ORIGINAL ARTICLE

Specific adverse events predict survival rates in a Chinese population diagnosed with hepatocellular carcinoma and treated with sorafenib

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Abstract

Hepatocellular carcinoma (HCC) is associated with a poor prognosis and a low chemotherapeutic efficiency except for when sorafenib is administered. The aim of this study was to evaluate the efficacy and adverse events (AEs) of sorafenib therapy in a Chinese population diagnosed with HCC.

Method: Data for the subjects with HCC receiving sorafenib at Taichung Veterans General Hospital from June 2012 to October 2016 were evaluated. All enrolled cases belonged to the HCC Barcelona Clinic Liver Cancer (BCLC) classification stage C. The AEs were defined as appearances of hand–foot syndrome reaction (HFSR), hypertension (HTN), or diarrhea. The exclusion criteria included a poor performance status, lack of compliance to drugs, and loss of follow-up within the following day.

Results: Of a total of 116 subjects enrolled, there were 43 (37.1%), 13 (11.2%), and 15 (12.9%) cases experiencing HFSR, HTN, and diarrhea, respectively. The cases with AE had both a longer time to progression (TTP) (HFSR 5.16 vs. 3.33 months, $P = 0.003$; HTN 6.62 vs. 3.68 months, $P = 0.001$; diarrhea 6.67 vs. 3.61 months, $P = 0.001$) and overall survival (OS) (HFSR 8.12 vs. 4.75 months, $P = 0.001$; HTN 9.08 vs. 5.61 months, $P = 0.008$; diarrhea 8.20 vs. 5.67 months, $P = 0.042$) than those without. More AEs were correlated with a longer TTP and OS.

Conclusion: The appearance of sorafenib AEs, including HFSR, HTN, and diarrhea, can predict a positive therapy efficacy to HCC.

Background

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer. The Barcelona Clinic Liver Cancer staging system (BCLC) is widely used to assist in the selection of HCC treatment, which is determined by particular tumor characteristics, such as size, number, presence of vascular invasion or extrahepatic metastasis, and the patients' hepatic function and performance status.[1] Recommended treatment for advanced HCC, such as BCLC stage C, involves sorafenib, an orally administered inhibitor of multiple protein kinases, such as c-Raf, B-Raf, mitogen-activated protein kinase, extracellular signal-regulated kinase, and vascular endothelial growth factor.[2] The Phase III SHARP trial and Asia-Pacific Trial both demonstrated that median overall survival (OS) and time to progression (TTP) of patients with advanced HCC is improved with sorafenib, when compared with a placebo.[3,4]

Although sorafenib is now the recommended first line of treatment for patients with BCLC stage C HCC, the ratio of no response to sorafenib, with a disease-control rate, is as high as 43%.[3] The significant predictive factors for sorafenib efficacy are not available. Analysis of serological markers in patients who participated in the SHARP trial showed that serum concentrations of vascular endothelial growth factor (VEGF) and angiopoietin-2 proved to be a predictor of patient survival but not of response to treatment.[5] On the contrary, the adverse events (AEs) of sorafenib treatment, such as diarrhea, hand–foot syndrome reaction (HFSR), and hypertension (HTN), may predict the efficacy of sorafenib in individuals with HCC according to previous studies.[6–8]

The aim of the present study was to determine the factors that influence the efficacy of sorafenib according to the common AEs such as HFSR, HTN, and diarrhea.

Methods

Data for subjects with HCC, as diagnosed according to the American Association for the Study of Liver Disease (AASLD) guidelines,[9] who were receiving sorafenib at Taichung Veterans General Hospital from June 2012 to October 2016 were evaluated. All enrolled cases belonged to the HCC BCLC

classification stage C. The general data of enrolled patients, including the age, gender, presence of chronic Hepatitis B (HBV) or Hepatitis C (HCV) infection, HCC with portal vein thromosis (PVT) or extra-hepatic metastasis, serum level of bilirubin, alanine aminotransferase (ALT), and alpha-fetoprotein (AFP) of each individual, were recorded. The initial dosage of sorafenib for each enrolled subject was also recorded. The exclusion criteria included those cases diagnosed with cirrhosis Child-Pugh stage B or C or HCC BCLC stage A or B, displayed a poor performance status, lacked compliance with drugs, or were lost to follow-up within the following day.

After the administration of sorafenib, the subjects were followed up in the outpatient clinic every 2–4 weeks by an experienced hepatologist. Tumor response on images, defined accroding to the modified RECIST criteria,[10] was assessed every 4–8 weeks by an experienced radiologist. Radiological TTP was defined as the time from the start of sorafenib administration to the radiological confirmation of tumor progression. OS was defined as the time from start of sorafenib until death or until last follow-up. The AEs were defined as appearances of all grades of HFSR, HTN, or diarrhea, which were assessed by the Common Terminology Criteria for Adverse Events (CTCAE). The associations between any AE and the efficacy of sorafenib were then analyzed.

Data are analyzed with SPSS 12.0 and expressed as the standard deviation of mean for each of the measured parameters. Gender and the positive ratio of each stratified group are both expressed as a percentage of the total patient number. Statistical comparisons were made using Pearson's chi-square test in order to compare the effects of gender and the positive ratio of each stratified group. An independent *t* test was used to analyze age, serum bilirubin, ALT, AFP, and daily sorafenib dosage. Cox regression analysis was used to adjust initial and maximal sorafenib dosage. A *P*-value below 0.05 was considered statistically significant. Survival analysis was carried out using the Kaplan–Meier method for univariate analysis and subsequently compared with the log-rank test.

Results

A total of 116 subjects were enrolled, and their general data are listed in Table 1. The average age of these cases was 64.03 years, and a male predominance (87.1%) was found. The ratios of PVT and extrahepatic metastasis were 56.0 and 49.1%, respectively. The presence of HBV and HCV infection were 49.1 and 43.1%, respectively. The average initial and maximal dosage of sorafenib was 3.39×200 mg per day and 3.59×200 mg per day, respectively. The AEs of sorafenib, including HFSR, HTN, and diarrhea, occurred in 43 (37.1%), 13 (11.2%), and 15 (12.9%) cases, respectively. The TTP of the enrolled cases was 4.01 ± 3.15 months, and the OS was 6.00 ± 4.50 months.

The characteristics of the individuals with HFSR, HTN, or diarrhea, and those without these AEs, are displayed in Tables 2–4, respectively. There were similar ages, gender distribution, presence of PVT, extrahepatic metastasis, HBV or HCV infection, and laboratory data between the subjects with AE and those without. The individuals with HFSR had significantly higher initial and maximal daily sorafenib dosages than those without HFRS (mean 3.63 vs. 3.26×200 mg, $P = 0.037$, 3.91 vs. $3.40 \times$

Table 1 The general data of all enrolled patients

	All (N = 116)		
	$M \pm SD$	N	%
Age (years)	64.03 ± 12.06		
Gender (male)		101	(87.1%)
BCLC stage C		116	(100%)
PVT		65	(56.0%)
Extrahepatic metastasis		57	(49.1%)
HBV		57	(49.1%)
HCV		50	(43.1%)
Bilirubin (U/L)	0.90 ± 0.47		
ALT (U/L)	69.12 ± 66.87		
AFP (×10⁴ ng/mL)	24.09 ± 1.32		
Sorafenib dosage (×200 mg/day)			
Initial	3.39 ± 0.92		
Maximal	3.59 ± 0.81		
Sorafenib AEs			
HFRS		43	(37.1%)
HTN		13	(11.2%)
Diarrhea		15	(12.9%)
TTP (months)	4.01 ± 3.15		
OS (months)	6.00 ± 4.50		

AE, adverse event; AFP, alpha-fetoprotein; ALT, alanine aminotransferase; BCLC, Barcelona Clinic Liver Cancer staging system; HBV, hepatitis B; HCV, hepatitis C; HFSR, hand–foot syndrome reaction; HTN, hypertension; M, mean; N, Number of patients; OS: overall survival; PVT, portal vein thrombosis; SD, standard derivation; TTP: time to ptogression.

200 mg, $P = 0.001$), but these differences did not occur between the cases with HTN or diarrhea and those without AEs.

The outcomes involving TTP and OS regarding our enrolled cases, with or without adjustment with initial and maximal sorafenib dosage, are shown in Table 5 and Figures 1 and 2. It can be noted that the subjects with AEs displayed a significantly longer TTP (HFSR, mean 5.16 vs. 3.33 months, $P = 0.003$, adjusted $P = 0.023$; HTN, mean 6.62 vs. 3.68 months, $P = 0.001$, adjusted $P = 0.001$; diarrhea, mean 6.67 vs. 3.61 months, $P = 0.001$, adjusted $P = 0.001$). Similarly, the cases with AEs had a significantly longer OS than those without (HFSR, mean 8.12 vs. 4.75 months, $P = 0.001$, adjusted $P = 0.001$; HTN 9.08 vs. 5.61 months, $P = 0.008$, adjusted $P = 0.006$; diarrhea, mean 8.20 vs. 5.67 months, $P = 0.042$, adjusted $P = 0.048$). Of all 116 enrolled subjects, there were 57 (49.1%), 47 (40.5%), and 12 cases (10.4%) having nil, one, and two AEs, respectively. The mean TTP of these three subgroups were 2.75, 4.42, and 8.33 months, while the mean OS were 4.07, 7.19, and 10.50 months. Both of these differences were significant (TTP, $P = 0.005$, adjusted $P = 0.014$; OS, $P = 0.029$, adjusted $P = 0.035$).

Discussion

Sorafenib is an orally ingested, active multikinase inhibitor that has a proven record of providing prolonged OS and TTP in advanced HCC.[3,4] The most common sorafenib-related AEs are diarrhea, fatigue, anorexia, HTN, and dermatological toxicities, primarily HFSR. In the SHARP trial, treatment-related AEs were

Table 2 The detailed data about the cases with or without hand-foot syndrome reaction

	HFSR (N = 43)			Non-HFSR (N = 73)			P-value
	M ± SD	N	%	M ± SD	N	%	
Age (years)	62.86 ± 10.41			64.73 ± 12.92			0.423[†]
Gender (male)		37	(86.0%)		64	(87.7%)	0.801[‡]
PVT		22	(51.2%)		43	(58.9%)	0.417[‡]
Extrahepatic metastasis		25	(58.1%)		32	(43.8%)	0.137[‡]
HBV		25	(58.1%)		32	(43.8%)	0.137[‡]
HCV		19	(44.2%)		31	(42.5%)	0.857[‡]
Bilirubin (U/L)	0.87 ± 0.44			0.91 ± 0.48			0.759[†]
ALT (U/L)	91.29 ± 88.50			56.19 ± 46.19			0.020[†]
AFP (×10⁴ ng/mL)	1.77 ± 4.54			1.05 ± 3.69			0.372[†]
Sorafenib dosage (×200 mg/day)							
Initial	3.63 ± 0.79			3.26 ± 0.97			0.037[†]
Maximal	3.91 ± 0.43			3.40 ± 0.92			0.001[†]

[†]P-values were analyzed with independent *t* test.
[‡]P-values were analyzed with Pearson's chi-square test.
AFP, alpha-fetoprotein; ALT, alanine aminotransferase; HBV, hepatitis B; HCV, hepatitis C; HFSR, hand–foot syndrome reaction; M, mean; N, number of patients; PVT, portal vein thrombosis; SD, standard derivation.

Table 3 The detailed data about the cases with or without hypertension

	HTN (N = 13)			Non-HTN (N = 103)			P-value
	M ± SD	N	%	M ± SD	N	%	
Age (years)	66.00 ± 11.45			63.79 ± 12.16			0.535[†]
Gender (male)		11	(84.6%)		87	(84.5%)	0.989[‡]
PVT		8	(61.5%)		57	(55.3%)	0.671[‡]
Extrahepatic metastasis		7	(53.8%)		50	(48.5%)	0.719[‡]
HBV		5	(38.5%)		52	(50.2%)	0.414[‡]
HCV		8	(61.5%)		42	(40.8%)	0.154[‡]
Bilirubin (U/L)	0.77 ± 0.42			0.92 ± 0.47			0.266[†]
ALT (U/L)	62.23 ± 38.13			70.01 ± 69.79			0.695[†]
AFP (×10⁴ ng/mL)	2.52 ± 6.70			1.15 ± 3.53			0.251[†]
Sorafenib dosage (×200 mg/day)							
Initial	3.23 ± 1.01			3.42 ± 0.91			0.494[†]
Maximal	3.54 ± 0.88			3.59 ± 0.81			0.823[†]

[†]P-values were analyzed with independent *t* test.
[‡]P-values were analyzed with Pearson's Chi-square test.
AFP, alpha-fetoprotein; ALT, alanine aminotransferase; HBV, hepatitis B; HCV, hepatitis C; HTN, hypertension; M, mean; N, Number of patients; PVT, portal vein thrombosis; SD, standard derivation.

more common in the sorafenib group and included diarrhea (8%), HFSR (8%), and HTN (2%).[3] In the Asia Pacific trial, the most frequent drug-related AEs in the sorafenib group were HFSR (10.7%), diarrhea (6.0%), and fatigue (3.4%).[4] The ratio of HFSR, HTN, and diarrhea with sorafenib for our enrolled individuals with HCC was 37.1, 11.2, and 12.9% respectively, which is higher than the ratio in these two clinical trials. The reason for this may be due to the self-reported design and the fact that all grade AEs were enrolled in our study.

HFSR is characterized by erythema, dysesthesia, or paresthesia on the palms and soles and causes a rash. This may indicate that the inhibition of one or more receptors/pathways plays a role in HFSR development, including VEGFR, PDGFR, c-KIT, or FLT-3.[11] In a previous study performed in Japan, patients developing HFSR (62%) experienced a significantly longer survival rate than

patients without cutaneous AEs (OR 0.449, 95% CI 0.256–0.786, P = 0.005).[12] In a Korean retrospective study of 99 patients with advanced (BCLC stage C) HCC, the presence of HFSR was found to be predictive of a prolonged TTP (OR 0.40, 95% CI 0.19–0.82, P = 0.007) and a better OS (OR 0.40; 95% CI 0.24–0.67; P = 0.001).[7] However, there have been additional studies reporting that HFSR does not offer any prognostic significance.[8,13]

With regard to our cases, the individuals with HFSR experienced better sorafenib efficacy on TTP (mean 5.16 vs. 3.33 months, P = 0.003, adjusted P = 0.023) and OS (mean 8.12 vs. 4.75 months, P = 0.001, adjusted P = 0.001) when compared to those without HFSR.

Arterial HTN is typically considered a class-specific toxicity requiring antiangiogenic treatments. As an impaired angiogenesis leading to a decrease in the density of microvessels, this

Table 4 The detailed data about the cases with or without diarrhea

	Diarrhea (N = 15)			Non-diarrhea (N = 101)			
	$M \pm SD$	N	%	$M \pm SD$	N	%	P-value
Age (years)	65.73 ± 10.51			63.78 ± 12.30			0.561[†]
Gender (male)		11	(73.3%)		90	(89.1%)	0.089[‡]
PVT		9	(60.0%)		56	(55.4%)	0.740[‡]
Extrahepatic metastasis		7	(46.7%)		50	(49.5%)	0.837[‡]
HBV		7	(46.7%)		50	(49.5%)	0.837[‡]
HCV		7	(47.7%)		43	(42.6%)	0.765[‡]
Bilirubin (U/L)	0.87 ± 0.41			0.91 ± 0.48			0.790[†]
ALT (U/L)	72.67 ± 76.83			68.59 ± 65.65			0.827[†]
AFP ($\times 10^4$ ng/mL)	0.17 ± 0.23			1.50 ± 4.30			0.235[†]
Sorafenib dosage ($\times$200 mg/day)							
Initial	3.07 ± 1.03			3.45 ± 0.90			0.138[†]
Maximal	3.60 ± 0.83			3.58 ± 0.82			0.944[†]

[†]P-values were analyzed with independent *t* test.
[‡]P-values were analyzed with Pearson's Chi-square test.
AFP, alpha-fetoprotein; ALT, alanine aminotransferase; HBV, hepatitis B; HCV, hepatitis C; M, mean; N, number of patients; PVT, portal vein thrombosis; SD, standard derivation.

Table 5 The outcomes of the cases with or without sorafenib-associated adverse events

	TTP (months)			OS (months)		
	$M \pm SD$	P-value	P-value*	$M \pm SD$	P-value	P-value*
HFRS (N = 43)	5.16 ± 3.34	0.003	0.023	8.12 ± 4.98	0.001	0.001
Non-HFRS (N = 73)	3.33 ± 2.84			4.75 ± 3.70		
HTN (N = 13)	6.62 ± 5.59	0.001	0.001	9.08 ± 6.20	0.008	0.006
Non-HTN (N = 103)	3.68 ± 2.55			5.61 ± 4.12		
Diarrhea (N = 15)	6.67 ± 5.69	0.001	0.001	8.20 ± 6.86	0.042	0.048
Non-diarrhea (N = 101)	3.61 ± 2.37			5.67 ± 3.99		
Non AE (N = 57)	2.75 ± 1.39	0.005	0.014	4.07 ± 2.52	0.029	0.035
One AE (N = 47)	4.42 ± 2.66			7.19 ± 4.45		
Two AEs (N = 12)	8.33 ± 5.90			10.50 ± 7.03		

All P-values were analyzed with the independent *t* test.
P-value*: analyzed with multivariate cox regression of each AE, initial, and maximal sorafenib dosage.
AE, adverse event; HFSR, hand–foot syndrome reaction; HTN, hypertension; M, mean; N, Number of patients; OS, overall survival; SD, standard derivation; TTP, time to progression.

endothelial dysfunction is associated with a decrease in nitric oxide production, and the activation of the endothelin 1 system is the proposed mechanism.[6] One study that had enrolled 41 patients with advanced HCC who had received sorafenib found that there was significantly longer OS in patients who had experienced any grade of HTN during treatment than it did in patients who did not develop HTN (median OS 18.2 vs. 4.5 months, $P = 0.016$).[14] Another study enrolling 38 patients with advanced HCC disclosed that the appearance of HTN within 2 weeks of beginning sorafenib treatment correlated with a better TTP (153 vs. 50.5 days, $P = 0.017$) and OS (1329 vs. 302 days, $P = 0.003$).[15] However, one other previous study concluded that treatment-related HTN did not show any correlation with clinical outcomes.[12]

Our results found both TTP (mean 6.62 vs. 3.68 months, $P = 0.001$, adjusted $P = 0.001$) and OS (mean 9.08 vs. 5.61 months, $P = 0.008$, adjusted $P = 0.006$) being significantly longer in the cases with HTN than in those without.

As VEGF plays a role in maintaining parts of the normal adult vasculature, VEGFR inhibition through the use of sorafenib may cause diarrhea by significantly reducing the capillary network in the intestinal villi. Other hypotheses have supported that sorafenib may cause diarrhea by inducing pancreatic exocrine dysfunction as VEGFR inhibitors can reduce the density of the capillaries in pancreatic islets and decrease zymogen granules.[6] One retrospective study enrolling 112 patients with advanced HCC found that diarrhea was an independent positive prognostic factor (OR 0.41, $P = 0.001$) in multivariate Cox regression models and that the cases involving diarrhea experienced a significantly longer median OS than those not having diarrhea (14.1 vs. 7.1 months, $P = 0.011$).[8] Another piece of prospective data regarded 46 patients with advanced HCC, which noted that subjects developing grade 2/3 diarrhea at any time during sorafenib treatment (41%, $n = 19$) had an increased OS when compared with those without diarrhea ($P = 0.009$).[13]
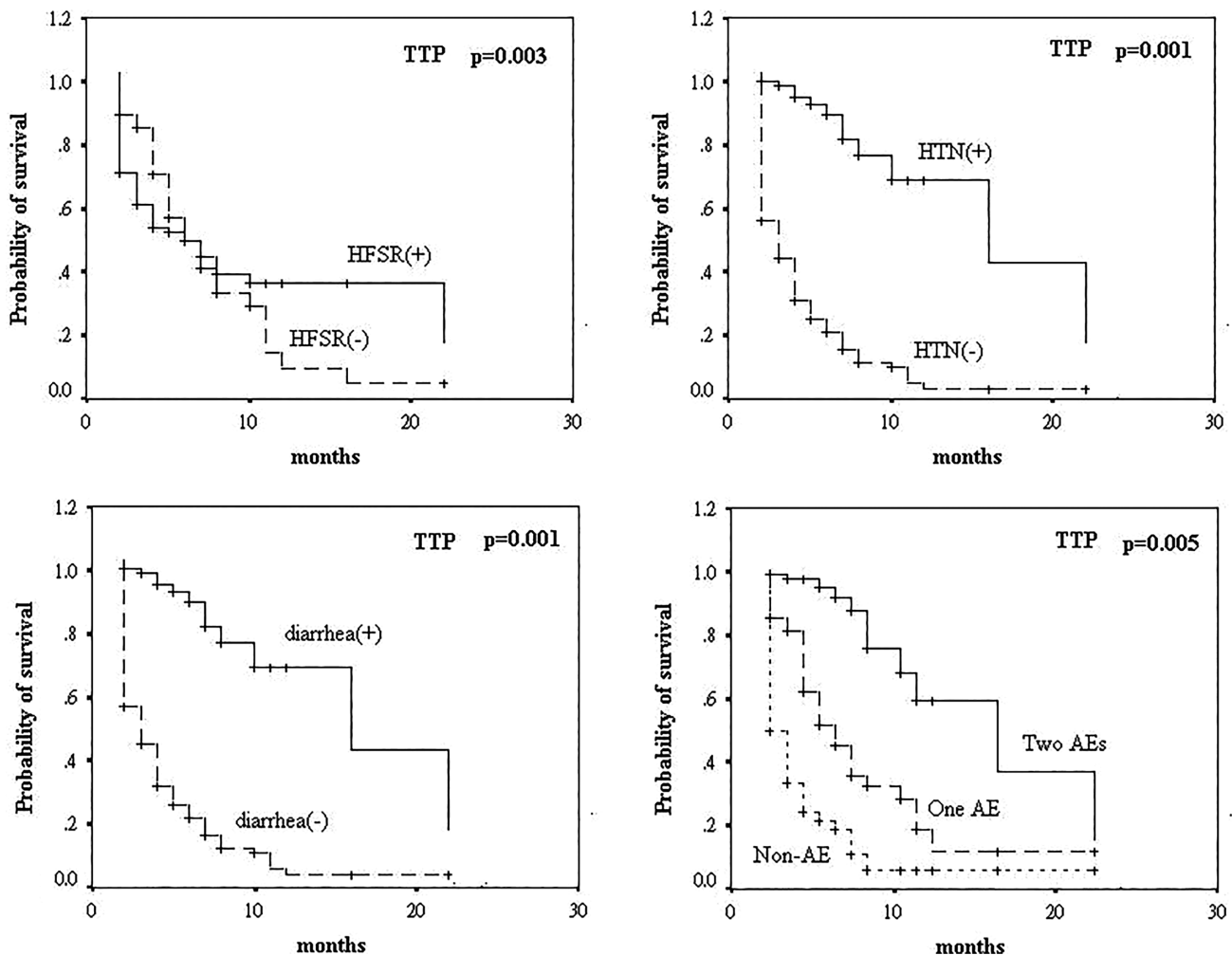
Figure 1 The associations of time to progression (TTP) and sorafenib-related AEs. (AE, adverse event; HFSR, hand–foot syndrome reaction; HTN, hypertension; TTP, time to progression).

Our results found that the presentation of diarrhea in patients was corrected with better outcomes, including TTP (mean 6.67 vs. 3.61 months, $P = 0.001$, adjusted $P = 0.001$) and OS (mean 8.20 vs. 5.67 months, $P = 0.042$, adjusted $P = 0.048$).

In an observational study involving 280 cases, the occurrence of diarrhea, skin toxicity, and arterial HTN within 1 month of treatment was evaluated. These subjects were classified into three groups: without AEs (Group 0), with one event (Group 1), or with two to three events (Group 2). The 3-month progression of disease at imaging was observed in 41.9, 25.9, and 12.7% of those in Groups 0, 1, and 2, respectively ($P = 0.014$). A progressive increase in median TTP and OS was confirmed from Group 0 to Group 2 ($P = 0.001$).[16]

Our results displayed a similar trend, in that the more often AEs occurred, the longer TTP or OS the patients would have (no AE vs. one AE vs. two AEs, TTP mean 2.75 vs. 4.42 vs. 8.33 months, $P = 0.005$, adjusted $P = 0.014$; OS mean 4.07 vs. 7.19 vs. 10.50 months, $P = 0.029$, adjusted $P = 0.035$).

The availability of reliable predictive markers would assist in identifying individuals who are likely to benefit from antitumoural treatment while avoiding exposure to unnecessary toxicity in potentially resistant subjects. In this setting, understanding whether the development of AEs could act as a surrogate marker of sorafenib efficacy in cases with HCC would be clinically relevant. With regard to our cases, the appearance of AEs, including HFRS, HTN, and diarrhea, act as predictive markers to sorafenib therapy response.

There were several limitations in our study, First, this study was retrospective and presented within a single tertiary care center. Selection bias may therefore have existed. Second, all grades of self-reported AEs were enrolled, so some errors may have occurred. Third, although we have reported the patients' outcomes adjusted by the initial and maximum sorafenib dosage, an estimated cumulative dose was not presented. The impact of the exposure of sorfenib to the TTP or OS of the individual case could not be evaluated. Finally, the status of a patient's medical hisory with regard to viral hepatitis, such as NUCs (nucleotide/nucleoside analogs), interferon, or DAAs (direct-acting antivirals), was not measured in each case. In addition, only subjects diagnosed with cirrhosis Child-
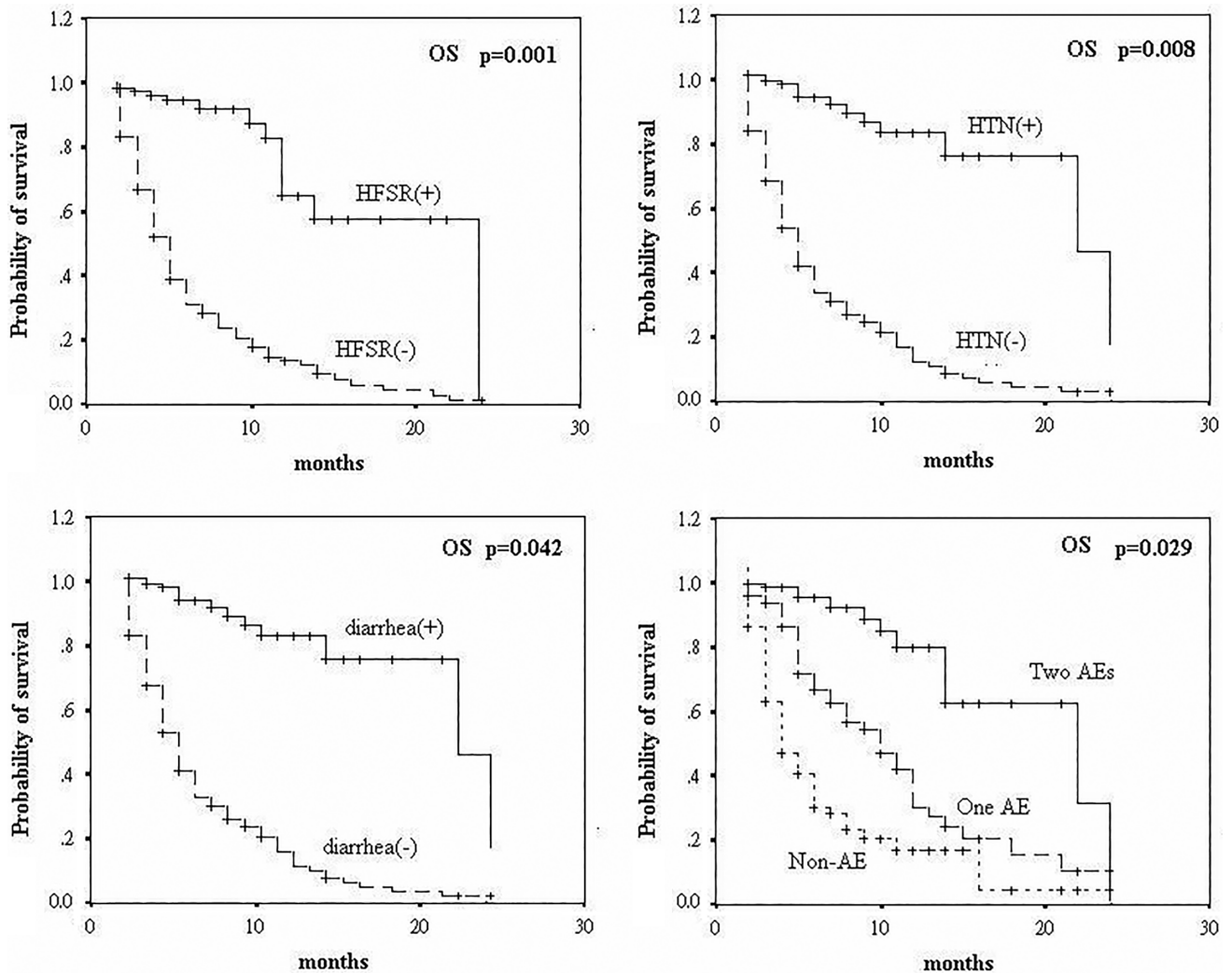
Figure 2 The association of overall survival (OS) and sorafenib-related AEs. (AE, adverse event; HFSR, hand–foot syndrome reaction; HTN, hypertension; OS, overall survival).

Pugh stage A and HCC BCLC stage C were enrolled in our study. Further prospective research involving analysis of more variables is still necessary.

In conclusion, our study discovered that sorafenib-related HFSR, HTN, and diarrhea is assoicated with better efficacy outcomes for patients, including longer TTP and OS.

References

1 Llovet JM, Brú C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. *Semin. Liver Dis.* 1999; **19**: 329–38.

2 Strumberg D. Preclinical and clinical development of the oral multikinase inhibitor sorafenib in cancer treatment. *Drugs Today (Barc.).* 2005; **41**: 773–84.

3 Llovet JM, Ricci S, Mazzaferro V *et al*. Sorafenib in advanced hepatocellular carcinoma. *N. Engl. J. Med.* 2008; **359**: 378–90.

4 Cheng A, Kang Y, Chen Z *et al*. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo controlled trial. *Lancet Oncol.* 2009; **10**: 25–34.

5 Llovet JM, Pena CE, Lathia CD, Shan M, Meinhardt G, Bruix J. Plasma biomarkers as predictors of outcome in patients with advanced hepatocellular carcinoma. *Clin. Cancer Res.* 2012; **18**: 2290–300.

6 Granito A, Marinelli S, Negrini G, Menetti S, Benevento F, Bolondi L. Prognostic significance of adverse events in patients with hepatocellular carcinoma treated with sorafenib. *Ther. Adv. Gastroenterol.* 2016; **9**: 240–9.

7 Cho J, Paik Y, Lim H *et al*. Clinical parameters predictive of outcomes in sorafenib-treated patients with advanced hepatocellular carcinoma. *Liver Int.* 2013; **33**: 950–7.

8 Bettinger D, Schultheiß M, Knuppel E, Thimme R, Blum H, Spangenberg H. Diarrhoea predicts a positive response to sorafenib in patients with advanced hepatocellular carcinoma. *Hepatology.* 2012; **56**: 789–90.

9 Heimbach JK, Kulik LM, Finn RS *et al*. AASLD guidelines for the treatment of hepatocellular carcinoma. *Hepatology.* 2018; **67**: 358–80.

10 Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. *Semin. Liver Dis.* 2010; **30**: 52–60.

11 Robert C, Soria J, Spatz A *et al*. Cutaneous side-effects of kinase inhibitors and blocking antibodies. *Lancet Oncol.* 2005; **6**: 491–500.

12 Otsuka T, Eguchi Y, Kawazoe S, Yanagita K, Ario K, Kitahara K. Skin toxicities and survival in advanced hepatocellular carcinoma patients treated with sorafenib. *Hepatol. Res.* 2012; **42**: 879–86.

13 Koschny R, Gotthardt D, Koehler C, Jaeger D. Diarrhoea is a positive outcome predictor for sorafenib treatment of advanced hepatocellular carcinoma. *Oncology.* 2013; **84**: 6–13.

14 Estfan B, Byrne M, Kim R. Sorafenib in advanced hepatocellular carcinoma: hypertension as a potential surrogate marker for efficacy. *Am. J. Clin. Oncol.* 2013; **36**: 319–24.

15 Akutsu N, Sasaki S, Takagi H *et al*. Development of hypertension within 2 weeks of initiation of sorafenib for advanced hepatocellular carcinoma is a predictor of efficacy. *Int. J. Clin. Oncol.* 2015; **20**: 105–10.

16 Di Costanzo GG, de Stefano G, Tortora R *et al*. Sorafenib off-target effects predict outcomes in patients treated for hepatocellular carcinoma. *Future Oncol.* 2015; **11**: 943–51.