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# Feasibility of therapeutic drug monitoring of sorafenib in patients with liver or thyroid cancer

Niels A.D. Guchelaar [a,*], Ruben A.G. van Eerden [a], Stefanie L. Groenland [b], Leni van Doorn [a], Ingrid M.E. Desar [c], Ferry A.L.M. Eskens [a], Neeltje Steeghs [b], Nielka P. van Erp [d], Alwin D. R. Huitema [e,f,g], Ron H.J. Mathijssen [a], Stijn L.W. Koolen [a,h], On behalf of the Dutch Pharmacology Oncology Group

[a] Department of Medical Oncology, Erasmus MC Cancer Institute, Rotterdam, the Netherlands
[b] Department of Clinical Pharmacology, Division of Medical Oncology, The Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Amsterdam, the Netherlands
[c] Department of Medical Oncology, Radboud University Medical Center, Nijmegen, the Netherlands
[d] Department of Pharmacy, Radboud University Medical Center, Nijmegen, the Netherlands
[e] Department of Pharmacy and Pharmacology, The Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Amsterdam, the Netherlands
[f] Department of Pharmacy, Prinses Máxima Center for Pediatric Oncology, University Medical Center Utrecht, the Netherlands
[g] Department of Clinical Pharmacy, University Medical Center Utrecht, Utrecht, the Netherlands
[h] Department of Pharmacy, Erasmus Medical Center, Rotterdam, the Netherlands

## ARTICLE INFO

## ABSTRACT

*Introduction:* Sorafenib is a tyrosine-kinase inhibitor approved for the treatment of renal cell carcinoma, hepatocellular carcinoma, thyroid carcinoma, and desmoid fibromatosis. As high inter-individual variability exists in exposure, there is a scientific rationale to pursue therapeutic drug monitoring (TDM). We investigated the feasibility of TDM in patients on sorafenib and tried to identify sub-groups in whom pharmacokinetically (PK) guided-dosing might be of added value.
*Methods:* We included patients who started on sorafenib (between October 2017 and June 2020) at the recommended dose of 400 mg BID or with a step-up dosing schedule. Plasma trough levels ($C_{trough}$) were measured at pre-specified time-points. Increasing the dose was advised if $C_{trough}$ was below the target of 3750 ng/mL and toxicity was manageable.
*Results:* A total of 150 samples from 36 patients were collected. Thirty patients (83 %) had a $C_{trough}$ below the prespecified target concentration at a certain time point during treatment. Toxicity from sorafenib hampered dosing according to target $C_{trough}$ in almost half of the patients. In 11 patients, dosing was adjusted based on $C_{trough}$. In three patients, this resulted in an adequate $C_{trough}$ without additional toxicity four weeks after the dose increase. In the remaining eight patients, dose adjustment based on $C_{trough}$ did not result in a $C_{trough}$ above the target or caused excessive toxicity.
*Conclusions:* TDM for sorafenib is not of added value in daily clinical practice. In most cases, toxicity restricts the possibility of dose escalations.

## 1. Introduction

Sorafenib is an oral small-molecule multi-kinase inhibitor targeting several protein kinases such as those from the receptors VEGFR-1,2,3; PDGFR-β, and the RAF kinases. [1] Sorafenib is currently approved for the treatment of renal cell carcinoma (RCC), unresectable hepatocellular carcinoma (HCC), iodine-refractory differentiated thyroid carcinoma (DTC), and desmoid fibromatosis. [2–5].

For many oral anticancer agents, systemic exposure as represented by plasma trough concentration ($C_{trough}$) is related with efficacy and/or toxicity. [6] Therapeutic drug monitoring (TDM), dosing based on the measured $C_{trough}$, has therefore become a subject of interest while using

these agents. [7] Oral antineoplastic therapies are usually administered at fixed doses, but as high inter-individual variability (coefficient of variation ~50 %) exists in exposure, TDM could provide a valuable tool for precision dosing. [8,9] Sorafenib has several characteristics that make it a suitable candidate for therapeutic drug monitoring. Various studies have shown a correlation between exposure and clinical outcomes such as overall survival in patients with hepatocellular carcinoma. [10–12] However, it was also unequivocally observed that the median overall exposure to sorafenib was significantly associated with toxicity. [13,14] Furthermore, sorafenib pharmacokinetics has shown a high interpatient variability. [9] Several factors, such as variable absorption, concomitant medication (e.g. drugs inhibiting/inducing CYP3A4), or genetic variability of polymorphic transporters (e.g. changes in expressions of UGT1A) have been considered causal. [8, 15–18] A target $C_{trough}$ of 3750 ng/mL has been proposed, based on the mean exposure in a large cohort treated with sorafenib at the approved dose of 400 mg twice daily (BID). [6].

The DPOG-TDM study evaluated prospectively the feasibility, tolerability and efficacy of TDM of 24 orally administered antineoplastic agents in 600 patients. In this study, it was demonstrated that TDM is feasible in daily clinical practice for the whole group of several oral anticancer drugs. [19] Here, we report TDM in patients receiving sorafenib. We aimed to assess the practical feasibility of TDM for the proposed target $C_{trough}$ level in this group and to investigate whether we could identify specific subgroups in whom dose adjustments according to TDM results could increase the number of patients reaching prespecified target plasma levels.

## 2. Methods

### 2.1. Patient population

Data were collected within the DPOG-TDM study (www.trialregister.nl; NL6695). [19,20] Patients who started directly on the recommended dose of sorafenib (400 mg BID) or in whom step-up dosing approach towards the recommended dose was pursued were included. Demographic data, tumor characteristics, sorafenib treatment details, sorafenib $C_{trough}$ levels, and clinical relevant toxicities (i.e. toxicities requiring dose reduction, treatment interruption or being the reasons for not escalating the dose) graded using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 [21] were collected prospectively.

### 2.2. Pharmacokinetically guided dosing

Plasma samples for $C_{trough}$ measurements were collected 4, 8, and 12 weeks after start of treatment and every 12 weeks thereafter until the end of treatment. Time since the last sorafenib ingestion was recorded. A sample was considered a $C_{trough}$ when the sample was withdrawn pre-dose. If a sample was not a $C_{trough}$, the plasma level was extrapolated to estimate the $C_{trough}$. [22] In the latter case, patients were instructed to let the blood sample be drawn after the time to maximum concentration was reached ($T_{max}$ = 3 h). Sorafenib concentrations were measured using a validated LC-MS/MS assay. [23].

The target $C_{trough}$ used for sorafenib was 3750 ng/mL. This target was based on the mean plasma trough level reached at the approved dose of 400 mg BID. [6,24] It was earlier shown that targeting the mean exposure in compounds with an exposure-response relationship amounts to 81 % of the average population exposure, and therefore supporting the view that targeting the mean concentration generally leads to an efficacious exposure. [6,25] After every measurement, the dose could be adjusted based on the $C_{trough}$. The treating physician assessed whether the tolerability of treatment could facilitate a dose increase and decided on whether or not to accept the advice. Patient adherence and drug-drug interactions were checked before the dose increase was performed. Doses were increased with 200 mg per

administration, but no increment exceeding the dose of 800 mg BID was either advised or pursued. After each dose adjustment, a new plasma sample for $C_{trough}$ measurement was taken after four weeks. TDM was considered successful if the median $C_{trough}$ following dose adjustment was above the predefined TDM target and if no dose reduction due to toxicity had to be pursued within four weeks.

### 2.3. Statistical methods

A patient was considered evaluable if at least one pharmacokinetic sample was collected and analyzed and if a corresponding dose adjustment was pursued. Descriptive statistics were performed using IBM SPSS Statistics, version 25 (IBM Corp, Armonk, NY, USA), and PK results were analyzed using R, version 4.1.2 (R Project, Vienna, Austria). As this was an explorative, descriptive analysis, no statistical tests were performed.

## 3. Results

### 3.1. Patient population

A total of 36 patients were included from October 2017 until June 2020. All patients had undergone at least one $C_{trough}$ measurement. The baseline characteristics are presented in Table 1. All patients with thyroid carcinoma had received radioiodine treatment. No carry-over effects on sorafenib pharmacokinetics were expected, as no interaction between sorafenib and radioiodine has been described. [26] Eleven patients started treatment on the standard dose of 400 mg BID sorafenib, whereas 25 patients started in a lower dose following a step-up dosing schedule.

### 3.2. PK samples

In total, 150 samples were collected with a median of three (IQR: 2–5) samples per patient (Fig. 1). Of all samples, 7 % was not a $C_{trough}$ measurement and had to be extrapolated to estimate the $C_{trough}$. The mean sampling time after dose of these samples was 4.4 h, and all were withdrawn after the $T_{max}$ was reached. 30 patients (83 %) had at least one $C_{trough}$ level below the target $C_{trough}$ (< 3750 ng/mL). Of all 150 measured samples, 71 % were below the target. Of six patients with adequate $C_{trough}$, four patients had to stop sorafenib treatment due to excessive toxicity at the time of plasma sampling. The median $C_{trough}$ in all patients was 2695 ng/mL (IQR: 1783–4104 ng/mL). Visually, we could not observe a clear relationship between sorafenib $C_{trough}$ and dose, see Fig. 1.

### 3.3. Pharmacokinetically guided dosing

For each patient, we analyzed whether at least one dose adjustment was successfully implemented during the treatment course. The results of therapeutic drug monitoring for sorafenib are presented in Fig. 2. Of 30 patients in whom the $C_{trough}$ was below the threshold, 17 could not be escalated due to actual toxicity and one patient had already stopped

**Table 1**
Baseline characteristics.

| Characteristic | Patients ($N$ = 36) |
| --- | --- |
| Age, median (range) | 68 (46–78) |
| Sex, $n$ (%) | 28 (78 %) |
|    Male | 8 (22 %) |
|    Female | |
| Primary tumor, $n$ (%) | 30 (83 %) |
|    Hepatocellular carcinoma | 6 (17 %) |
|    Thyroid carcinoma | |
| Previous systemic treatment, $n$ (%) | 6 (17 %) |
|    Radioiodine | 30 (83 %) |
|    None | |
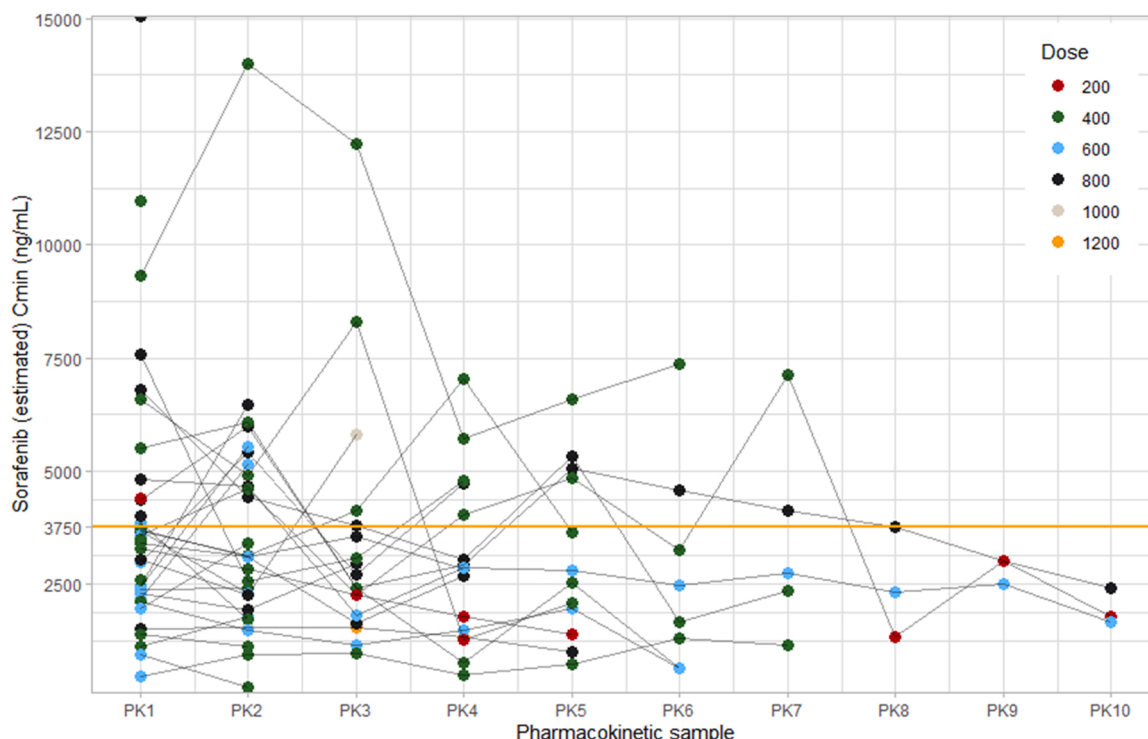
**Fig. 1.** Individual sorafenib concentrations per patient. The sorafenib concentrations are visually illustrated per patient. The color of the dot indicates the sorafenib cumulative daily dose (in mg/day) that was used at the time of the pharmacokinetic sample. The orange line indicates the target exposure for sorafenib of 3750 ng/mL. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)
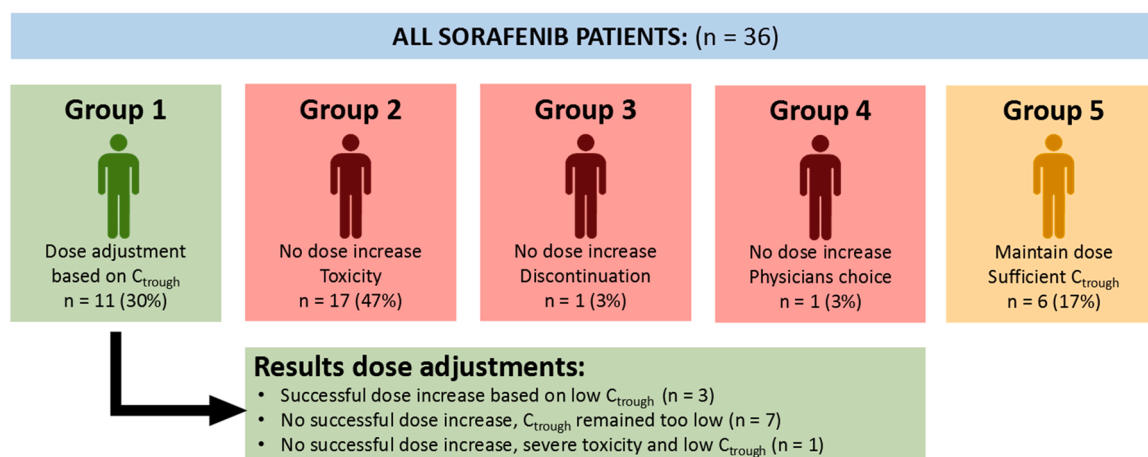


**Fig. 2.** Results of Therapeutic Drug Monitoring in patients using sorafenib. Abbreviations: $C_{trough}$ = plasma trough concentration, TDM = Therapeutic Drug Monitoring.

treatment shortly after the blood sample was taken. The most common cause for not escalating the dose was elevated liver enzymes (n = 5), followed by fatigue (n = 4), hand-foot skin reaction (n = 4), diarrhea (n = 2), pruritus (n = 1), and thrombocytopenia (n = 1). In one patient, the dose adjustment advice was not followed by the treating physician.

In 11 patients, the dose was adjusted based on the $C_{trough}$ level. A detailed overview of these patients is presented in Table 2. In three patients, the dose adjustment was considered successful. One patient had a sub-therapeutic $C_{trough}$ at 400 mg BID, and was successfully escalated to 1000 mg daily dose. In two out of three patients, dose adjustment was applied during the step-up phase of dosing and in fact supported the decision to further pursue dose escalating. In the remaining seven patients, the pharmacokinetically guided dose intervention was not successful (patients 4–11 in Table 1). These patients

received a TDM-based dose escalation, but the $C_{trough}$ remained below target. Moreover, patient 11 had severe toxicity (fatigue grade 3) after the dose increase.

In six patients, no dose adjustment was given as $C_{trough}$ was adequate at all measurements. In one patient, $C_{trough}$ was found to be 4400 ng/mL at a dose of 200 mg once daily (OD). This patient had to stop treatment after one month due to severe toxicity (fatigue and elevated liver enzymes grade 3). Treatment in three other patients with adequate $C_{trough}$ levels (one at 200 mg BID, two at 400 mg BID) was stopped due to toxicity after one to two months, as well. One patient was dose reduced to 200 mg BID because of severe toxicity (pruritus grade 3), and had a high $C_{trough}$ (7570 ng/mL). The sorafenib trough concentration at this reduced dose was still above the target (4780 ng/mL). The patient continued treatment on 200 mg BID with less treatment-related toxicity

**Table 2**

Detailed overview of patients who received a pharmacokinetically guided dose adjustment for sorafenib. Before is defined as the $C_{trough}$ level, sorafenib dose, and toxicity before the dose adjustment. After is defined as the $C_{trough}$ level 4 weeks measured after the dose adjustment. Target $C_{trough}$ was 3750 ng/mL. Abbreviations: ADR: adverse drug reaction leading to a dose decrease or restricting further increase of the dose, $C_{trough}$= minimum plasma concentration, d = day, int. = dose intervention, F = female, M = male, yrs = years.

| Patient | Age (yrs) | Sex | Dose before int. (mg/d) | $C_{trough}$ before (ng/mL) | ADR before | Dose after int. (mg/d) | $C_{trough}$ after (ng/mL) | ADR after | Success |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 70 | M | 600 | 2870 | None | 800 | 5400 | None | Yes |
| 2 | 64 | M | 600 | 2460 | None | 800 | 6460 | None | Yes |
| 3 | 50 | M | 800 | 2250 | None | 1000 | 5810 | None | Yes |
| 4 | 62 | M | 600 | 1670 | None | 800 | 1750 | Diarrhea grade 2 | No |
| 5 | 74 | M | 400 | 1110 | None | 600 | 1790 | None | No |
| 6 | 71 | M | 600 | 2290 | None | 800 | 1930 | Diarrhea grade 2 | No |
| 7 | 68 | M | 800 | 1520 | None | 1200 | 1550 | None | No |
| 8 | 69 | M | 400 | 2120 | None | 600 | 1480 | None | No |
| 9 | 70 | M | 400 | 3700 | None | 800 | 3560 | None | No |
| 10 | 60 | F | 200 | 1290 | None | 400 | 2090 | None | No |
| 11 | 68 | M | 200 | 1950 | None | 400 | 3390 | Fatigue grade 3 | No |

(pruritus grade 1). In the remaining patient with adequate drug concentrations, treatment was continued for more than one year at 200 mg BID sorafenib with a median $C_{trough}$ of 8330 ng/mL.

## 4. Discussion

Here we describe the feasibility of sorafenib TDM in a cohort of 36 patients derived from a large, prospective, multicenter study in the Netherlands investigating the feasibility of TDM in 24 orally administered antineoplastic agents. We found that 83 % of patients treated with sorafenib had at least one sample lower than the target $C_{trough}$ for sorafenib of 3750 ng/mL, but that in most patients dose adjustment according to TDM was not feasible primarily due to drug-related toxicity.

TDM has shown to be of interest for new oral anticancer agents that have become available in the last decades. As treatment strategies in oncology are shifting towards a more personalized approach, pharmacokinetically guided dosing seems to be a compelling and promising step. [27] For several oral anticancer agents, such as imatinib, sunitinib, and pazopanib, clear exposure-response relationships were established and TDM was found to be feasible. [28] However, for compounds such as sorafenib, the added value of TDM still needs confirmation. In several phase I studies, significant interpatient variability in sorafenib exposure has been observed (~50 %). [29–31] Several reasons have been suggested, such as slow dissolution in the gastrointestinal tract, genetic polymorphisms, or co-medication. [32].

If dosing according to TDM indeed could become feasible, it is at least mandatory that a dosing adjustment strategy according to $C_{trough}$ is feasible, tolerable, and ultimately leads to better clinical outcomes. Unfortunately, we found that drug-related toxicity was a common reason for not being able to escalate the dose of sorafenib according to the obtained pharmacokinetic data. In addition, in this cohort of patients, we observed no clear linear relationship between sorafenib dose and exposure (visually shown in Fig. 1). This is in accordance with results from earlier studies. [33,34] For instance, in patient 7 sorafenib was increased up to 1200 mg per day, but the subsequently obtained $C_{trough}$ remained virtually unchanged. This can be explained by the limited and saturated gastrointestinal solubility of sorafenib. [35] Two patients that were classified as successful per protocol, received their dose adjustment advice during the step-up phase of their dosing. TDM in these patients therefore just endorsed the decision of the physician to continue the step-up schedule. Taken all these observations together we therefore have to conclude that adjusting the dose of sorafenib according to TDM with the proposed target $C_{trough}$ of 3750 ng/mL is not practically feasible in daily practice. But after having said so, we still believe that TDM of sorafenib can be useful for specific groups of patients. In patients in whom a step-up approach in the initial phases of treatment is pursued and who experience side-effects at the lower than recommended doses, determining the $C_{trough}$ could be considered. With adequate or maybe even supra-therapeutic $C_{trough}$ levels obtained during this phase, additional dose escalations with additional toxicities can likewise be prevented. Also in patients in whom pharmacokinetic interactions between sorafenib and other drugs are expected, determining $C_{trough}$ can also be helpful in considering the optimal dose of sorafenib under these circumstances.

A strength of this current study is its prospective design in an all-day clinical care setting. A limitation of this analysis is that the used target $C_{trough}$ level of 3750 ng/mL has not yet been confirmed prospectively. This target was chosen based on preclinical experiments and the mean exposure of sorafenib in humans. [6,24,36] Earlier, a $C_{trough}$ of 4500 ng/mL for efficacy was proposed in a small prospective study in 12 patients, while preclinical experiments considered a $C_{trough}$ of 3750–4650 ng/mL to be a good estimate. [34,36] Moreover, it was shown that a higher AUC exposure was associated with improved overall survival. [12] However, based on our results, a $C_{trough}$ of 3750 ng/mL does not seem to be feasible in a real-life population. A recent real-life study found that dose reductions to 200 mg BID resulted in increased patient tolerance and adherence, and thus a higher cumulative dose and improved progression-free survival, compared to 400 mg BID sorafenib. [37] Therefore, focusing on patient tolerance instead of the target threshold of 3750 ng/mL should remain directive.

## 5. Conclusion

TDM of sorafenib targeting the proposed target $C_{trough}$ of 3750 ng/mL is not feasible in clinical practice due to the observed small clinical therapeutic window of this well-established oral anticancer agent.

## Institutional review board statement

The study was conducted according to the guidelines of the Declaration of Helsinki. The study included in this analysis was approved by the institutional review board of The Netherlands Cancer Institute (Amsterdam, Netherlands) and approval from the board of directors of each individual hospital was obtained for all participatingcenters.

## Informed consent statement

Informed consent was obtained from all subjects involved in the study.

## CRediT authorship contribution statement

Conceptualization: **S.L.G., I.M.E.D., N.S., N.P.v.E., A.D.R.H., R.H.J.M., S.L.W.K.**; Methodology: **S.L.G., I.M.E.D., N.S., N.P.v.E., A.D.R.H., R.H.J.M., S.L.W.K.**; Software, not applicable: Validation, not applicable; Formal analysis, **N.A.D.G.**; Investigation: **N.A.D.G., R.A.G.**

v.E., S.L.G., L.v.D., I.M.E.D., F.A.L.M.E., N.S., N.P.v.E., A.D.R.H., R. H.J.M., S.L.W.K.; Resources, not applicable; Data curation, **N.A.D.G.**; Writing – original draft, **N.A.D.G., R.H.J.M., S.L.W.K.**; Writing – review & editing: **N.A.D.G., R.A.G.v.E., S.L.G., L.v.D., I.M.E.D., F.A.L. M.E., N.S., N.P.v.E., A.D.R.H., R.H.J.M., S.L.W.K.**; Visualization: **N. A.D.G.**; Supervision: **S.L.W.K.**; Project administration: **N.A.D.G.**; Funding acquisition: **S.L.G., I.M.E.D., N.S., N.P.v.E., A.D.R.H., R.H.J. M., S.L.W.K**. All authors have read and agreed to the published version of the manuscript.

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## Conflict of interest statement

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## Data availability statement

Data from this study can be made available to other researchers in the field upon request and approval by the Dutch Pharmacology Oncology Group and subject to appropriate data transfer agreements. Requests should be directed to S.L.G. and N.S.

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## References

[1] G.M. Keating, A.Sorafenib Santoro, Drugs 69 (2) (2009) 223–240.

[2] B. Escudier, T. Eisen, W.M. Stadler, C. Szczylik, S. Oudard, M. Siebels, et al., Sorafenib in advanced clear-cell renal-cell carcinoma, N. Engl. J. Med. 356 (2) (2007) 125–134.

[3] J.M. Llovet, S. Ricci, V. Mazzaferro, P. Hilgard, E. Gane, J.-F. Blanc, et al., Sorafenib in advanced hepatocellular carcinoma, N. Engl. J. Med. 359 (4) (2008) 378–390.

[4] M.S. Brose, C.M. Nutting, B. Jarzab, R. Elisei, S. Siena, L. Bastholt, et al., Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial, Lancet 384 (9940) (2014) 319–328.

[5] M.M. Gounder, M.R. Mahoney, B.A. Van Tine, S. Ravi, S. Attia, H.A. Deshpande, et al., Sorafenib for advanced and refractory desmoid tumors, N. Engl. J. Med. 379 (25) (2018) 2417–2428.

[6] H. Yu, N. Steeghs, C.M. Nijenhuis, J.H. Schellens, J.H. Beijnen, A.D. Huitema, Practical guidelines for therapeutic drug monitoring of anticancer tyrosine kinase inhibitors: focus on the pharmacokinetic targets, Clin. Pharmcokinet. 53 (4) (2014) 305–325.

[7] A. Mueller-Schoell, S.L. Groenland, O. Scherf-Clavel, M. van Dyk, W. Huisinga, R. Michelet, et al., Therapeutic drug monitoring of oral targeted antineoplastic drugs, Eur. J. Clin. Pharmacol. 77 (4) (2021) 441–464.

[8] S.L. Groenland, R.H.J. Mathijssen, J.H. Beijnen, A.D.R. Huitema, N. Steeghs, Individualized dosing of oral targeted therapies in oncology is crucial in the era of precision medicine, Eur. J. Clin. Pharmacol. 75 (9) (2019) 1309–1318.

[9] D. Strumberg, J.W. Clark, A. Awada, M.J. Moore, H. Richly, A. Hendlisz, et al., Safety, pharmacokinetics, and preliminary antitumor activity of sorafenib: a review of four phase i trials in patients with advanced refractory solid tumors, Oncologist 12 (4) (2007) 426–437.

[10] M. Shimada, H. Okawa, Y. Kondo, T. Maejima, Y. Kataoka, K. Hisamichi, et al., Monitoring serum levels of sorafenib and Its N-oxide is essential for long-term sorafenib treatment of patients with hepatocellular carcinoma, Tohoku J. Exp. Med. 237 (3) (2015) 173–182.

[11] N. Pécuchet, C. Lebbe, O. Mir, B. Billemont, B. Blanchet, N. Franck, et al., Sorafenib in advanced melanoma: a critical role for pharmacokinetics? Br. J. Cancer 107 (3) (2012) 455–461.

[12] S. Noda, D. Hira, R. Osaki, T. Fujimoto, H. Iida, S. Tanaka-Mizuno, et al., Sorafenib exposure and its correlation with response and safety in advanced hepatocellular carcinoma: results from an observational retrospective study, Cancer Chemother. Pharmacol. 86 (1) (2020) 129–139.

[13] P. Boudou-Rouquette, S. Ropert, O. Mir, R. Coriat, B. Billemont, M. Tod, et al., Variability of sorafenib toxicity and exposure over time: a pharmacokinetic/ pharmacodynamic analysis, Oncologist 17 (9) (2012) 1204–1212.

[14] M. Fukudo, T. Ito, T. Mizuno, K. Shinsako, E. Hatano, S. Uemoto, et al., Exposure–toxicity relationship of sorafenib in Japanese patients with renal cell carcinoma and hepatocellular carcinoma, Clin. Pharmcokinet. 53 (2) (2014) 185–196.

[15] C.J. Peer, T.M. Sissung, A. Kim, L. Jain, S. Woo, E.R. Gardner, et al., Sorafenib is an inhibitor of UGT1A1 but is metabolized by UGT1A9: implications of genetic variants on pharmacokinetics and hyperbilirubinemia, Clin. Cancer Res. 18 (7) (2012) 2099–2107.

[16] S. Bins, A. Lenting, S. El Bouazzaoui, L. van Doorn, E. Oomen-de Hoop, F.A. Eskens, et al., Polymorphisms in SLCO1B1 and UGT1A1 are associated with sorafenib-induced toxicity, Pharmacogenomics 17 (14) (2016) 1483–1490.

[17] S. Bins, L. van Doorn, M.A. Phelps, A.A. Gibson, S. Hu, L. Li, et al., Influence of OATP1B1 function on the disposition of sorafenib-β-D-glucuronide, Clin. Transl. Sci. 10 (4) (2017) 271–279.

[18] K. Hussaarts, L. van Doorn, K. Eechoute, J. Damman, Q. Fu, N. van Doorn, et al., Influence of probenecid on the pharmacokinetics and pharmacodynamics of sorafenib, Pharmaceutics 12 (9) (2020).

[19] S.L. Groenland, R.A.G. van Eerden, K. Westerdijk, M. Meertens, S.L.W. Koolen, D. Moes, et al., Therapeutic drug monitoring based precision dosing of oral targeted therapies in oncology: a prospective multicentre study, Ann. Oncol. (2022).

[20] S.L. Groenland, R.A.G. van Eerden, R.B. Verheijen, S.L.W. Koolen, D.J.A.R. Moes, I. M.E. Desar, et al., Therapeutic drug monitoring of oral anticancer drugs: the Dutch Pharmacology Oncology Group–therapeutic drug monitoring protocol for a prospective study, Ther. Drug Monit. 41 (5) (2019).

[21] Services UDoHaH. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03. 2013.

[22] R.A.G. van Eerden, E. Oomen-de Hoop, A. Noordam, R.H.J. Mathijssen, S.L. W. Koolen, Feasibility of extrapolating randomly taken plasma samples to trough levels for therapeutic drug monitoring purposes of small molecule kinase inhibitors, Pharmaceuticals 14 (2) (2021).

[23] M. Herbrink, N. de Vries, H. Rosing, A.D. Huitema, B. Nuijen, J.H. Schellens, et al., Quantification of 11 Therapeutic kinase inhibitors in human plasma for therapeutic drug monitoring using liquid chromatography coupled with tandem mass spectrometry, Ther. Drug Monit. 38 (6) (2016) 649–656.

[24] R.G. Maki, D.R. D'Adamo, M.L. Keohan, M. Saulle, S.M. Schuetze, S.D. Undevia, et al., Phase II study of sorafenib in patients with metastatic or recurrent sarcomas, J. Clin. Oncol. 27 (19) (2009) 3133–3140.

[25] R.B. Verheijen, H. Yu, J.H.M. Schellens, J.H. Beijnen, N. Steeghs, A.D.R. Huitema, Practical recommendations for therapeutic drug monitoring of kinase inhibitors in oncology, Clin. Pharmacol. Ther. 102 (5) (2017) 765–776.

[26] Food and Drug Administration, Center for Drug Evaluation and Research. Sorafenib Clinical Pharmacology and Biopharmaceutics Review 2005. 〈htt ps://www.accessdata.fda.gov/drugsatfda_docs/nda/2005/021923_s000_Nexavar_ BioPharmR.pdf〉.

[27] S.L. Groenland, R.B. Verheijen, M. Joerger, R.H.J. Mathijssen, A. Sparreboom, J. H. Beijnen, et al., Precision dosing of targeted therapies is ready for prime time, Clin. Cancer Res. 27 (24) (2021) 6644–6652.

[28] K. Westerdijk, I.M.E. Desar, N. Steeghs, W.T.A. van der Graaf, N.P. van Erp, et al., on behalf of the Dutch P, Imatinib, sunitinib and pazopanib: From flat-fixed dosing towards a pharmacokinetically guided personalized dose, Br. J. Clin. Pharmacol. 86 (2) (2020) 258–273.

[29] D. Strumberg, H. Richly, R.A. Hilger, N. Schleucher, S. Korfee, M. Tewes, 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. 23 (5) (2005) 965–972.

[30] J.W. Clark, J.P. Eder, D. Ryan, C. Lathia, H.J. Lenz, Safety and pharmacokinetics of the dual action Raf kinase and vascular endothelial growth factor receptor inhibitor, BAY 43-9006, in patients with advanced, refractory solid tumors, Clin. Cancer Res. 11 (15) (2005) 5472–5480.

[31] M. Moore, H.W. Hirte, L. Siu, A. Oza, S.J. Hotte, O. Petrenciuc, et al., Phase I study to determine the safety and pharmacokinetics of the novel Raf kinase and VEGFR inhibitor BAY 43-9006, administered for 28 days on/7 days off in patients with advanced, refractory solid tumors, Ann. Oncol. 16 (10) (2005) 1688–1694.

[32] S. Bouchet, M. Molimard, Pharmacokinetics and therapeutic drug monitoring of anticancer protein/kinase inhibitors, Therapies 77 (2) (2022) 157–170.

[33] C. Fucile, S. Marenco, M. Bazzica, M.L. Zuccoli, F. Lantieri, L. Robbiano, et al., Measurement of sorafenib plasma concentration by high-performance liquid chromatography in patients with advanced hepatocellular carcinoma: is it useful the application in clinical practice? A pilot study, Med. Oncol. 32 (1) (2014) 335.

[34] S. Thomas, A. Prasanna Thankappan, U. Devi Padma, P. Keechilat, Therapeutic drug monitoring of sorafenib in hepatocellular carcinoma patients, Ther. Drug Monit. 42 (2) (2020) 345–347.

[35] L. Jain, S. Woo, E.R. Gardner, W.L. Dahut, E.C. Kohn, S. Kummar, et al., Population pharmacokinetic analysis of sorafenib in patients with solid tumours, Br. J. Clin. Pharmacol. 72 (2) (2011) 294–305.

[36] M. Kuckertz, M. Patz, A. Veldurthy, I. Gehrke, J. Claasen, L.P. Frenzel, et al., Comparison of the effects of two kinase inhibitors, sorafenib and dasatinib, on chronic lymphocytic leukemia cells, Onkologie 35 (7–8) (2012) 420–426.

[37] K.Y. Tak, H.C. Nam, J.Y. Choi, S.K. Yoon, C.W. Kim, H.Y. Kim, et al., Effectiveness of sorafenib dose modifications on treatment outcome of hepatocellular carcinoma: analysis in real-life settings, Int. J. Cancer 147 (7) (2020) 1970–1978.