On-target sorafenib toxicity predicts improved survival in hepatocellular carcinoma: a multi-centre, prospective study

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JH designed the study, performed the analyses and wrote the manuscript. DJP designed the study and wrote the manuscript. RR, DB, TA, CF, CY, AG, MB, GG, LS, JB, MP, MK, RT and JWP all contributed data and reviewed the manuscript. RS designed and lead the study, provided data and wrote the manuscript.

Background:

Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide and has high mortality despite treatment. Whilst sorafenib has a survival benefit for patients with advanced HCC, clinical response is highly variable.

Aim: To determine whether development of sorafenib toxicity is a prognostic marker of survival in HCC.

Methods:

In this prospective multicentre cohort study, patients with advanced-stage HCC receiving sorafenib were recruited from five international specialist centres. Demographic and clinical data including development and grade of sorafenib toxicity during treatment, radiological response to sorafenib and survival time (months) were recorded prospectively.

Results: 634 patients with advanced stage HCC receiving sorafenib were recruited to the study, with a median follow up of 3392 person-years at risk. The majority of patients were male (81%) with child-pugh A stage liver disease (74%) and BCLC stage C HCC (64%). Median survival time was 8.1 months (IQR3.8-18.6months). 94% experienced at least one sorafenib-related toxicity: 34% diarrhoea, 16% hypertension and 37% hand-foot syndrome. 21% ceased sorafenib due to toxicity and 59% ceased treatment due to progressive disease or death. On multivariate analysis, sorafenib-related diarrhoea (HR 0.76, 95% CI 0.61-0.95, p=0.017), hypertension (HR 0.531, 95% CI 0.37-0.76, p<0.0001) and hand-foot syndrome (HR 0.65, 95% CI 0.51-0.81, p<0.0001) were all significant independent predictors of overall survival after adjusting for age, severity of liver disease, tumour stage and sorafenib dose.

Conclusion:

Development of sorafenib-related toxicity including diarrhoea, hypertension and hand-foot syndrome is associated with prolonged overall survival in patients with advanced stage HCC on sorafenib.

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Hepatocellular carcinoma (HCC) is the third most common cause of cancer-related death worldwide, with an escalating global incidence and mortality(1). Despite extensive research efforts, the oral multi- tyrosine kinase inhibitor (TKI) sorafenib remains the only established treatment with proven efficacy for advanced HCC that is recommended in current HCC management guidelines (2-4). Clinical response to sorafenib is highly variable(2) and currently there are no validated biomarkers to predict tumour response to therapy. Due to the modest survival benefit induced by treatment and the potential for sorafenib-related adverse events to worsen patient quality of life, there is an unmet need for better prognostic markers to guide clinicians in initiating and maintaining sorafenib therapy in patients with advanced HCC.

The evolving experience in the clinical use of sorafenib has demonstrated that the development of drug-related toxicity is associated with prolonged survival in advanced HCC (5-15). Sorafenib-induced diarrhoea(9, 13, 16), hypertension(9) and hand-foot skin toxicity(6, 9, 16) have been shown to identify a subset of patients with significantly improved survival outcomes. Such trends have been confirmed by further studies showing that treatment cessation due to toxicity predicts for longer survival compared to when sorafenib is ceased due to disease progression (8). Toxicity from TKIs is the result of a complex interplay between the pharmacokinetic profile of the drug and diverse end-organ susceptibility towards the drug or its

metabolites. In some instances, drug therapy may produce an exaggerated pharmacodynamic modulation of the target of interest when this is expressed in non-tumorous tissues, resulting in so-called "on target" toxicity(17).

It is hypothesized that "on target" toxicity, whilst producing undesired effects in non-cancerous tissues, might correspond to a clinically desirable, more potent inhibition of the target within the tumour, therefore acting as a clinical surrogate of efficacy (18). However, reports on the association between adverse event profiles and survival have been inconsistent and further validation studies to confirm this relationship are needed(6).

This retrospective analysis of a large, multicentre prospective HCC patient cohort was designed to further investigate whether sorafenib-induced toxicities are independently associated with prolonged survival in advanced HCC.

Patients and Methods

Patients with HCC were consecutively recruited to the study from five tertiary centres with specialist multidisciplinary services for HCC management: Osaka, Japan (183 patients, 28.9%); Novara, Italy (156, 24.6%); London, UK (103, 16.3%); Freiburg, Germany (71, 11.2%), and Goyang, South Korea (121, 19.1%). Inclusion criteria included all adult patients (>18 years of age) with confirmed HCC who were to commence sorafenib as per standard of care. Exclusion criteria included patients under the age of 18 years. All patients had a diagnosis of HCC based either on imaging or histologic criteria according to international guidelines (19). Patients were staged using the Barcelona Clinic Liver Cancer (BCLC) staging system, which describes liver functional impairment using the Child Turcotte Pugh score (CTP) (2). Demographic data, imaging and other clinical details including development of sorafenib-mediated adverse events were collected prospectively and were entered directly into a clinical HCC database at the end of the clinic visit by a member of the research team. The primary study endpoint was overall survival (OS) after commencing sorafenib, with the clinical endpoint being either death or end date of study follow up, censored on the 30th March 2015. The study was approved by local

institutional ethics committees and conducted in accordance with the Declaration of Helsinki (update 2004).

Sorafenib treatment and toxicity development

Patients were commenced on sorafenib therapy in accordance with BCLC guidelines(19). At each centre, patients were routinely reviewed in the HCC clinic at baseline, 2 weeks, 4-6 weeks and 6-8 weeks post commencement of sorafenib for safety and tolerability review. Patients with decompensated liver disease and performance scores ≥2 were excluded. Treatment duration, dose modifications and sorafenib tolerability were recorded. Sorafenib was either commenced at full dose or at a lower dose then rapidly titrated up to the recommended dose within 1-2 weeks in order to improve tolerability. Cause for cessation of therapy due to toxicity, patient preference, disease progression or death was also recorded. Tumour response to sorafenib was also recorded, with disease progression defined by mRECIST criteria(20). The onset of sorafenib-related toxicities including hand-foot syndrome, diarrhoea, hypertension, non-hand-foot-syndrome, rash and mucositis was recorded, and toxicities were graded according to the Common Toxicity Criteria Adverse Events (version 3.0), using the most severe grade recorded for the purposes of study analysis. To be included in the analysis, toxicities were defined as new diagnoses developing within 6 weeks of commencing maximum intended dose of sorafenib. Diarrhoea was determined to be sorafenib-related by the treating clinician and members of the research team if temporally associated with commencing sorafenib, in the absence of other causes including infection (excluded by faecal microscopy and culture) or increased lactulose dosing for encephalopathy. Sorafenib-related fatigue was not included in the analysis as fatigue may be multi-factorial and assessment more subjective than other sorafenib-mediated toxicities.

Statistical methods

Variables were described using mean and standard deviation or median and interquartile range (IQR). Univariate analysis of variables associated with survival was performed using Log-rank testing. Factors shown to be associated with survival on univariate analysis ($p<0.10$) were included in the multivariable analysis, along

with factors well-known to be associated with survival in HCC in the published literature- namely CTP score, BCLC score and age. Multivariable analysis was performed using Cox proportional hazards regression modelling with backward elimination and likelihood ratio testing. Proportional hazards assumption was tested using log-log plots and Schoenfeld residuals. All analyses were performed using STATA version 12.1 (Stata Corporation, College Station, Texas, USA).

Results

Six hundred and thirty-four patients with HCC receiving sorafenib therapy were recruited to the study, with a median follow up time of 6692.3 person-months at risk. Of these, sorafenib-related toxicity data were available for 620 patients (97.7%). The majority of patients were male (81.1%) with CTP A stage liver cirrhosis (74.1%) and BCLC C stage HCC (64.5%), with a mean age of 67 +/- 11.3 years. 34% had hepatitis C, 26% had hepatitis B and 46.2% had alcohol-related liver disease. A total of 489 patients (77.1%) died during follow up and the median overall survival time for the cohort was 8.1 months (IQR 3.8-18.6 months). The distribution of clinical factors among the study group is outlined in **Supplementary Table 1**.

Occurrence of sorafenib-related toxicities and their severity within the study group

Almost all patients ceased sorafenib therapy during the study period (96.6%), and the median duration of sorafenib therapy was 3.97 months (IQR 1.6-10.3 months). Indications for treatment withdrawal included unacceptable toxicity in 20.6% (124/ 602) or progressive HCC or death in 59% (355/ 602), with 14% due to other reasons.

Overall, 93.8% (595/ 634) of patients experienced at least one sorafenib-related side effect (grade 1 severity or above) within the first 6 weeks of treatment. In total, 38% of patients developed diarrhoea on sorafenib, 16% developed hypertension, 37% developed hand-foot syndrome, 5% developed non-hand-foot-syndrome skin rash and 2% developed mucositis. Most patients only experienced grade 1 or 2 level sorafenib-related toxicity, with less than 10% of patients experiencing grade 3-4 adverse events. There were no deaths directly attributable to sorafenib treatment. The distribution of

sorafenib-related toxicity within the study group, graded by severity, is outlined in **Table 1**.

Sorafenib-related toxicities are associated with prolonged overall survival

The development of any grade toxicity from sorafenib therapy was associated with prolonged survival in patients with a diagnosis of HCC. The median survival time was 8.8 months (IQR 4.3-17.4) in those who developed sorafenib toxicity (irrespective of severity or type), compared with 5.4 months (IQR 2.7-8.8) in those who did not develop toxicity (p=0.004, **Figure 1**). However, on post-hoc analysis no difference in OS was observed between patients who ceased therapy due to toxicity compared to patients who ceased therapy for other reasons, such as progressive disease (9.2 months compared with 7.5 months, p=0.354; n=620, **Figure 2**).

On univariate Log-rank analysis, sorafenib-induced hand-foot-syndrome (p<0.0001), diarrhoea (p=0.004) and hypertension (p<0.0001) were all significantly associated with prolonged survival. In addition, BCLC stage (p<0.0001), CTP class (p=0.034) and age when sorafenib commenced (p<0.0001) were also significantly associated with survival (**Table 2)**.

We further assessed the presence of a linear association between grade of toxicity and survival on univariate analysis. There was no significant linear trend in hazard ratios evident across categories of side effect severity (**Table 3)**. For this reason, we chose to categorise each adverse event as a binary variable (toxicity present or absent) and these were included in a multivariable Cox proportional hazards model. The model was also adjusted for factors associated with HCC survival in our dataset and also known from the published literature, namely CTP class (p=0.034), BCLC stage (p<0.0001) and age when sorafenib was commenced (p<0.0001)(21). 464 patients had complete data for all independent variables of interest and were included in the final multivariable Cox proportional hazards model for survival. The only significant clinical differences between patients for whom complete data were available and those that did not have complete data available was female preponderance (26.2% compared with 17.5%, p=0.036) and a higher proportion with CTP class B liver

disease (36.5% compared with 23.7%, p=0.006) in the group without complete data available (**Supplementary Table 2**).

Due to significant heterogeneity in HCV treatment access and eradication rates between international centres during the period of follow up, hepatitis C diagnosis was not included in our final model presented in Table 4. However, when hepatitis C was included in the multivariable model, sorafenib-related diarrhoea (p=0.019), hypertension (p<0.0001) and hand-foot syndrome (p=0.001) remained significantly associated with overall survival, with no significant change in hazard ratios (Supplementary Table 5).

On multivariable analysis, only sorafenib-related diarrhoea (HR 0.78, 95% CI 0.62-0.97, p=0.024), hand-foot syndrome (HR 0.67, 95% CI 0.53-0.84, p<0.0001) and hypertension (HR 0.50, 95% CI 0.35-0.71, p<0.0001) remained significantly associated with prolonged survival when adjusted for BCLC stage, CTP class and age (Table 4). The median survival time was 20.3 months (IQR 8.5-46.1 months) in those who developed hypertension on sorafenib, compared with 7.0 months (IQR 3.3-15.7 months) in those who did not (Figure 3A). Moreover, median survival time was 9.7 months (IQR 8.5-46.1 months) in patients who developed sorafenib-mediated diarrhoea of any severity, compared to 6.7 months (IQR 3.4-16.3 months) in those who did not (Figure 3B). and median survival was significantly longer in patients with hand-foot syndrome compared to patients without (12.7 months (95% CI 6.6-20.0) compared with 6.4 months (95% CI 2.9-15.1, p<0.0001; Figure 3C).

There were significant differences in age, gender, aetiology of liver disease, CTP class and HCC stage of disease between the patient populations at the participating study centres (Supplementary Table 3). There was also an association between study centre and survival (p=0.001), reflecting the proportion of patients with advanced-stage HCC at each centre. To ensure that study centre was not a confounder for the apparent relationship between sorafenib-mediated toxicity and survival, we adjusted our proportional hazards model for study centre. The addition of study centre did not alter the significant association between sorafenib-mediated hand-foot-syndrome, hypertension or diarrhoea and survival (Supplementary Table 4), suggesting despite

significant clinical differences between the HCC patient cohorts at each study site, centre per se was not a significant confounding factor for survival in our dataset.

The association between sorafenib-mediated diarrhoea, hand-foot syndrome, hypertension and survival is independent of dose reductions during treatment

Finally, an important consideration was whether the requirement for dose reductions during treatment was a confounding factor for the apparent association between sorafenib-mediated diarrhoea, hand-foot-syndrome and hypertension and survival. There was no significant difference in survival between those with a sorafenib start dose of 400mg or less per day (59%) compared with greater than 400mg per day (41%, χ^2 p=0.341). There was also no significant difference in sorafenib-mediated toxicity and starting dose (χ^2 p=0.243). Data describing dose reductions during therapy were only available for 109 patients (25%). However, in a post-hoc analysis, sorafenib dose reduction was not associated with survival (Log-rank p=0.211) or with development of diarrhoea (χ^2 p=0.122) or hypertension (χ^2 p=0.698). Though limited by incomplete data and small sample size, these data suggest that dose reduction was not a significant confounding factor for the association between diarrhoea, hand-foot-syndrome and hypertension and survival in patients with HCC treated with sorafenib in this study.

Discussion

Targeted therapies have significantly re-shaped cancer care over the last three decades. The possibility of targeting specific oncogenic molecular traits with orally available, non-myelosuppressive small molecule inhibitors has significantly broadened the therapeutic armamentarium available for a wide range of solid tumours including HCC(2). Conventionally, the early phase clinical development of TKIs has followed that of cytotoxic chemotherapy, in that dose escalation occurs until maximum tolerated dose (MTD) is attained. However, there is increasing evidence that for targeted agents, target modulation does not linearly reflect MTD, making the identification of an optimal biologically active dose in relationship with treatment-induced toxicity a contentious point in early-phase trials(22).

This study is the largest study to our knowledge to address the prognostic utility of sorafenib toxicity for survival in advanced stage HCC. In this multi-institutional cohort study, which includes patients of diverse ethnicity and liver disease aetiologies, we demonstrated that the development of sorafenib-related adverse events is associated with a significant survival advantage. Moreover, survival of patients with advanced HCC receiving sorafenib is specifically predicted by development of diarrhoea, hand-foot syndrome and hypertension, but not other sorafenib toxicities. Importantly, when patients were stratified by well-recognised prognostic factors in HCC (23, 24), namely CTP class (A versus B), BCLC class (A, B and C) and age, the significant association between sorafenib-induced diarrhoea and hypertension and survival remained, with minimal change in hazard ratio, strongly suggesting the absence of confounding or effect modification. These data therefore demonstrate that both sorafenib-mediated diarrhoea and hypertension are independently associated with survival, across CTP class and HCC BCLC disease stages.

Various groups have previously reported the association between survival and sorafenib toxicity(5-15), corroborating the evidence from our study that suggests on-target effects of sorafenib may prove useful prognostic biomarkers. Importantly, this association with prolonged survival appears independent of CTP class, age and tumour stage, suggesting broad utility of sorafenib-mediated diarrhoea and hypertension as potential prognostic markers in all patients receiving sorafenib therapy for advanced stage HCC. This finding was also independent of sorafenib dose reduction during treatment, however this post-hoc analysis was only performed in a limited subset of 109 patients.

In this study, the majority of patients experienced at least one grade 1 sorafenib-associated side effect, whilst cessation due to grade 3 or 4 toxicity was 20%. Our data concurs with the original SHARP trial, where over 80% experienced at least one adverse event whilst on sorafenib therapy compared to 52% in the placebo group and temporary cessation rates due to toxicity were in the order of 38% and permanent cessation rates 11% (2). In a further Asian study, the cessation rate due to sorafenib toxicity was 19.5%(4). The mixed Asian and Caucasian sample in the current study likely explains why the sorafenib cessation rate due to adverse effects in this study lies between that reported in these two pivotal randomised controlled trials (25).

We demonstrated that sorafenib-mediated hypertension was significantly associated with prolonged survival, a finding that has been previously shown by others (9). The mechanisms underlying the efficacy of sorafenib, a multi-targeted inhibitor of Raf, Platelet-derived growth factor-receptor (PDGF-R) and Vascular-endothelial growth factor-receptor (VEGF-R), are poorly understood in HCC (25). Evidence suggests that the anti tumour-effects at least in part relate to its anti-angiogenic properties (26).

Arterial hypertension is a well- known class-effect of anti-angiogenics and consolidated evidence from the clinical use of bevacizumab, sunitinib, axitinib and sorafenib suggests that this adverse event might be the surrogate marker of an effective obliteration of tumour neovasculature, therefore substantiating the prognostic value of this adverse event.

Diarrhoea is also a well-described toxicity of sorafenib therapy(27) and several studies including the current study have demonstrated an association between diarrhoea and survival (9, 13, 16). Bettinger et al (13) reported survival was twice as long in patients who developed diarrhoea on sorafenib compared to those who did not (7.1 months versus 14.1 months). Diarrhoea may therefore represent a marker of on-target drug concentration and efficacy. An alternative potential hypothesis regarding the association between the onset of diarrhoea and sorafenib outcome, may relate to the impact sorafenib has on the gut microbiome. The gut microbiome and the role of bacterial translocation in portal hypertension and advanced liver disease are well established, contributing to liver decompensation, encephalopathy and spontaneous bacterial peritonitis (SBP) and directly impacting survival (28-32). Innate immune stimulation via Toll-like receptors TLR2 and TLR4 by translocated bacterial products, such as lipopolysaccharide, is well described in liver disease and contributes to inflammatory-mediated liver damage and decompensation (33). Therapeutic strategies to reduce bacterial translocation include the use of lactulose as both aperient and modulator of nitrogenous bacterial load, as well as antibiotics such as norfloxacin and rifaximin to directly alter the gut microbiome in advanced liver disease(31, 34, 35). Sorafenib-induced diarrhoea may lead to alterations in gut flora or reduction in the load of nitrogenous commensal bacteria, therefore reducing bacterial translocation and ammonia absorption, akin to the therapeutic effects of lactulose or rifaximin (33,

36). In turn, this may improve survival by reducing adverse events such as liver decompensation and SBP. However, there is currently no evidence to substantiate this theory and further studies are needed to elucidate the mechanism of the association between sorafenib-mediated diarrhoea and survival.

Several groups have shown hand-foot-syndrome to be associated with survival in sorafenib treatment of advanced HCC (16). Reig et al demonstrated in a large, well-designed cohort study that skin toxicities requiring dose reduction were associated with prolonged survival in a cohort of 147 HCC patients treated with sorafenib(5). Cho et al demonstrated skin toxicity was associated with prolonged survival in a study of 99 predominantly hepatitis B infected patients with BCLC stage C disease(16). Di Constanzi et al(9) reported that hand-foot-syndrome, hypertension and diarrhoea were all independently associated with prolonged survival in patients receiving sorafenib in a cohort of 226 patients, along with AFP level and radiological response to sorafenib. The authors went on to validate sorafenib toxicities as prognostic markers in a validation cohort of 57 patients. In a further study by Shin et al(15) (n=99), hand-foot-syndrome was found to be associated with survival, but not hypertension. However, several of these studies are limited by their retrospective nature (9, 15-16) and generally studies have been performed in relatively homogenous cohorts of patients with respect to aetiology of liver disease and ethnicity (5, 9, 15), with two of the studies performed in Asian cohorts of patients with viral hepatitis. In this study, we also demonstrated a significant association between developing hand-foot syndrome and survival in advanced stage HCC.

Iavarone et al(8) also demonstrated in a prospective study of 260 patients that cessation of sorafenib due to toxicity compared with ceasing sorafenib for other reasons was associated with prolonged post-sorafenib treatment survival. Though these data support our finding that sorafenib toxicity is associated with survival, unlike Iavarone and colleagues(8), we did not demonstrate a significantly longer survival time in patients who ceased sorafenib due to toxicity compared with those who ceased sorafenib for other reasons such as disease progression in our large prospective cohort. However, this was not a primary endpoint in our study, which focussed on the association between sorafenib toxicity and survival, therefore there may have been reduced power to discern a difference in survival between those who

ceased sorafenib due to toxicities compared with other reasons in our study. The difference in findings may also be explained by differences in the underlying patient cohort. In the Iavarone study, patients generally had more advanced HCC disease (41% macrovascular invasion compared with 33% in the current study), and more advanced liver disease (42% CTP class B compared with 25% in the current study). Additionally, Iavarone et al classified all patients who ceased sorafenib due to progressive disease and toxicities as ceasing due to progressive disease only, whereas in our study these categories were not mutually exclusive, therefore some patients who ceased treatment due to side effects may also have had progressive disease in our study.

There are limitations to our study. Data for sorafenib toxicities was incomplete for some participants due to differences in side effect recording practices between the three centres, particularly for hypertension. Whilst the study cohort was followed prospectively and all data recorded prospectively, data on sorafenib-mediated toxicities were not systematically collected at all centres throughout the study period as this was not a primary objective of the original cohort study design. We did not impute data and did not seek to retrieve missing data retrospectively to reduce observer bias and this limited the number of patients who provided data for the multivariable analysis, potentially reducing study power to detect associations between sorafenib toxicities and survival. Selection bias may also have been introduced due to systematic differences in patients for whom sorafenib toxicity data were recorded and those who did not have these data recorded. However, we demonstrated that the only significant clinical differences between patients with complete toxicity data and those without was female preponderance and CTP B disease (Supplementary Table 2). As gender was not associated with survival in our dataset and CTP class was accounted for in the analysis, it is unlikely that these differences resulted in significant bias of the results. Moreover, HCC management was similar in all centres of the study in accordance with international guidelines and recruitment site was not significantly associated with either side effect reporting or with survival (Supplementary Tables 3 and 4). Finally, adjusting our survival model for treatment centre did not appreciably change the strength of association between sorafenib-related toxicities and survival (Supplementary Table 4), suggesting centre-related factors were not significant confounding factors in this study.

A further potential confounder for the relationship between sorafenib-mediated toxicity and survival is duration of sorafenib treatment, as longer duration would reasonably be associated with a higher probability of developing toxicity and also surviving longer to remain on sorafenib. In our study, we sought to minimise this effect by only including toxicities that developed within 6 weeks of commencing sorafenib therapy, particularly as adjusting the model for duration of sorafenib is problematic due to strong collinearity between duration of sorafenib and survival. Another limitation was that dose reduction data was only available for 25% of the study cohort and no data were available for temporary dose alterations during treatment. However, post-hoc analysis of these limited data coupled with the lack of association between sorafenib dose, sorafenib-related toxicities and survival do not support a confounding or effect modifying role of sorafenib dose on the relationship between sorafenib toxicity and survival. Finally, we did not demonstrate a relationship between grade of toxicity and overall survival. This may reflect the relatively small numbers of patients per strata available for analysis when overall survival was stratified by toxicity grade. However, our data are also consistent with published data from the use of TKIs in other malignancies, suggesting that in this drug class it is the presence of toxicity rather than the grade that is prognostic (34).

In this large, retrospective analysis of prospectively collected sample data, the data demonstrate a clear relationship between the development of diarrhoea, hand-foot syndrome and hypertension and survival in a large cohort of patients receiving sorafenib for advanced HCC, spanning various aetiologies, ethnicities and disease severities. Moreover, hypertension, change in stool frequency and/ or consistency and hand-foot syndrome can be reliably determined in the clinic. These data suggest development of these toxicities may have broad applicability as potentially useful prognostic markers across a wide spectrum of HCC patients treated with sorafenib.

Conclusion

The development of sorafenib-related toxicity is associated with prolonged survival in patients with advanced HCC receiving sorafenib therapy. Specifically, development of diarrhoea, hand-foot-syndrome and hypertension are independently associated with

prolonged survival, independent of age, underlying liver disease severity or stage of HCC. Development of diarrhoea, hand-foot-syndrome and/ or hypertension whilst on sorafenib may therefore prove to be a potentially useful prognostic biomarker in HCC and further validation studies are urgently warranted.

Authorship Statement

Guarantor of article: A/ Prof Rohini Sharma

JH lead the study, performed all analyses and wrote the manuscript. DJP also lead the study and wrote the manuscript. RR, DB, TA, CF, CY, AG, MB, GG, LS, JB, MP, MK, RT and JWP all provided data and clinical input into the study and manuscript. RS conceived the study design, supervised the study, provided data and clinical input and provided mentorship for the study.

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

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Figure Legends

Figure 1. Comparison of Kaplan-Meier survival time (months) between HCC patients who developed sorafenib toxicity of any severity grade, compared with HCC patients who did not develop sorafenib toxicity (8.8 months (IQR 4.3-17.4) vs. 5.4 months (IQR 2.7-8.8), Log-rank p=0.004, n= 634).

Figure 2. Comparison of Kaplan-Meier survival time (months) between HCC patients who ceased sorafenib due to sorafenib-related toxicity and HCC patients who ceased sorafenib for other reasons (9.2 months (IQR 2.87-19.37 months) compared with 7.5 months (IQR 4.07-17.50 months); Log-rank p=0.354, n=620).

Figure 3A. Comparison of Kaplan-Meier survival time (months) between HCC patients who developed sorafenib-related hypertension compared with HCC patients who did not develop sorafenib-related hypertension (hypertension median survival time 20.3 months (IQR 8.5-46.1), no hypertension 7.0 months (IQR 3.3-15.7), Log-rank p<0.0001, n=489).

3B. Comparison of Kaplan-Meier survival time (months) between HCC patients who developed sorafenib-related diarrhoea compared with HCC patients who did not develop sorafenib-related diarrhoea (diarrhoea median survival time 9.7 months (IQR 5.4-20.0), no diarrhoea 6.7 months (IQR 3.4-16.3), Log-rank p=0.004; n=572).

3C. Comparison of Kaplan-Meier survival time (months) between HCC patients who developed sorafenib-related hand-foot syndrome compared with HCC patients who did not develop sorafenib-related hand-foot-syndrome (hand-foot-syndrome median survival time 12.7 months (IQR 6.6-23.2); no hand-foot-syndrome 6.4 months (IQR 2.9-15.1), Log-rank p<0.0001; n=571).

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Table 1. Distribution of sorafenib-related toxicities among the study cohort (n=634)

Clinical variable (Grade of severity)	N (%)
Sorafenib-related diarrhoea (n=572)	216 (37.8%)
1	140 (71.4%)
2	44 (22.4%)
3	17 (8.7%)
4	15 (7.7%)
Sorafenib-related hypertension (n=489)	80 (16.4%)
1	44 (55.0%)
2	24 (30.0%)
3	12 (15.0%)
Sorafenib-related hand-foot syndrome (n=571)	209 (36.6%)
1	105 (50.2%)
2	57 (27.3%)
3	46 (22.0%)
4	1 (0.4%)
Sorafenib-related non-hand-foot-syndrome rash (n=571)	30 (5.2%)
1	14 (46.7%)
2	5 (16.7%)
3	6 (20.0%)
4	5 (16.7%)
Sorafenib-related mucositis (n=571)	12 (2.1%)
1	11 (91.7%)
2	1 (8.3%)

Table 2. Clinical variables associated with survival in patients with advanced HCC on sorafenib on univariate Log-rank analysis

Clinical Variable	Median Survival Time (IQR; months)	P-value
Sorafenib-related diarrhoea (n=572)		0.004
Yes	9.7 (IQR 5.37-20.0)	
No	6.7 (IQR 3.40-16.30)	
Sorafenib-related hypertension (n=489)		<0.0001
Yes	20.3 (IQR 8.47-46.10)	
No	7.0 (IQR 3.30-15.68)	
Sorafenib-related hand-foot syndrome (n=571)		<0.0001
Yes	12.7 (IQR 6.60-23.20)	
No	6.4 (IQR 2.90-15.10)	
Sorafenib-related rash* (n=571)		0.892
Yes	9.8 (IQR 6.20-20.00)	
No	8.1 (IQR 3.80-18.63)	
Sorafenib-related mucositis (n=571)		0.861
Yes	9.6 (IQR 6.30-29.57)	
No	11.6 (IQR 4.47-25.07)	
BCLC Stage (n=634)		<0.0001
A	17.4 (IQR 7.40-40.70)	
B	9.7 (IQR 4.50-20.00)	
C	6.8 (IQR 3.10-15.00)	
CTP class (n=622)		0.034
A	8.9 (IQR 4.10-19.50)	
B	6.8 (IQR 2.83-16.70)	
Age when commenced sorafenib (years)		<0.0001
<50 years	5.4 (IQR 2.60-9.00)	
50-59 years	7.5 (IQR 3.40-13.40)	
60-69 years	8.3 (IQR 3.70-20.50)	
70-79 years	9.3 (IQR 4.43-20.20)	
≥80 years	15.5 (IQR 5.33-26.93)	

Hepatitis B (n=486)		0.100
Yes	6.4 (IQR 2.87-15.60)	
No	8.9 (IQR 4.20-19.37)	
Hepatitis C (n=615)		0.010
Yes	9.3 (IQR 4.70-21.20)	
No	7.5 (3.43-16.67)	
Alcohol (n=447)		0.051
Yes	6.9 (3.00-12.20)	
No	7.5 (4.11-16.70)	

*Rash excluding hand-foot syndrome; BCLC, Barcelona Clinic Liver Cancer stage; CTP, Child-Turcotte Pugh class.

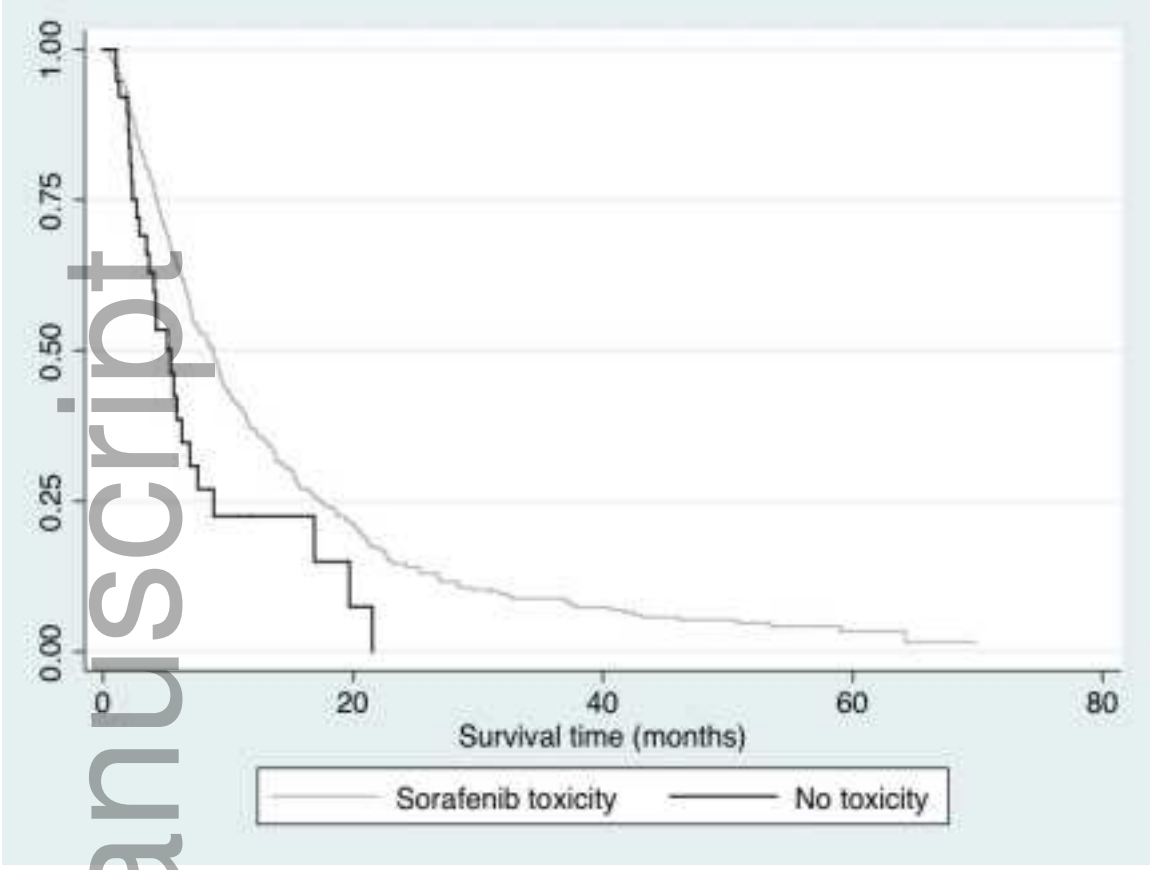
Table 3. Log-rank univariate association between sorafenib-related toxicity severity and survival in patients with HCC treated with sorafenib

Clinical variable	HR	95% CI	P-value
Sorafenib-related diarrhoea grade (n=572)			
1	0.496	0.390-0.630	<0.0001
2	0.813	0.581-1.139	0.229
3	0.351	0.180-0.686	0.002
4	0.594	0.338-1.045	0.071
Sorafenib-related hypertension grade (n=489)			
1	0.299	0.195-0.458	<0.0001
2	0.396	0.238-0.660	<0.0001
3	0.119	0.030-0.481	0.003
Sorafenib-related hand-foot syndrome grade (n=571)			
1	0.461	0.353-0.601	<0.0001
2	0.487	0.349-0.678	<0.0001
3	0.335	0.229-0.491	<0.0001
4	1.528	0.214-10.929	0.673

Table 4. Clinical variables associated with survival in patients with advanced HCC on sorafenib: Cox proportional hazards multivariable analysis (n=464).

Clinical Variable	HR	95% CI	p-value
Sorafenib-related hypertension	0.500	0.353-0.708	<0.0001
Sorafenib-related diarrhoea	0.776	0.623-0.967	0.024
Sorafenib-related hand-foot-syndrome	0.667	0.531-0.837	<0.0001
BCLC stage	1.266	1.098-1.461	0.001
Age when started sorafenib	0.986	0.977-0.996	0.006

BCLC, Barcelona Clinic Liver Cancer stage;



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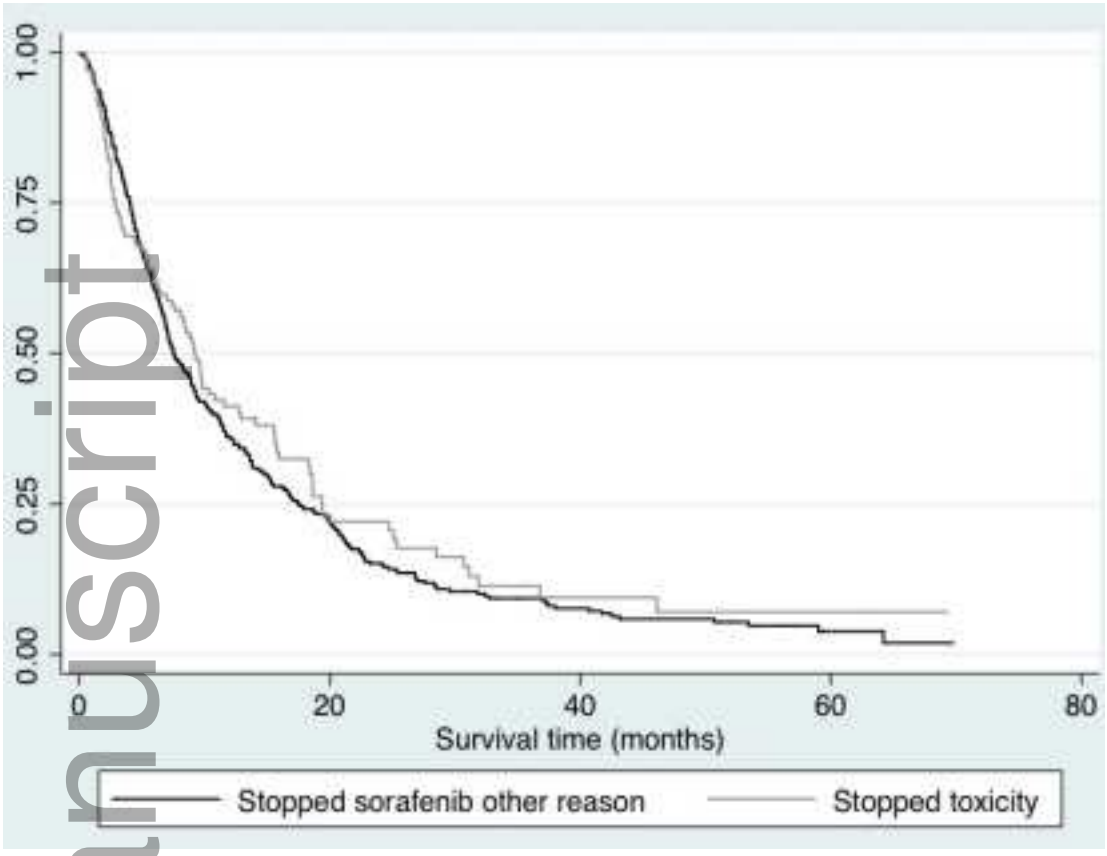

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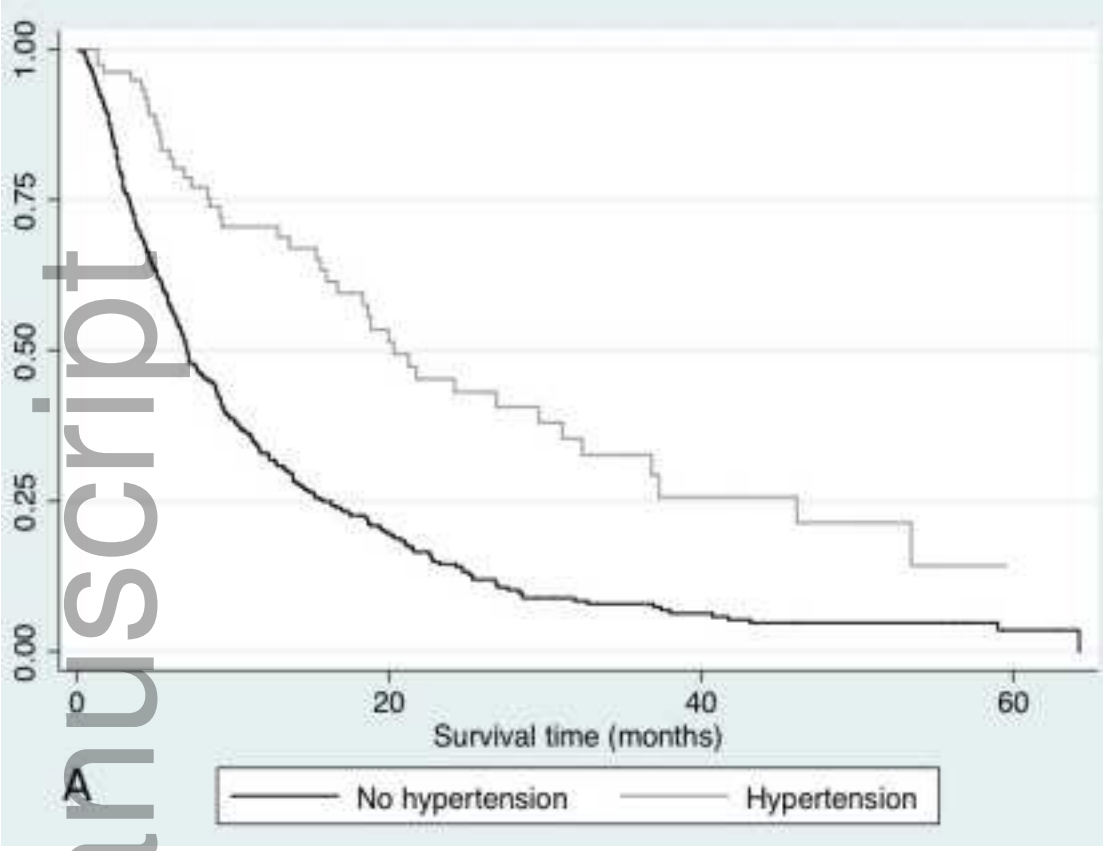

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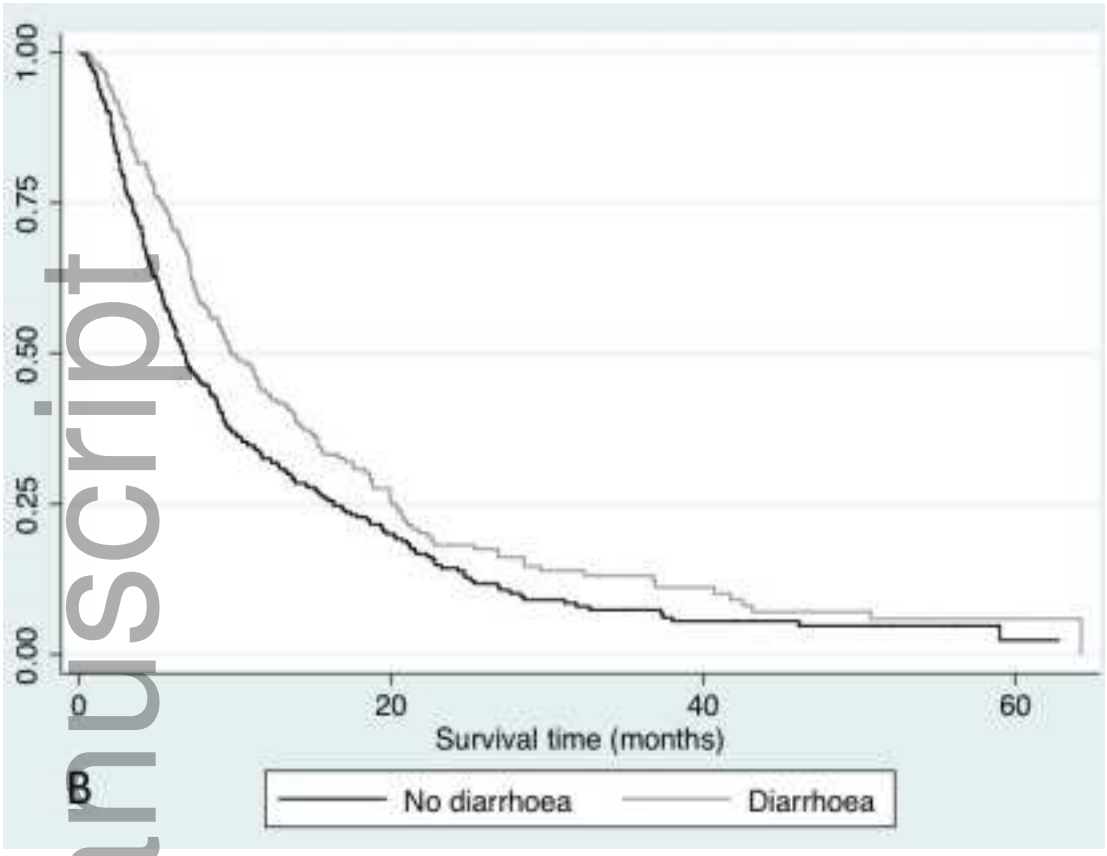

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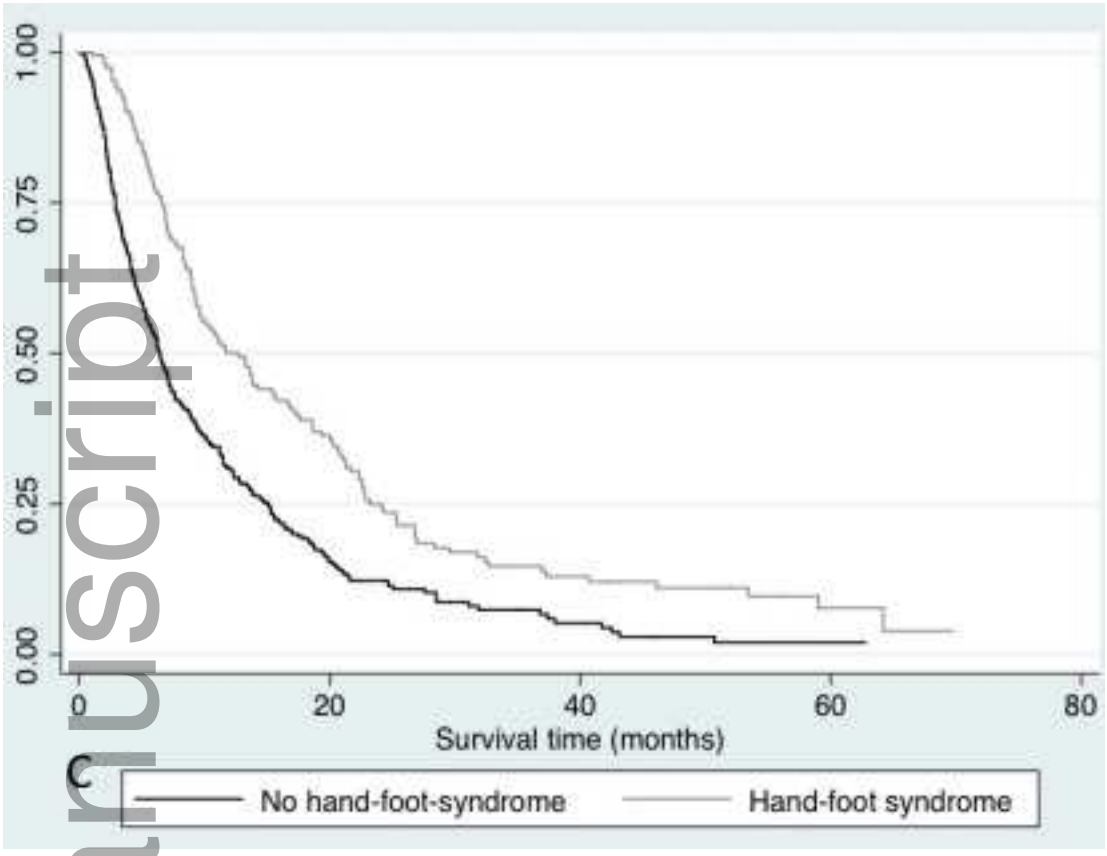

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