	2.2
T_{k0} (h)	3.26	8.8	−2.3	3.25	2.3	−4.1
V (L/m^2)	86.9	10.8	2.7	85.1	10.5	−6.9
CL (L/h/m^2)	1.56	16.6	5.6	1.62	11.9	6.1
IIV						
T_{lag}	0.56	15.8		0.56	16.3	
T_{k0}	0.35			0.35		
V	0.61	13.1		0.46	26.5	
CL	0.76	19.0		0.54	21.2	
IOV						
V				0.38	25.9	
CL				0.30	36.2	
Residual error						
Absolute	5.29	58.0		4.99	30.1	
Proportional	0.27	9.4		0.28	7.9	

Abbreviations: CL, clearance; IIV, interindividual variability; IOV, interoccasion variability; RSE%, relative standard error; T_{k0}, zero-order absorption duration; T_{lag}, absorption delay; V, volume.
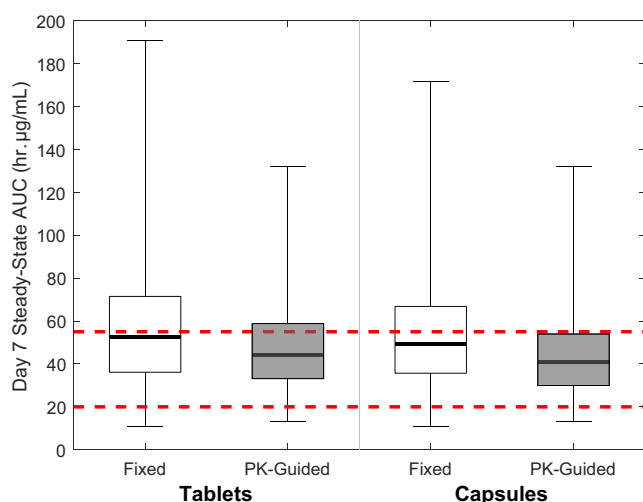

FIGURE 1 Sorafenib at steady-state area under the concentration curve from 0 to 12-h ($AUC_{0-12 h}$) based on samples taken from the conditional distribution (10 replicates per individual/day). The solid black lines are the median AUC, the boxes are the quartile range, and the whiskers are the ranges. Fixed: fixed dose of 90 mg/m^2; pharmacokinetic (PK)-guided: pharmacokinetically guided dose. All doses were rounded to the nearest tablet or capsule size. The red dashed lines represent the upper and lower range of the target AUC

Power calculations

Next, we estimated the probability of successfully targeting 60% of studies given the number of individuals ($n = 6$,
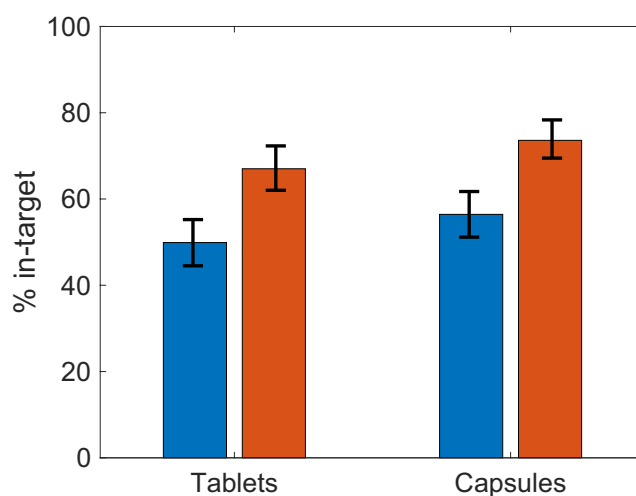

FIGURE 2 Percent of studies in target range. Blue bars: fixed 90 mg/m^2/day dose; red bars: pharmacokinetically guided dose. Whiskers represent the 95% confidence intervals

12, or 24) expected to be enrolled in the first phase of the study. When tablets were used, our simulations showed that we expect between a 72% and 83% chance of a successful study given a study population size of 6 to 24 individuals. However, if capsules were used, we can expect between 80% and 96% chance of a successful study. In contrast, if we were to use a fixed dosage of 90 mg/m^2 we would only expect between a 32% and 58% chance of a successful study (Figure 3).

FIGURE 3 Probability of successfully targeting 60% of individuals. Blue bars: fixed 90 mg/m^2/day dose; red bars: pharmacokinetically guided dose. (a) Tablets; (b) capsules
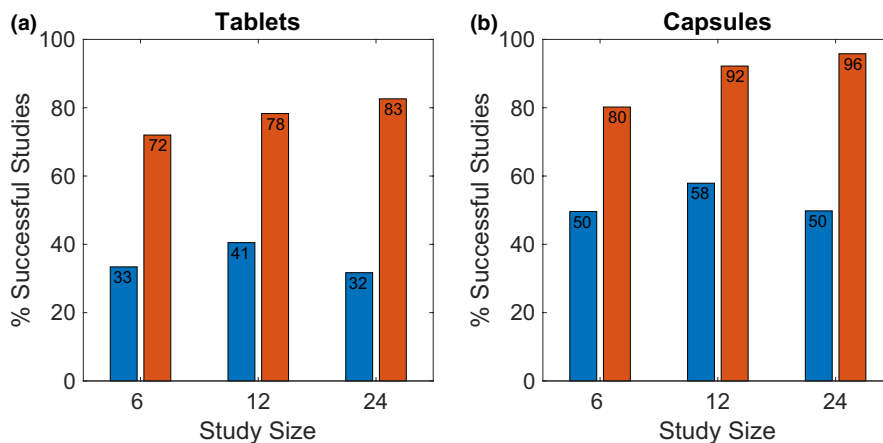
Probability of HFSR

We used the observed relationship between sorafenib exposure and grade 2/3 HFSR from our previous study to simulate the effects pharmacokinetically guided dosing of sorafenib has on the probability of HFSR.[13]

The simulations using the tablet formulation showed that pharmacokinetically guided dosing could reduce the rate of grade 2/3 HFSR toxicity from 22.1% (95% CI = 19.4%–24.9%) given fixed dosing of 90 mg/m^2 to 17.3% (95% CI = 15.1%–19.4%; Figure 4). If instead the capsule formulation was used, the pharmacokinetically guided dosing could reduce the rate of grade 2/3 HFSR toxicity from 20.8% (18.3%–23.7%) given fixed dosing of 90 mg/m^2 to 15.8% (14.0%–17.7%; Figure 4). This represents an 8.7% reduction in the estimated rate of toxicity relative to dosing using the tablet formulation. This lower rate of HFSR when capsules were used was due to the lower exposure observed when using capsules compared to tablets (median = 44.3 vs. 40.8 h μg/ml; p = 0.007; tablets vs. capsules).

Next, we estimated the percentage of successful simulated studies, defined as studies having fewer than 25% grade 2/3 HFSR toxicities, given the expected number of individuals to be enrolled in the second phase of the study (n = 24 or 36; Figure 5). Using the tablet formulation, we estimated a 77% versus 51% probability of observing less than 6 of 24 individuals with a grade 2/3 HFSR toxicity using pharmacokinetically guided versus fixed dosing, respectively, and a 84% versus 55% probability of observing less than 9 of 36 individuals with a grade 2/3 HFSR toxicity using pharmacokinetically guided versus fixed dosing, respectively. If instead we considered using only the capsule formulation, we estimated an 88% versus 56% probability of observing less than 6 of 24 individuals with a grade 2/3 HFSR toxicity using pharmacokinetically guided versus fixed dosing, respectively, and a 93% versus 59% probability of observing less than 9 of 36 individuals with a grade 2/3 HFSR toxicity using pharmacokinetically guided versus fixed dosing, respectively.

DISCUSSION

The results of this simulation study showed that pharmacokinetically guided dosing of sorafenib could both increase the percentage of studies with steady-state exposures within the target range and reduce the occurrences of the dose limiting toxicity HFSR. In addition, the simulations showed that, given the expected size of the proposed clinical study, we have power to show that we can successfully target greater than 60% of the studies and maintain an HFSR toxicity rate less than 25%. Thus, the results of this simulation study support the inclusion of sorafenib pharmacokinetically guided dosing in the proposed clinical study.

Pediatric HCC is very rare in children making it difficult to design clinical studies with sufficient power to address study objectives. PK and pharmacodynamic modeling and simulation approaches, which leverage existing data are one way to test multiple hypotheses and determine those that have the highest chance of being successfully tested in a clinical study. For example, as previously noted, Goulooze et al.[24] showed that it would take more than 1000 individuals to power a study to show a significant exposure-response relationship with sunitinib. However, using simulations, they showed that pharmacokinetically guided dosing could potentially increase the time to tumor progression by about 1 to 2 months. In addition, the Dutch Pharmacology Oncology Group[28] has an ongoing study where they are prospectively evaluating the feasibility, tolerability, and efficacy of therapeutic drug monitoring for 23 different oral anticancer drugs, including sorafenib. Their study design suggests that with 30 patients they have 80% power to detect a reduction in "under-targeted exposures" of sorafenib from 50% given fixed doses of 400 mg b.i.d. to 25% using their therapeutic drug monitoring approach.

The idea of using pharmacokinetically guided dosing for oral TKIs, including sorafenib, has been reviewed extensively.[28–36] These reviews discuss the need to address the large interindividual variability observed in TKIs and suggest that

there is potential in modifying dosing based on the PKs to improve efficacy and/or reduce toxicity. Several features that support pharmacokinetically guided dosing are described in these reviews. They include a known exposure-response relationship (efficacy and/or toxicity); a defined therapeutic range; and large interindividual variability. Sorafenib PKs satisfy these features in several ways. First, studies of the PKs of sorafenib have shown that it has large interindividual variability[6–12] and we observed higher interindividual variability compared to interoccasion variability (43% vs. 35% coefficient of variation [CV%]) in our sorafenib PK study.[5,13] Second, decreases in systemic exposure to sorafenib over time have been observed.[14] Specifically, sorafenib AUC decreased significantly over time with the median $AUC_{0-12 h}$ during the third month of treatment being lower than after 1 month (43.0 vs. 60.3 mg/L*h, $p = 0.008$). Most importantly, the median sorafenib AUC at the time of progression was almost two-fold lower than that observed after 1 month of therapy (33.2

vs. 60.3 mg/L*h, $p = 0.007$). Third, multiple studies have shown a relationship between sorafenib exposure and the dose limiting toxicity HFSR.[13,15–21] Additionally, published data show that efficacy is related to sorafenib exposure.[20,21,25] Finally, several studies have demonstrated that longer continuous exposure to sorafenib, even when lower doses were used to manage toxicities, led to improved outcomes.[22,23] Specifically, these studies showed that sorafenib exposure of less than 2 months related to worse survival (hazard ratio [HR] = 4, $p < 1e-4$), sorafenib dosage reductions used to manage tolerability in those with grade 2 or greater adverse events improved disease control relative to those with grade 0 or 1 (78% vs. 48%; $p < 1e-4$) including time to progression (9.5 vs. 3 months; $p < 1e-4$) and survival (12.5 vs. 5.7 months; $p < 1e-4$), and sorafenib related dermatologic adverse events in patients with HCC related to a better outcome ($p = 0.022$).

An additional challenge to accurate pharmacokinetically guided dosing of sorafenib in pediatrics is its commercially available formulation (200 mg tablets; Nexavar; Bayer HealthCare). Although these tablets can be quartered to provide more granularity in providing actual BSA normalized doses to individuals with small BSAs, substantial variance still exists between the dosage given (in mg) and the prescribed BSA normalized dose (as much as 39% difference). To help address this issue, we have previously developed a capsule formulation with capsule sizes down to 10 mg. We have shown that these capsules are bioequivalent to the tablets[26] and, due to their smaller size, we can reduce the variance between the dosage and the prescribed BSA normalized dose to 11% or less. In addition, because the capsules can be sprinkled on food, they provide a more practical formulation for individuals who cannot swallow tablets.

For our simulation study, we leveraged sorafenib data (PKs and HFSR toxicity profile) from our previous study in children with refractory or recurrent solid tumors,[5] to help guide and validate our pharmacokinetically guided dosing study design. This study was appropriate because the proposed protocol had a similar study design with the main difference being the addition of atezolizumab.
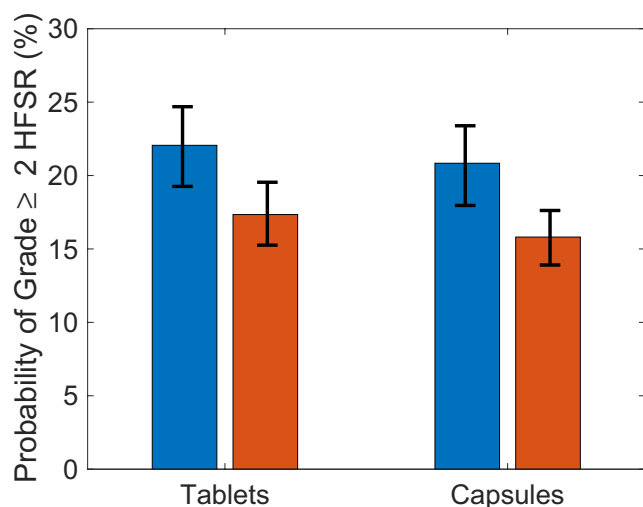

FIGURE 4 Probability of grade greater than or equal to 2 HSFR toxicity. Blue bars: fixed 90 mg/m²/day dose; red bars: pharmacokinetically guided dose. Whiskers represent the 95% confidence intervals. HFSR, hand foot skin reaction
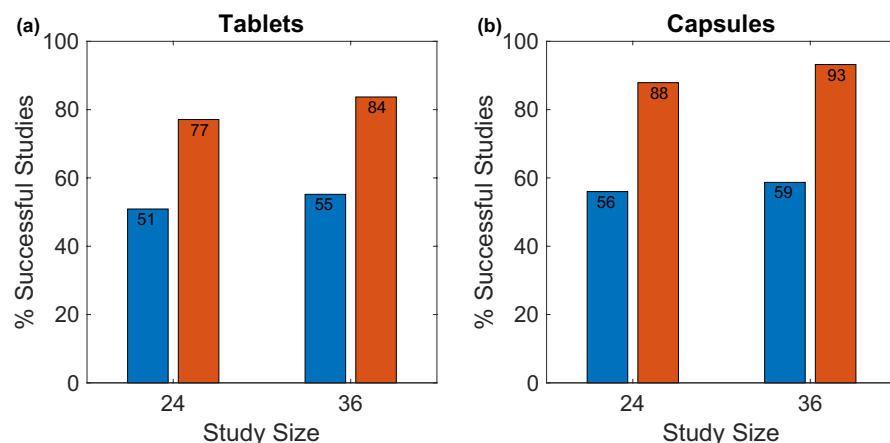

FIGURE 5 Probability of successfully maintaining less than 25% HFSR. Blue bars: fixed 90 mg/m²/day dose; red bars: pharmacokinetically guided dose. (a) Tablets; (b) capsules. HFSR, hand foot skin reaction

The results of our simulation study support the feasibility of pharmacokinetically guided dosing of sorafenib. They showed that we can expect a significantly higher percentages of studies in the target range compared to giving a fixed dose of sorafenib (67% vs. 50% with tablets and 74% vs. 56% with capsules). Furthermore, the simulations showed that we have reasonable power (at least 72% when using tablets and at least 80% when using capsules) to successfully target 60% of the studies given the number of individuals expected to be enrolled in this part of the protocol ($n = 6$ to 24).

The results of our simulation study also supported our goal of reducing the probability of HFSR. Specifically, the simulations show that pharmacokinetically guided dosing can reduce the rate of grade 2/3 HFSR from between 21% (using capsules) and 22% (using tablets) given a fixed dose of sorafenib to 16% (using capsules) and 17% (using tablets) using pharmacokinetically guided dosing. In addition, the simulations showed that we have reasonable power (at least 77% when using tablets and at least 88% when using capsules) to maintain fewer than 25% grade 2/3 HFSR toxicities given the number of individuals expected to be enrolled in this part of the protocol ($n = 24$ to 36).

This simulation study is contingent on the assumption that our data set used for the simulations is like that of the proposed study. However, this may not be true. For example, it is possible that the proposed study may enroll younger individuals at a higher percentage than the simulation study, or the effects of the addition of atezolizumab may influence either the sorafenib PKs or HFSR toxicity profile. Therefore, we plan to update these simulations dynamically as data become available in the proposed protocol. These interim analyses will help inform amendments to the protocol to address these possible differences.

The design of our pharmacokinetically guided studies for sorafenib in our proposed clinical trial will include serial sampled PK studies on day 1 (5 samples over 24 h) and days 7, 14, and 21 (3 samples over 5 h) of the first course of sorafenib. Like the simulation study, the day 1 PKs will be used to determine the sorafenib dosage needed to attain the target steady-state exposure. The adjustment to the sorafenib dose will be made on or before day 4. Furthermore, the protocol includes the option to make additional dosage adjustments after the weekly PK studies to maintain sorafenib exposures in the target steady-state range. For all subsequent courses of sorafenib therapy, we will evaluate the PKs on day 7 (3 samples over 5 h) of the course and make dosage adjustments as needed. This continued monitoring of sorafenib exposure is necessary due to the decrease in sorafenib exposure over time observed in other studies.[14]

In conclusion, our simulations showed that we could increase the percentage of patients within a target range from 50% using fixed doses with tablets to 74% using pharmacokinetically guided dosing with capsules. With the use of sorafenib capsules, the power to observe at least 4 of 6 patients in the target range increased from 33% for a fixed dosage to 80% using pharmacokinetically guided dosing. The expected HFSR toxicity rate decreased from 22% using fixed doses with tablets to 16% using pharmacokinetically guided dosing with capsules. Thus, our simulations provide the rationale to use pharmacokinetically guided sorafenib dosing to maintain effective exposures that potentially improve tolerability in pediatric clinical trials.

CONFLICT OF INTEREST

The authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

J.C.P., O.C., J.G., W.F., and C.F.S. wrote the manuscript. J.C.P., O.C., J.G., W.F., and C.F.S. designed the research. J.C.P. performed the research. J.C.P., O.C., and C.F.S. analyzed the data.

REFERENCES

1. Lau CS, Mahendraraj K, Chamberlain RS. Hepatocellular Carcinoma in the pediatric population: a population based clinical outcomes study involving 257 Patients from the Surveillance, Epidemiology, and End Result (SEER) Database (1973–2011). *HPB Surg*. 2015;2015:670728.
2. Allan BJ, Wang BO, Davis JS, et al. A review of 218 pediatric cases of hepatocellular carcinoma. *J Pediatr Surg*. 2014;49:166-171; discussion 171.
3. Katzenstein HM, Krailo MD, Malogolowkin MH, et al. Hepatocellular carcinoma in children and adolescents: results from the Pediatric Oncology Group and the Children's Cancer Group intergroup study. *J Clin Oncol*. 2002;20:2789-2797.
4. Murawski M, Weeda VB, Maibach R, et al. Hepatocellular carcinoma in children: does modified platinum- and doxorubicin-based chemotherapy increase tumor resectability and change outcome? Lessons learned from the SIOPEL 2 and 3 studies. *J Clin Oncol*. 2016;34:1050-1056.
5. Navid F, Baker SD, McCarville MB, et al. Phase I and clinical pharmacology study of bevacizumab, sorafenib, and low-dose cyclophosphamide in children and young adults with refractory/recurrent solid tumors. *Clin Cancer Res*. 2013;19:236-246.
6. Awada A, Hendlisz A, Gil T, et al. Phase I safety and pharmacokinetics of BAY 43–9006 administered for 21 days on/7 days off in patients with advanced, refractory solid tumours. *Br J Cancer*. 2005;92:1855-1861.
7. Strumberg D, Richly H, Hilger RA, et al. Phase I clinical and pharmacokinetic study of the Novel Raf kinase and vascular endothelial growth factor receptor inhibitor BAY 43–9006 in patients with advanced refractory solid tumors. *J Clin Oncol*. 2005;23:965-972.
8. Jain L, Woo S, Gardner ER, et al. Population pharmacokinetic analysis of sorafenib in patients with solid tumours. *Br J Clin Pharmacol*. 2011;72:294-305.
9. Hornecker M, Blanchet B, Billemont B, et al. Saturable absorption of sorafenib in patients with solid tumors: a population model. *Invest New Drugs*. 2012;30:1991-2000.
10. Widemann BC, Kim AeRang, Fox E, et al. A phase I trial and pharmacokinetic study of sorafenib in children with refractory

solid tumors or leukemias: a Children's Oncology Group Phase I Consortium report. *Clin Cancer Res*. 2012;18:6011-6022.

11. Kim A, Dombi E, Tepas K, et al. Phase I trial and pharmacokinetic study of sorafenib in children with neurofibromatosis type I and plexiform neurofibromas. *Pediatr Blood Cancer*. 2013;60:396-401.

12. Inaba H, Rubnitz JE, Coustan-Smith E, et al. Phase I pharmacokinetic and pharmacodynamic study of the multikinase inhibitor sorafenib in combination with clofarabine and cytarabine in pediatric relapsed/refractory leukemia. *J Clin Oncol*. 2011;29:3293-3300.

13. Inaba H, Panetta JC, Pounds SB, et al. Sorafenib population pharmacokinetics and skin toxicities in children and adolescents with refractory/relapsed leukemia or solid tumor malignancies. *Clin Cancer Res*. 2019;25:7320-7330.

14. Arrondeau J, Mir O, Boudou-Rouquette P, et al. Sorafenib exposure decreases over time in patients with hepatocellular carcinoma. *Invest New Drugs*. 2012;30:2046-2049.

15. Blanchet B, Billemont B, Cramard J, et al. Validation of an HPLC-UV method for sorafenib determination in human plasma and application to cancer patients in routine clinical practice. *J Pharm Biomed Anal*. 2009;49:1109-1114.

16. Strumberg D, Awada A, Hirte H, et al. Pooled safety analysis of BAY 43–9006 (sorafenib) monotherapy in patients with advanced solid tumours: Is rash associated with treatment outcome? *Eur J Cancer*. 2006;42:548-556.

17. Boudou-Rouquette P, Narjoz C, Golmard JL, et al. Early sorafenib-induced toxicity is associated with drug exposure and UGTIA9 genetic polymorphism in patients with solid tumors: a preliminary study. *PLoS One*. 2012;7:e42875.

18. Boudou-Rouquette P, Ropert S, Mir O, et al. Variability of sorafenib toxicity and exposure over time: a pharmacokinetic/pharmacodynamic analysis. *Oncologist*. 2012;17:1204-1212.

19. Henin E, Blanchet B, Boudou-Rouquette P, et al. Fractionation of daily dose increases the predicted risk of severe sorafenib-induced hand-foot syndrome (HFS). *Cancer Chemother Pharmacol*. 2014;73:287-297.

20. Fukudo M, Ito T, Mizuno T, et al. Exposure-toxicity relationship of sorafenib in Japanese patients with renal cell carcinoma and hepatocellular carcinoma. *Clin Pharmacokinet*. 2014;53:185-196.

21. Noda S, Hira D, Osaki R, et al. Sorafenib exposure and its correlation with response and safety in advanced hepatocellular carcinoma: results from an observational retrospective study. *Cancer Chemother Pharmacol*. 2020;86:129-139.

22. Ponziani FR, Bhoori S, Germini A, et al. Inducing tolerability of adverse events increases sorafenib exposure and optimizes patient's outcome in advanced hepatocellular carcinoma. *Liver Int*. 2016;36:1033-1042.

23. Reig M, Torres F, Rodriguez-Lope C, et al. Early dermatologic adverse events predict better outcome in HCC patients treated with sorafenib. *J Hepatol*. 2014;61:318-324.

24. Goulooze SC, Galettis P, Boddy AV, Martin JH. Monte Carlo simulations of the clinical benefits from therapeutic drug monitoring of sunitinib in patients with gastrointestinal stromal tumours. *Cancer Chemother Pharmacol*. 2016;78:209-216.

25. Maki RG, D'Adamo DR, Keohan ML, et al. Phase II study of sorafenib in patients with metastatic or recurrent sarcomas. *J Clin Oncol*. 2009;27:3133-3140.

26. Navid F, Christensen R, Inaba H, et al. Alternative formulations of sorafenib for use in children. *Pediatr Blood Cancer*. 2013;60:1642-1646.

27. Lavielle M, Ribba B. Enhanced method for diagnosing pharmacometric models: random sampling from conditional distributions. *Pharm Res*. 2016;33:2979-2988.

28. Groenland SL, Mathijssen RHJ, Beijnen JH, Huitema ADR, Steeghs N. Individualized dosing of oral targeted therapies in oncology is crucial in the era of precision medicine. *Eur J Clin Pharmacol*. 2019;75:1309-1318.

29. Klumpen HJ, Samer CF, Mathijssen RH, Schellens JH, Gurney H. Moving towards dose individualization of tyrosine kinase inhibitors. *Cancer Treat Rev*. 2011;37:251-260.

30. Gao B, Yeap S, Clements A, et al. Evidence for therapeutic drug monitoring of targeted anticancer therapies. *J Clin Oncol*. 2012;30:4017-4025.

31. Drenberg CD, Baker SD, Sparreboom A. Integrating clinical pharmacology concepts in individualized therapy with tyrosine kinase inhibitors. *Clin Pharmacol Ther*. 2013;93:215-219.

32. Widmer N, Bardin C, Chatelut E, et al. Review of therapeutic drug monitoring of anticancer drugs part two–targeted therapies. *Eur J Cancer*. 2014;50:2020-2036.

33. Yu H, Steeghs N, Nijenhuis CM, et al. Practical guidelines for therapeutic drug monitoring of anticancer tyrosine kinase inhibitors: focus on the pharmacokinetic targets. *Clin Pharmacokinet*. 2014;53:305-325.

34. Terada T, Noda S, Inui K. Management of dose variability and side effects for individualized cancer pharmacotherapy with tyrosine kinase inhibitors. *Pharmacol Ther*. 2015;152:125-134.

35. Herviou P, Thivat E, Richard D, et al. Therapeutic drug monitoring and tyrosine kinase inhibitors. *Oncol Lett*. 2016;12:1223-1232.

36. Verheijen RB, Yu H, Schellens JHM, et al. Practical recommendations for therapeutic drug monitoring of kinase inhibitors in oncology. *Clin Pharmacol Ther*. 2017;102:765-776.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.