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Tim A. Labeur[a,b,c,d] (iD), Quincy Hofsink[a,b], R. Bart Takkenberg[c], Otto M. van Delden[d], Ron A. A. Mathôt[e], Regina Schinner[f] (iD), Peter Malfertheiner[g] (iD), Holger Amthauer[h] (iD), Kerstin Schütte[i] (iD), Bristi Basu[j] (iD), Christiane Kuhl[k] (iD), Julia Mayerle[g] (iD), Jens Ricke[f]* (iD) and Heinz-Josef Klümpen[a,b]* (iD)

[a]Department of Medical Oncology, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, The Netherlands; [b]Cancer Center Amsterdam, Amsterdam, The Netherlands; [c]Department of Gastroenterology and Hepatology, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, The Netherlands; [d]Department of Radiology and Nuclear Medicine, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, The Netherlands; [e]Hospital Pharmacy, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, The Netherlands; [f]Department of Radiology, University Hospital, LMU Munich, Munich, Germany; [g]Department of Medicine II, University Hospital, LMU Munich, Munich, Germany; [h]Department of Nuclear Medicine, Charité-Universitätsmedizin Berlin, Berlin, Germany; [i]Department of Internal Medicine and Gastroenterology, Niels-Stensen-Kliniken, Marienhospital Osnabrück, Osnabrück, Germany; [j]Department of Oncology, University of Cambridge, Cambridge, UK; [k]Department of Diagnostic and Interventional Radiology, University Hospital RWTH Aachen, Aachen, Germany

ABSTRACT

Background: Sorafenib for advanced hepatocellular carcinoma (HCC) is dose adjusted by toxicity. Preliminary studies have suggested an association between plasma concentrations of sorafenib and its main metabolite (M2) and clinical outcomes. This study aimed to validate these findings and establish target values for sorafenib trough concentrations.

Methods: Patients with advanced HCC were prospectively recruited within a multicenter phase II study (SORAMIC). Patients with blood samples available at trough level were included for this pharmacokinetic (PK) substudy. Trough plasma concentrations of sorafenib and its main metabolite (M2) were associated with sorafenib-related toxicity and overall survival (OS).

Results: Seventy-four patients were included with a median OS of 19.7 months (95% CI 16.1–23.3). Patients received sorafenib for a median of 51 weeks (IQR 27–62) and blood samples were drawn after a median of 25 weeks (IQR 10–42). Patients had a median trough concentration of 3217 ng/ml (IQR 2166–4526) and 360 ng/ml (IQR 190–593) with coefficients of variation of 65% and 146% for sorafenib and M2, respectively. Patients who experienced severe sorafenib-related toxicity received a lower average daily dose (551 vs 730 mg/day, $p = .003$), but showed no significant differences in sorafenib (3298 vs 2915 ng/ml, $p = .442$) or M2 trough levels (428 vs 283 ng/ml, $p = .159$). Trough levels of sorafenib or M2 showed no significant association with OS.

Conclusions: In patients with advanced HCC treated with sorafenib, the administered dose, trough levels of sorafenib or M2, and clinical outcomes were poorly correlated. Toxicity-adjusted dosing remains the standard for sorafenib treatment.

Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver cancer and ranks as the fourth most common cause of cancer-related death worldwide [1]. Despite surveillance programs for patients at risk for developing HCC, around 40% of patients present with advanced-stage HCC that is incurable and has a poor prognosis. These patients have tumors with macrovascular invasion, extrahepatic metastases or cancer-related symptoms. Systemic treatment with sorafenib was the first therapy to show a survival benefit over placebo

(median of 2–3 months) in advanced HCC patients or those ineligible for locoregional treatment [2,3]. After sorafenib's implementation other first- and second-line targeted therapies have been approved [4], but sorafenib remains the standard of care as first-line treatment for patients with advanced HCC (Barcelona Clinic Liver Cancer [BCLC-C]) and preserved liver function [5,6].

There is great variability in sorafenib tolerability and survival benefit. Sorafenib treatment frequently causes adverse events (AEs) leading to treatment interruption (44%) or permanent discontinuation (11%), whereas objective radiological

responses to sorafenib are uncommon (2–10%) [3,6]. Survival outcomes of patients treated with sorafenib can vary from <3 months to more than 3 years [2,3,7]. In the absence of good predictive biomarkers for response or toxicity to sorafenib, the standard practice is to dose sorafenib at 400 mg twice daily (b.i.d.) orally, adjusted by clinical signs of toxicity and continued until signs of disease progression.

Prior studies have shown a high degree of interpatient variability in sorafenib exposure with a coefficient of variation (CV) ranging between 15 and 91% [8–10]. Preliminary studies have suggested an association between plasma concentrations of sorafenib and toxicity [11–13] and to a lesser extent with treatment efficacy [12,13]. A Japanese study suggested that the plasma concentration of the pyridine N-oxide metabolite (M2) of sorafenib, which is the main metabolite with similar *in vitro* potency to the parent drug [8], or the M2/sorafenib ratio of concentrations, had an even stronger correlation with treatment outcomes [13]. This suggests that individualized dosing guided by sorafenib pharmacokinetics (PK) could lead to less underdosing and reduce the toxicity rates due to overdosing. Moreover, the sorafenib area under the plasma concentration curve (AUC) has been shown to decrease significantly during the course of sorafenib treatment [14–17]. Therapeutic drug monitoring (TDM) may allow treatment personalization and improve the treatment tolerability and efficacy. Because the current evidence is preliminary, consisting of studies with small sample size ($n \leq 36$) and heterogeneous exposure parameters (AUC, trough level, maximum concentration), no target value of sorafenib plasma concentration has been defined yet [9,10,18,19]. Therefore, the present study aimed to validate whether plasma levels of sorafenib or M2 was associated with toxicity and survival in a large cohort of patients treated with sorafenib in the context of the SORAMIC trial [20]. Our study aimed to establish target values for sorafenib trough concentrations to aid clinicians in optimizing sorafenib treatment.

Methods

Study population

This study was a pre-planned PK substudy of the SORAMIC trial, a prospective, randomized-controlled, phase II trial conducted at 38 sites in 12 countries in Europe and Turkey [20]. The SORAMIC trial consisted of three parts: a diagnostic part, a curative part and a palliative part [21]. The present study was performed within the palliative part of SORAMIC, where patients were randomized to receive sorafenib monotherapy (standard of care) or selective internal radiation therapy (SIRT) plus sorafenib [20]. A full list of eligibility criteria for the palliative part of SORAMIC is shown in Supplementary Appendix A. In summary, patients were eligible if they had preserved liver function (Child-Pugh ≤ B7), an Eastern Cooperative Oncology Group performance status (ECOG PS) ≤2 and unresectable tumors not eligible for curative treatment or Transarterial Chemoembolization (TACE). Extrahepatic metastases were permitted if patients displayed liver-dominant disease and did not have pulmonary metastases. For this PK substudy, eligible patients required ≥1 blood sample suitable for trough level analysis, as defined below.

Written informed consent was obtained from each participant and the study protocol was approved by the institutional review board (IRB).

Sorafenib treatment

In the sorafenib monotherapy arm, sorafenib was started directly after randomization, whereas sorafenib was started 3 days after completion of SIRT in the combination therapy arm. In both groups, patients started with sorafenib at a dose of 200 mg b.i.d. for 1 week before increasing the dose to the target dose of 400 mg b.i.d. In case of toxicity, dose modifications followed pre-defined dosing guidelines depending on the type and severity of AEs (Supplementary Figure 1). The lowest accepted dose level (level–2) was 200 mg b.i.d. on alternate days. After the resolution of toxicities to grade 0–1, a stepwise dose-escalation was considered, aiming to maintain the highest tolerable dose level in each patient. Patients received follow-up every two months with the recording of all treatment-emergent adverse events (TEAEs) and routine laboratory assessment. Sorafenib was continued until unacceptable toxicity or disease progression.

PK sampling and analysis

PK analysis was performed on blood samples (3.5–5 mL EDTA plasma tubes) collected during routine follow-up visits, which were centrifuged and stored locally at –80° Celsius. The plasma levels of sorafenib and M2 were analyzed centrally (AMC Hospital Pharmacy laboratory, Amsterdam, The Netherlands) using liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) (Appendix B). With a sample volume of 100 μL, the sensitivity of LC-MS/MS is sufficient to determine sorafenib levels far below the therapeutic level with a lower limit of quantification of 20 ng/mL.

Sorafenib is administered orally twice daily, approximately every 12 h, therefore trough levels were taken just before sorafenib dosing. Patients were instructed to take sorafenib without food at least 1 h before or 2 h after a meal. To correct for discrepancies from planned sampling times, trough plasma levels of sorafenib and M2 were estimated using the measured concentrations and time (t) between last sorafenib dose and PK sampling, based on the first-order kinetics expression (Supplementary Figure 2A), assuming the half-life of sorafenib to be 36.5 h [8,22]. Trough levels were calculated with the following equation:

$$\text{Trough level at 12 hours} = \text{Concentration } (t) \times e^{(-\ln 2/36.5 \times (12-t))}.$$

Samples taken within 4–22 h after sorafenib intake were used, causing a maximum adjustment of 17% in plasma level (Supplementary Figure 2B). Steady-state trough levels are achieved after 1 week of sorafenib usage at the same dose level [8].

Patients included in this substudy required ≥1 PK samples which met the following criteria:

- Blood sample drawn within 4–22 hours following last sorafenib intake (trough level)
- Blood sample drawn after ≥7 consecutive days of sorafenib treatment without dose modifications (steady state)
- The blood sample had measurable sorafenib levels.

In case of multiple trough level samples per patient, the *mean* and *highest* value of trough levels for sorafenib and M2 were used for analyses.

Outcome measures

This study explored the association between trough plasma levels of sorafenib and M2 with two main clinical outcomes: toxicity and overall survival. Adverse events were recorded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. The relationship of each AE to sorafenib was assessed by the treating physician on a scale from 'none'(0) to 'definite'(5). For the toxicity analyses, AEs with a 'probable' (4) or 'definite' (5) relationship with sorafenib were included. Overall survival (OS) was calculated from date of randomization in the SORAMIC trial to date of death or last follow-up.

Although certain subgroups (age <65, nonalcoholic etiology, no cirrhosis) showed increased OS with SIRT plus sorafenib, the main SORAMIC study showed no significant differences between patients treated with sorafenib monotherapy or SIRT plus sorafenib in OS or the occurrence of treatment-related adverse events [20]. Therefore, both treatment arms were retained in the present substudy, provided that these treatment subgroups were balanced for parameters factors associated with survival differences (age, nonalcoholic etiology, cirrhosis) [20].

Statistical analysis

Categorical parameters were described as absolute and relative counts and continuous parameters as mean with standard deviation (SD) or medians with interquartile range (IQR) where appropriate. The correlation between measurements was expressed using Spearman's rank correlation test (ρ). The Kaplan–Meier method was used to estimate and plot the OS with median and 95% confidence interval (95% CI). Baseline, treatment and PK characteristics were compared in subgroups of patients with and without grade 3–4 sorafenib-related AEs using the Pearson Chi-Square, Fisher's exact, Student *t*-test or Mann–Whitney *U*-test. For efficacy, the mean trough levels of sorafenib, M2 and M2/sorafenib ratio were selected for exploratory analyses with OS. For both sorafenib and M2, there are no validated cutoff values for efficacy or toxicity, although based on preclinical experience 3750 ng/mL has been proposed as an appropriate target for sorafenib (parent compound) [19]. Another study suggested an M2/Sorafenib ratio of

0.13 as optimum cutoff [13]. Therefore, multiple cutoffs were tested, including quartile-based stratification and dichotomization of patients according to the 3750 ng/ml cut-point for sorafenib. The survival rates were compared using log-rank tests and Cox proportional hazard analysis.

Results

Patient characteristics

Of the 424 patients randomized within the palliative arm of the SORAMIC trial between 5 January 2011 and 19 April 2016, 141 (33%) underwent PK sampling. Of these, 58 patients were excluded because they lacked a blood sample at trough level ($n = 48$), there was a recent dose modification prior to PK sampling ($n = 7$) or sorafenib levels were non-measurable ($n = 3$) (Figure 1). Consequently, a total of 74 patients were included in this study. The patient characteristics are summarized in Table 1. Twenty-nine (39%) patients were treated with SIRT plus sorafenib and 45 patients received sorafenib monotherapy (61%). There were no significant baseline differences between these treatment groups, especially with regard to factors that have been associated with an increased survival benefit of the addition of SIRT to sorafenib (age <65, nonalcoholic etiology, non-cirrhosis).
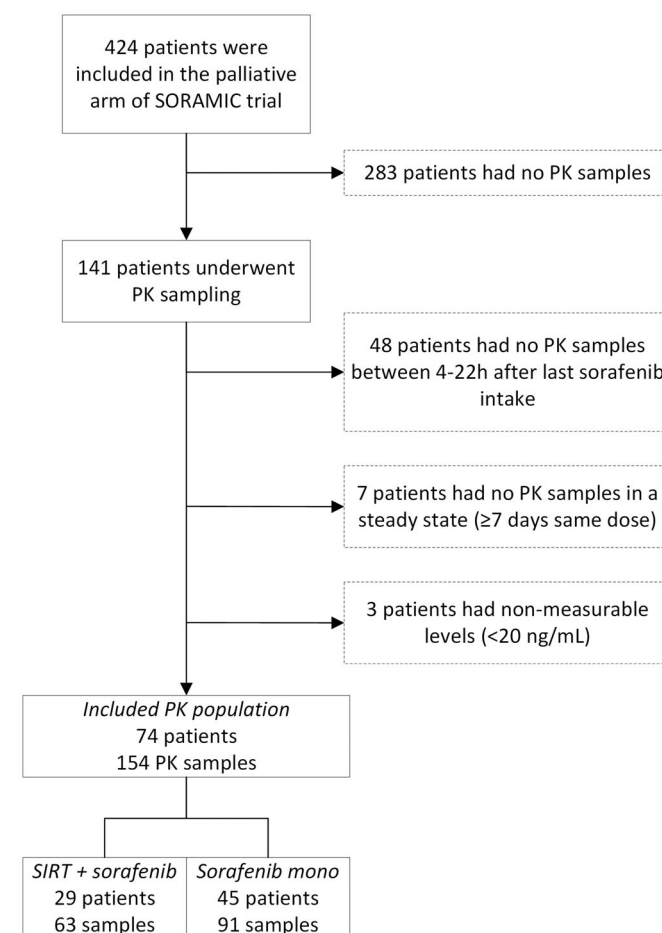

Figure 1. Study flowchart.

Variable	PK population ($n = 74$)
Demographics	
Age, years – mean (SD)	65 (8.7)
Male sex – no. (%)	66 (89)
BMI – mean (SD)	28 (5.2)
BSA – mean (SD)	2.0 (0.2)
Liver disease	
Etiology, multiple possible – no. (%)	
HBV	9 (12)
HCV	16 (22)
Alcohol	35 (47)
NAFLD-NASH	13 (18)
Other / Unknown	12 (16)
Cirrhosis – no. (%)	61 (82)
Child-Pugh class – no. (%)	
A	72 (97)
B	2 (3)
Tumor parameters	
ECOG PS – no. (%)	
0	50 (68)
1	24 (32)
Largest tumor size, mm – median (IQR)	52 (31-84)
Multifocal or diffuse no. (%)	67 (84)
Macrovascular invasion – no. (%)	32 (43)
Extrahepatic metastases – no. (%)	
Lymph node	6 (8)
Other	3 (4)
BCLC stage – no. (%)	
A	0 (0)
B	24 (32)
C	50 (68)
Received prior treatments – no. (%)	35 (47)
Serum tests (median, IQR)	
AFP, ng/ml – median (IQR)	29 (6-1525)
Albumin, g/l – mean (SD)	40 (4.7)
Total bilirubin, μmol/L – median (IQR)	12 (9-15)
Treatment details	
SORAMIC treatment arm – no. (%)	
SIRT plus sorafenib (palliative)	29 (39)
Sorafenib monotherapy	45 (61)
Duration sorafenib treatment, weeks – median (IQR)	51 (27-62)

AFP: Alpha-fetoprotein; BCLC: Barcelona Clinic Liver Cancer; BMI: body-mass index; BSA: body-surface area; ECOG PS: Eastern Cooperative Oncology Group performance status; HBV: hepatitis B virus; HCV: hepatitis C virus; IQR: interquartile range; NAFLD-NASH: Nonalcoholic fatty liver disease-nonalcoholic steatohepatitis; no: number; PK: pharmacokinetic; SD: standard deviation; SIRT: selective internal radiation therapy.

Sorafenib treatment and PK sampling

Median duration of sorafenib administration was 51 weeks (IQR 27–62), which was significantly longer in the sorafenib monotherapy arm compared with the SIRT plus sorafenib arm (53 vs 34 weeks, $p = .029$). The mean daily dose was 676 mg (IQR 453–782). A total of 154 PK samples were suitable for trough level analysis, ranging between 1 and 6 samples per patient and drawn after a median of 25 weeks (IQR 10–42) after the start of sorafenib treatment. The trough level was determined in a single sample in 30 (41%) patients or, in patients with two ($n = 19$, 26%) or ≥3 samples ($n = 25$, 34%), the average and highest value was calculated. Patients had a mean trough level of sorafenib and M2 of 3217 ng/ml (IQR 2166–4526, range 452–11,995) and 360 ng/ml (IQR 190–593, range 27–6272) with CVs of 65% and 146%, respectively. There was no significant correlation between mean daily doses and mean trough levels of sorafenib ($\rho = 0.091$, $p = .439$) or M2 ($\rho = 0.022$, $p = .851$). The highest

measured trough level of sorafenib and M2 in each patient was 3653 ng/ml (IQR 2318–6083, range 491–11995) and 468 ng/ml (IQR 214–871, range 27–6927), respectively. There were no significant differences in mean trough levels of sorafenib (3258 vs 2745 ng/ml, $p = .230$) or M2 (522 vs 344 ng/ml, $p = .089$) between patients treated with SIRT plus sorafenib or sorafenib, respectively.

Association between sorafenib toxicity and trough levels

The sorafenib-related AEs are summarized in Supplementary Table 1. The most common AEs were hand-foot syndrome or rash (43%), diarrhea (38%) and asthenia (28%). There were no treatment-related deaths, but treatment-related severe AEs (grade 3–4) were reported in 27 patients (37%). There were no baseline or clinical differences in patients developing grade 3–4 AEs (Supplementary Table 2), except that these patients received a lower daily sorafenib dose (551 mg/day, IQR 409-716) than patients with no or limited toxicity (730 mg/day, IQR 593–788) ($p = .003$), reflecting previous dose reductions in these patients.

The timing of PK sampling was poorly matched with the occurrence of AEs: most AEs (45%) occurred in the first 8 weeks of treatment, whereas the median time to PK sampling was 25 weeks (IQR 10–42) and investigators reported in only 42/154 PK samples (28%) that the patient had an AE at that time. In the available samples, there were no significant differences in trough levels of sorafenib or M2 (mean or highest) between patients with and without severe (grade 3–4) sorafenib-related toxicity (Figure 2, Supplementary Table 2), suggesting that similar serum levels were present once a tolerable dose had been identified. There also was no difference in the M2/sorafenib ratio between patients with and without severe toxicity (Supplementary Table 2).

Association between survival and trough levels

After a median follow-up period of 50.3 months (95% CI 20.9–79.7), 57 of the 74 patients (77%) had died. The median OS was 19.7 months (95% CI 16.1–23.3), which was not significantly different between patients treated with SIRT plus sorafenib or sorafenib monotherapy ($p = .157$)(Supplementary Figure 3). There were no significant differences in OS based on the literature suggested cut-point of 3750 ng/ml (Figure 3(A)), or between the different quartiles of trough levels of sorafenib (Table 2, Figure 3(B)). Similarly, there was no significant association between steady-state trough levels of the M2 metabolite or M2/sorafenib ratio and OS (Table 2, Figure 3(C,D)).

Discussion

In this multicenter study, the largest prospective PK study of sorafenib for HCC patients, no significant association was found between trough values of sorafenib or its main metabolite (M2) and treatment outcomes (toxicity and OS). Patients who underwent dose reduction for severe toxicity had similar
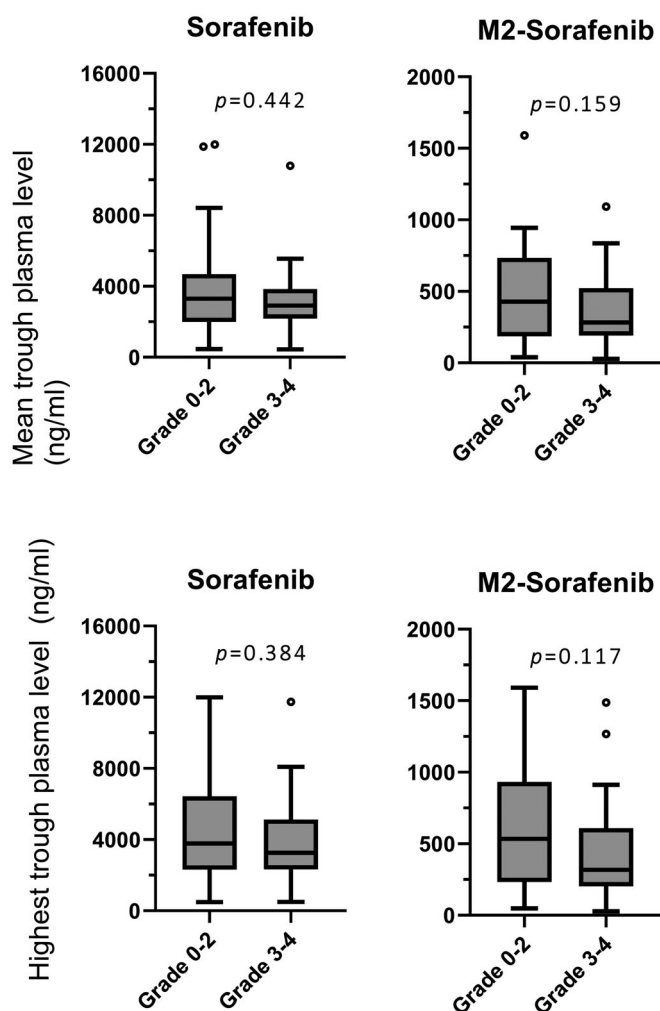
Figure 2. Boxplot distribution of mean and highest sorafenib and M2 trough levels according to the severity sorafenib-related toxicity. Boxes and line represent 25–75 percentiles and median value, the whiskers are drawn according to the Tukey method. Outliners are represented by ○.

trough levels to patients who tolerated a higher dose, suggesting that toxicity-adjusted dosing leads to similar trough levels.

Toxicity-adjusted dosing remains the current practice in sorafenib treatment of advanced HCC. Our study showed comparable plasma levels and confirmed the large inter-patient variability in plasma concentrations of sorafenib (65%) and its M2 metabolite (146%) as shown by prior studies [9,10,19]. Although the incidence and distribution of sorafenib-related toxicity was similar to previous studies [3,23,24], the present study did not confirm the association between plasma concentrations of sorafenib and toxicity as suggested by preliminary studies [11–13,17]. These studies had smaller sample size ($n = 12$–54), studied a variety of PK parameters (AUC, peak level, trough level) and all included PK sampling preceding the toxicity during the first four weeks of treatment as opposed to median sampling time of 25 weeks in this study. As the majority of sorafenib-induced AEs occur within the first 8 weeks of treatment and dose reductions are performed accordingly, the difference in timing of PK blood sampling might be a potential explanation for these different findings. While there was no difference in trough levels in

patients who experienced grade 3–4 AEs, these patients did receive a lower daily dose compared with patients without severe toxicity (551 vs 730 mg/day, $p = .003$), suggesting that patients had similar serum levels once a tolerable dose had been established after dose reductions. These findings are in accordance with three prior studies, showing a poor association between the maximum-tolerated sorafenib dose and plasma concentration [13,17,25]. For many tyrosine kinase inhibitors (TKIs), the molecular mechanism of action (target modulation) poorly correlates with the maximum tolerated dose [26]. Unlike conventional cytotoxic agents, a clear linear relationship between increasing dose and toxicity grade is often not seen in TKIs. This underscores the need for studies to elucidate the mechanisms driving the onset of sorafenib-related toxicity.

Regarding treatment efficacy, monitoring plasma concentration is currently not recommended for sorafenib treatment. Based on preclinical studies and the mean sorafenib exposure in humans, a sorafenib level of 3750 ng/ml was suggested as a potential target value that needed further validation [18,19]. In our study, this cutoff showed no significant association with OS. Two prior Japanese studies have analyzed PK (AUC and maximum levels) in relation to OS and progression-free survival (PFS) [12,13]. Fukudo et al. showed in 36 patients a trend toward longer OS in patients who achieved a maximum concentration of >4780 ng/ml [12]. Shimada et al. showed in 25 patients a longer PFS in patients with an $AUC_{N-oxide} >2.0$ µg·day/mL and recommended monitoring the M2/sorafenib ratio with a cutoff of 0.13 [13]. Our study did not reveal significant differences in OS between the different quartiles of sorafenib, M2 trough levels or M2/sorafenib ratio in patients with advanced HCC. Moreover, the arbitrary cutoffs suggested by these preliminary studies were not confirmed in our study. Consequently, the optimal plasma concentration remains unknown.

For the majority of TKI's, the value of dose individualization using TDM is still exploratory and the dose is only adjusted in case of intolerable toxicity [19]. The value of TDM in TKI's was demonstrated in imatinib treatment for chronic myeloid leukemia (CML) and gastrointestinal stromal tumors [27,28]. Imatinib has high response rates in CML (69–87%) compared with the low rates of objective responses to sorafenib in HCC ($<10\%$) [3,29]. Advanced HCC is a complex disease in which the patient's survival is impacted by both the tumor biology and severity of the underlying liver disease. Despite extensive studies, no single predictive marker with a strong association with survival outcomes has been identified [30]. Still, refinement of sorafenib dosing has been shown to be feasible: a lower starting dose with toxicity-adjusted ramp dosing has been shown to reduce the toxicity with similar survival outcomes and improved cost-effectiveness compared to a full-dose strategy [31–33].

A potentially interesting application of TDM could be verification of the patient's compliance to treatment. Of all patients who underwent PK sampling within SORAMIC ($n = 141$), 36 patients (26%) did not have detectable sorafenib levels despite having reported to have taken sorafenib
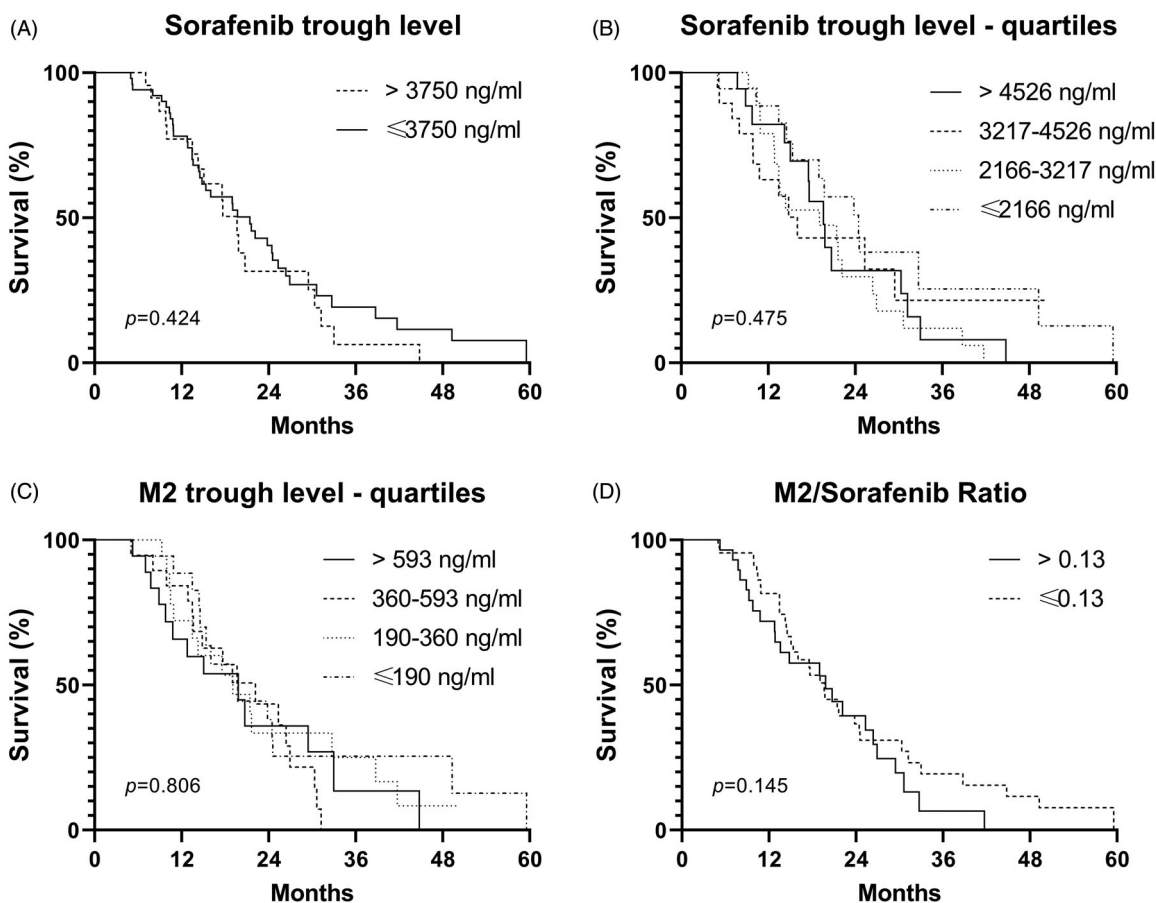
Figure 3. Overall survival according to (A) mean trough plasma level of sorafenib ≤3750 (21.4 months, 95% CI 15.2–27.6) or >3750 ng/ml (19.6 months, 95% CI 15.7–23.5), (B) quartiles of trough levels of sorafenib, (C) quartiles of through levels of M2 and D) M2/Sorafenib ratio.

Table 2. Survival according to mean trough levels of sorafenib and M2 sorafenib.

Group	N	Median OS, months (95% CI)	Hazard ratio (95% CI)	p-value
Sorafenib – Mean trough plasma level (ng/ml)				
≤2166	18	24.5 (15.3–33.6)	1	Reference
2167–3217	19	19.1 (8.3–29.8)	1.79 (0.85–3.75)	.125
3218–4526	19	16.0 (11.7–20.3)	1.55 (0.69–3.46)	.288
>4526	18	19.6 (16.1–23.1)	1.53 (0.70–3.33)	.288
M2 – Mean trough plasma level (ng/ml)				
≤190	18	19.7 (12.6–26.8)	1	Reference
191–360	19	19.1 (10.4–27.7)	1.08 (0.51–2.32)	.837
361–593	19	22.2 (14.2–30.1)	1.39 (0.66–2.94)	.393
>593	18	19.8 (7.9–31.7)	1.32 (0.61–2.87)	.487
M2/sorafenib ratio				
≤0.13	50	21.4 (15.6–27.2)	1	Reference
>0.13	29	19.8 (11.3–28.3)	1.48 (0.87–2.53)	.148

less than a day ago, suggesting treatment noncompliance. Noncompliance to therapy dosing is a well-recognized problem in oncology, with estimates for patients taking oral anti-cancer medications ranging between 10-50%, a finding which has health economic implication [34].

This study has several limitations. Firstly, (early) PK sampling was not the primary aim nor a mandatory procedure in the SORAMIC trial. Consequently, not all patients in SORAMIC underwent PK sampling and patients with a longer duration of treatment and might have had a higher chance of undergoing (trough level) PK sampling. Sample availability was mandatory for this PK substudy, causing a selection bias toward patients with a longer treatment duration and survival. In addition, the sample size of 74 patients was not sufficient to perform meaningful subgroup analyses with respect to factors associated with OS in patients treated with SIRT/sorafenib [20]. Also, few patients had samples available during the first treatment weeks, so the prognostic value of plasma concentrations in an early treatment phase could not be assessed.

Despite these limitations, this is the largest prospective study investigating the value of trough level PK sampling in patients treated with sorafenib. Future PK studies in patients treated with sorafenib or other TKIs should implement early (i.e., within 4 weeks after the start of treatment) PK sampling and additional blood samples in case of toxicity. There is accumulating evidence that early sorafenib-related toxicity, including hand-foot syndrome, diarrhea and hypertension, is associated with improved OS [35–37]. Therefore, improved insight into the toxicity-response mechanism and the role of drug exposure is warranted. More frequent sampling would allow for more advanced methods of exposure analysis (i.e., nonlinear mixed-effects modelling). These models are more likely to reflect real-life drug exposure compared with (single sample) through levels.

In conclusion, our study confirmed the large variability in plasma levels of sorafenib and its main metabolite (M2).

There was no significant association between steady-state trough levels of sorafenib or M2 and toxicity or OS. Given the poor association between administered dose, plasma concentrations and clinical outcomes, a target plasma concentration for sorafenib or M2 cannot be established and toxicity-adjusted dosing remains the standard for sorafenib treatment.

Acknowledgements

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Study registration: EudraCT 2009-012576-27, NCT0112 6645

Informed consent: Written informed consent was obtained from all individual participants included in the study. This study protocol was approved by the institutional review board (IRB).

Author contributions

TL lead the study, performed data acquisition and analysis, and wrote the manuscript. TL, QH and RS performed and supervised data analysis. RBT, OvD, RM, PM, HA, KS, BB, CK, JM, JR and HJK supervised the study, provided data and clinical input and provided mentorship for the study. HJK conceived the study design and is the guarantor of the article.

All authors have reviewed and approved the final version of the manuscript.

Disclosure statement

RBT has served as a speaker for Gore WL, Bayer, and Norgine. He is a member of the advisory board for Gilead and Norgine. He has received grants from the Netherlands Organization for Health Research and Development (ZonMw) and The Netherlands Society for Gastroenterology (NVGE). OvD has served as a consultant for Cook Medical. RM has served as an advisor for Bayer, CSL Behring, Merck Sharp & Dohme, Shire and Zeria (all honoraria/fees paid to the department). He has received grants from Bayer, CSL Behring, Shire and ZonMw. PM reports grants from Bayer, grants from Sirtex, during the conduct of the study. HA reports lecture fees from Pfizer, Sirtex, Novartis, GE healthcare and Norgine. BB has served as a member of advisory boards for Eisai Limited, Celgene, Astex, GenMab, received personal fees from Bayer, speakers fees from Biocompatibles Ltd and Eisai Europe Limited (honoraria/fees paid to institution). JR reports grants from Sirtex Medical, grants from Bayer AG, during the conduct of the study; personal fees from Sirtex Medical, personal fees from Bayer, personal fees from Bristol-Myers Squibb, personal fees from LaForce, personal fees from Roche, personal fees from Lilly Deutschland GmbH, personal fees from Siemens Healthineers, personal fees from Medison Pharma, personal fees from MCI Deutschland, personal fees from LIAM GmbH, outside the submitted work. HJK was member of an advisory board for Ipsen and Sirtex. He has received grants from the Dutch Cancer Society (KWF) and an unrestricted research grant from Bayer outside the submitted work.

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Funding

ORCID

Tim A. Labeur http://orcid.org/0000-0002-9988-5077
Regina Schinner http://orcid.org/0000-0002-3082-6570
Peter Malfertheiner http://orcid.org/0000-0001-8439-9036
Holger Amthauer http://orcid.org/0000-0003-4414-0657
Kerstin Schütte http://orcid.org/0000-0003-2472-8074
Bristi Basu http://orcid.org/0000-0002-3562-2868
Christiane Kuhl http://orcid.org/0000-0002-7698-9252
Julia Mayerle http://orcid.org/0000-0002-3666-6459
Jens Ricke http://orcid.org/0000-0001-8762-8594
Heinz-Josef Klümpen http://orcid.org/0000-0002-7290-1823

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