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Sorafenib treatment on Chinese patients with advanced hepatocellular carcinoma

A study on prognostic factors of the viral and tumor status

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Abstract

Sorafenib is of proven efficacy in treating patients of hepatocellular carcinoma (HCC). Our study was aimed to determine the factors influence the sorafenib efficacy.

We evaluated data of HCC patients receiving sorafenib from June 2012 to October 2016. All HCC cases were of the Barcelona Clinic Liver Cancer (BCLC) classification stage C. The exclusion criteria: those of BCLC classification stage A or B, with the absence or co-infection of hepatitis B (HBV) and hepatitis C (HCV). The presence of HBV, HCV, macoscopic vascular invasion (MVI) or extrahepatic spread (EHS) was recorded for each patient. Time-to-progression (TTP) and overall survival (OS) were analyzed.

Among a total of 90 HCC patients, 48 (53.3%) had HBV infection, 42 (46.7%) had HCV infection, 51 (56.7%) had MVI, and 39 (43.3%) had EHS. Patients with HCV infection showed better TTP and OS than those with HBV infection. Patients with EHS had a longer TTP and OS than those with MVI. For patients with HBV infection, those with EHS had a longer TTP (mean 4.60 vs 2.64 months, $P = .002$) and OS (mean 6.65 vs 4.53 months, $P = .045$) compared to those with MVI. Among those with MVI, patients with HBV infection had a poorer TTP (mean 2.64 vs 4.74 months, $P = .019$) and shorter OS (mean 4.53 vs 7.00 months, $P = .059$) compared to those with HCV infection.

HCC patients with HCV infection or with the presence of EHS showed better sorafenib efficacy.

Abbreviations: EHS = extrahepatic spread, HCC = hepatocellular carcinoma, MVI = macoscopic vascular invasion, OS = overall survival, TTP = time-to-progression.

Keywords: hepatitis B, hepatitis C, hepatocellular carcinoma, sorafenib

1. Introduction

Hepatocellular carcinoma (HCC) is the most prevalent type of primary liver cancer, being the third leading cause of cancer deaths worldwide.[1] HCC has well-established causal links with chronic viral hepatitis types B (HBV) and C (HCV) as well as other causes of chronic liver diseases.[2] The Barcelona Clinic Liver Cancer staging system (BCLC) is a widely used guide for choosing its treatment. BCLC considers collectively a number of disease features like the tumor characteristics, such as tumor size and number, the presence or absence of macroscopic vascular invasion (MVI) or extrahepatic spread (EHS), and the hepatic functionality and performance status of the patient.[3] Advanced HCC, such as BCLC stage C, is typically treated with the drug sorafenib. This drug is an orally administered inhibitor of multiple protein kinases (such as C-Raf, B-Raf, mitogen-activated protein kinase kinase, extracellular signal-regulated kinase, and vascular endothelial growth factor).[4]

Previous studies suggested that sorafenib might be more efficacious in subjects positive for HCV or with EHS. [5–8] However, most studies are on patients in the Western countries. The real-world data of sorafenib in HBV high-incident areas like Eastern countries remains few.

The aim of the present study was to determine what factors affect the sorafenib efficacy in terms of the presence of HBV or HCV infection and other occurrence of MVI or EHS.

2. Methods

We evaluated data from HCC patients as diagnosed according to the American Association for the Study of Liver Disease guidelines. Patients were admitted to the Taichung Veterans General Hospital from June 2012 to October 2016, and they all received sorafenib treatment. All HCC cases were of the BCLC classification stage C. Their general data analyzed include the following: age, gender, presence of chronic HBV or HCV infection, HCC with MVI or EHS, serum level of bilirubin, alanine aminotransferase (ALT) and alpha-fetoprotein (AFP). The initial dosage of sorafenib given was

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Table 1

	HBV (N = 48, 53.3%)			HCV (N = 42, 46.7%)			*P*-value
	M ± SD	N	%	M ± SD	N	%	
Age, yr	60.80 ± 12.29			66.62 ± 9.39			.013*
Gender (male)		44	(91.7%)		33	(78.6%)	.078†
Bilirubin, U/L	1.07 ± 0.09			1.08 ± 0.23			.920*
ALT, U/L	84.60 ± 80.29			64.71 ± 57.57			.186*
AFP, $\times 10^4$ ng/mL	1.94 ± 5.11			1.01 ± 3.61			.343*
HCC status							.733†
MVI		28	(58.3%)		23	(54.8%)	
EHS		20	(41.7%)		19	(45.2%)	
Sorafenib dosage, ×200 mg/d							
Initial	3.50 ± 0.88			±3.29	0.97		.274*
Maximal	3.63 ± 0.79			±3.57	0.83		.755*

AFP = alpha-fetoprotein, ALT = alanine aminotransferase, EHS = extrahepatic spread, HBV = hepatitis B, HCC = hepatocellular carcinoma, HCV = hepatitis C, M = mean, MVI = macoscopic vascular invasion, N = number of patients, SD = standard derivation.

* *P*-values were analyzed with independent *t* test.

† Pearson Chi-square test.

also recorded. The exclusion criteria included those cases diagnosed with cirrhosis Child-Pugh stage B or C, HCC BCLC stage A or B, or absence or co-infection of HBV and HCV. This study was approved by the Institutional Review Board of Taichung Veterans General Hospital.

After the administration of sorafenib, subjects went through follow-ups conducted by an experienced hepatologist in the outpatient clinic at intervals of 2 to 4 weeks. Tumor responses based on imaging were determined by an experienced radiologist every 4 to 8 weeks. Radiological time-to-progression (TTP) was defined as the time duration from the start of sorafenib use to the radiological confirmation of tumor progression. Overall survival (OS) was defined as the time duration from the start of sorafenib use to death of patient or the last follow-up. The associations between viral and tumor status and the efficacy of sorafenib, were then statistically analyzed.

Data for each measured parameters were expressed as mean and standard deviation. Gender, along with the positive ratios of each stratified group were expressed as the percentage of total patient number. Statistical comparisons were made using the Pearson Chi-square test for gender and the positive ratios of each stratified group. Independent *t* tests were used to assess the effects of age, serum bilirubin, ALT, AFP, and daily sorafenib dosages. Statistical significance was set at $P < .05$. Survivals were compared using the Cox proportional hazards regression model for multivariate analysis and subsequently with the log-rank test.

3. Results

Among 108 patients underwent sorafenib, the numbers who not adhere to sorafenib and ceased to go to the hospital were 10 and 8 cases, respectively. From a total of 90 subjects we had analyzed, 48 (53.3%) of them were infected with HBV, and 42 (46.7%) with HCV infection. Table 1 shows the general data of the patients. Those with HCV infection were significantly older in age than those with HBV infection (mean 66.62 vs 60.80 years, $P = .013$). No difference in gender distribution was found between the 2 infection groups (male ratio 91.7 vs 78.6%, $P = .78$). Also, laboratory data and recorded sorafenib dosage were similar across the 2 groups. For the HBV group, the tumor status of MVI was found in 28 (58.3%) of them, and EHS in 20 (41.7%) of them. For the HCV group, MVI was found in 23 (54.8%) patients and EHS in 19 (45.2%) patients.

The characteristics of patients with either MVI (51 cases, 56.7%) or EHS (39 cases, 43.3%) are shown in Table 2. The 2

Table 2

	MVI (N = 51, 56.7%)		EHS (N = 39, 43.3%)		*P*-value
	M ± SD	N (%)	M ± SD	N (%)	
Age, yr	62.22 ± 12.76		65.23 ± 9.07		.214*
Gender (male)		43 (84.3%)		34 (87.2%)	.702†
Bilirubin, U/L	1.07 ± 0.07		1.08 ± 0.24		.764*
ALT, U/L	72.25 ± 62.59		79.33 ± 81.23		.642*
AFP, $\times 10^4$ ng/mL	1.60 ± 4.84		1.38 ± 4.00		.823*
Viral status					.733†
HBV		28 (58.3%)		20 (41.7%)	
HCV		23 (54.8%)		19 (45.2%)	
Sorafenib dosage, ×200 mg/d					
Initial	3.33 ± 0.95		3.49 ± 0.88		.436*
Maximal	3.53 ± 0.86		3.69 ± 0.73		.344*

AFP = alpha-fetoprotein, ALT = alanine aminotransferase, EHS = extrahepatic spread, HBV = hepatitis B, HCC = hepatocellular carcinoma, HCV = hepatitis C, M = mean, MVI = macoscopic vascular invasion, N = number of patients, SD = standard derivation.

* *P*-values were analyzed with independent *t* test.

† Pearson Chi-square test.

Table 3.

	N	TTP, mo M ± SD	*P*-value	OS, mo M ± SD	*P*-value
HBV	48	3.46 ± 2.19	.031	5.42 ± 3.63	.067
HCV	42	4.98 ± 4.19		7.21 ± 5.47	
PVT	51	3.59 ± 3.21	.061	5.65 ± 4.66	.156
EHS	39	4.92 ± 3.42		7.05 ± 4.57	

EHS = extrahepatic spread, HBV = hepatitis B, HCV = hepatitis C, M = mean, MVI = macoscopic vascular invasion, N = number of patients, OS = overall survival, SD = standard derivation, TTP = time-to progression.

P-values were analyzed with independent *t* test.

groups of subjects had similar age, gender ratio, HBV and HCV infections, laboratory data, and sorafenib dosage.

Table 3 and Figure 1 shows the comparisons of treatment outcomes in the 2 infection groups, based on TTP and OS, or on MVI or EHS. General speaking, subjects with HCV infection had a better TTP and OS than those with HBV infection. Also, those with EHS had a longer TTP and OS than those with MVI. HCV subjects also displayed a significantly longer TTP (mean 4.98 vs 3.46 months, $P = .031$) compared to HBV subjects.

Table 4 and Figure 2 shows the results of TTP and OS pooled from subjects with HBV and HCV infections, and with MVI or EHS. For patients with HBV, those with EHS had a significantly longer TTP (mean 4.60 vs 2.64 months, $P = .002$) and OS (mean 6.65 vs 4.53 months, $P = .045$) than those with MVI.

Table 4 and Figure 3 shows the results of TTP and OS compared between the subjects with MVI or EHS, against subjects with HBV or HCV infection. Among subjects with MVI, those with HBV infection had a significant poorer TTP (mean 2.64 vs 4.74 months, $P = .019$) but similar OS (mean 4.53 vs 7.00 months, $P = .059$) compared to those with HCV infection. On the contrary, no difference was found regarding TTP and OS between EHS patients with HBV and those with HCV.

4. Discussion

The incidence of HCC is rising steadily and the survival rate for HCC patients is poor. Patients with HCC most often are presented at their intermediate and advanced stages, and those therapies, involving surgery or radiofrequency ablation, are no longer effective. The recommended treatment for these patients are locoregional therapies, such as transarterial chemoembolization, and systemic therapy.[9–11]

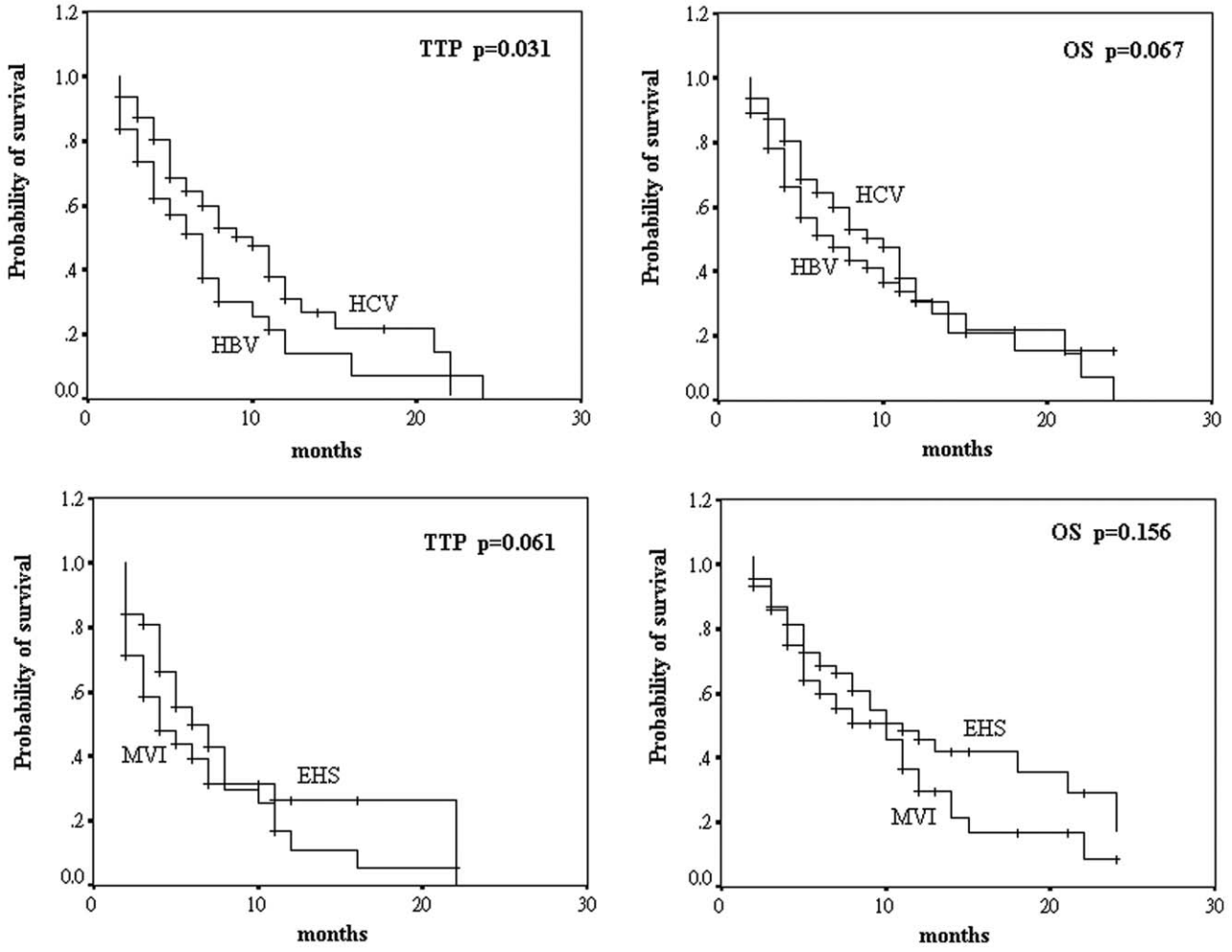

Figure 1. The association between sorfaenib efficacy and the viral and tumor status of patients. EHS = extrahepatic spread, HBV = hepatitis B, HCV = hepatitis C, MVI = macoscopic vascular invasion, OS = overall survival, TTP = time-to-progression.

Table 4.

	N	TTP, mo M ± SD	*P*-value	OS, mo M ± SD	*P*-value
HBV + MVI	28	2.64 ± 0.91	.002	4.53 ± 3.18	.045
HBV + EHS	20	4.60 ± 2.89		6.65 ± 3.94	
HCV + MVI	23	4.74 ± 4.45	.692	7.00 ± 5.78	.784
HCV + EHS	19	5.26 ± 3.96		7.47 ± 5.22	
MVI + HBV	28	2.64 ± 0.91	.019	4.53 ± 3.18	.059
MVI + HCV	23	4.74 ± 4.45		7.00 ± 5.78	
EHS + HBV	20	4.60 ± 2.89	.552	6.65 ± 3.94	.580
EHS + HCV	19	5.26 ± 3.96		7.47 ± 5.22	

EHS = extrahepatic spread, HBV = hepatitis B, HCV = hepatitis C, M = mean, MVI = macoscopic vascular invasion, N = number of patients, OS = overall survival, SD = standard derivation, TTP = time-to progression.
P-values were analyzed with independent *t* test.

Sorafenib is currently the first-line systemic medication approved for the treatment of unresectable HCC. The approval is based on the results of a multicenter, randomized, phase III SHARP study that has demonstrated the benefit of sorafenib on OS over placebo (sorafenib vs placebo, 10.7 vs 7.9 months; hazard ratio [HR], 0.69; 95% confidence interval [CI], 0.55–0.87; $P = .001$).[12] Similar benefits of sorafenib were also reported in a phase III Asia Pacific study conducted in patients from the Asia Pacific region (sorafenib vs placebo, 6.5 vs 4.2 months; HR, 0.68; 95% CI, 0.50–0.93; $P = .014$).[13]

One limitation of the sorafenib treatment is that a substantial number of patients fail to respond to the medication, at a disease-control rate as high as 43%.[12] In an exploratory subgroup analysis of the SHARP trial, patients positive for HCV show a well improved median OS of 14 months compared with 7.4 months in the placebo, and this benefit is also seen in terms of time to tumor progression (7.6 vs 2.8 months) and disease control rate (44.2% vs 29.6%).[5]

Comparing HBV and HCV infection, HR relative to OS was 0.76 in the HBV group (95% CI, 0.38–1.50), compared to 0.50 (95% CI, 0.32–0.77) in the HCV group. This tendency appears also regarding time to progression (HR1.03 for HBV patients, and 0.43 for HCV patients.[5] Results are consistent with another study on HBV positive-HCC patients based on subgroup analysis of the phase III AP study, where the HR for OS was 0.74 (95% CI 0.51–1.06) compared to an HR of 0.57 (0.29–1.33) for patients with other etiology.[8]

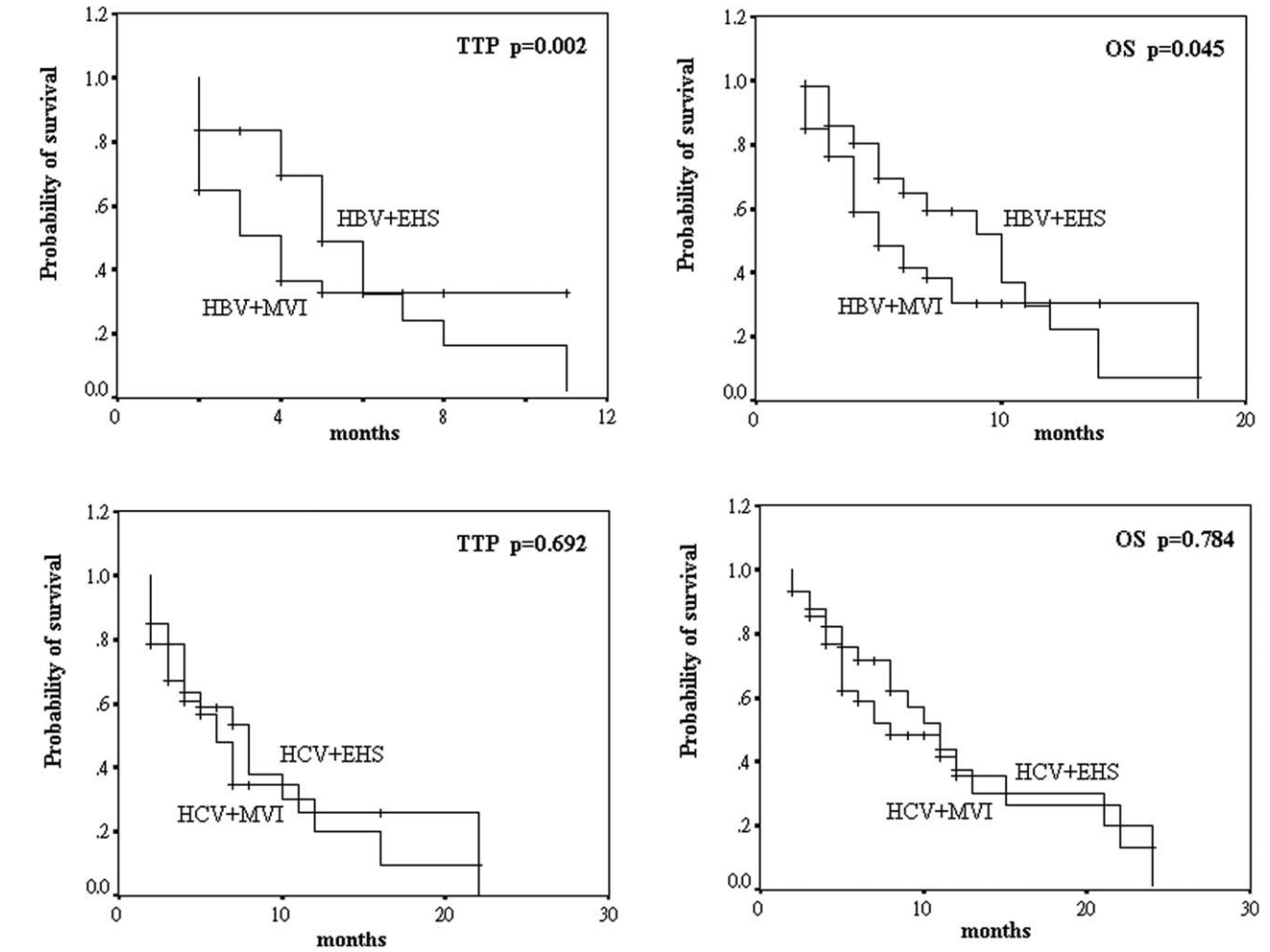

Figure 2. The association between sorfaenib efficacy and tumor status in the HBV- or HCV-positive patients. EHS = extrahepatic spread, HBV = hepatitis B, HCV = hepatitis C, MVI = macoscopic vascular invasion, OS = overall survival, TTP = time-to-progression.

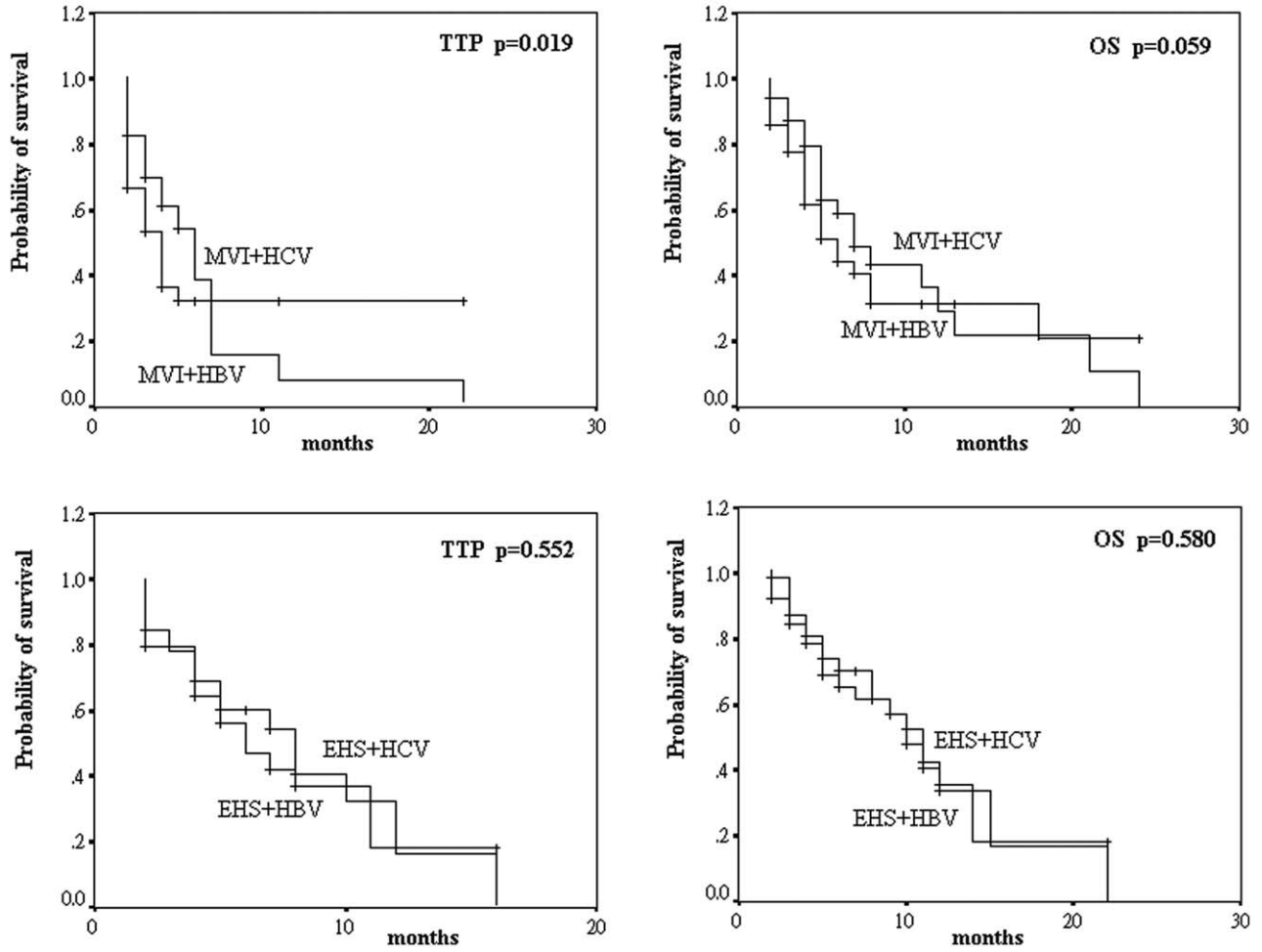

Figure 3. The association between sorfaenib efficacy and viral status in the MVI- or EHS-presented patients. EHS = extrahepatic spread, HBV = hepatitis B, HCV = hepatitis C, MVI = macoscopic vascular invasion, OS = overall survival, TTP = time-to-progression.

A pooled exploratory analysis of 827 patients from the SHARP and the AP phase III studies, reported that the presence of MVI and high levels of AFP are strong prognostic factors for poorer OS. Significantly greater OS sorafenib benefit over the placebo was observed in patients with HCV infection (HR, 0.47 vs 0.81).[7] An aggregate meta-analysis enrolling 4 clinical trials suggested that sorafenib is more efficacious for patients with HCV infection (HR 0.65, 95% CI 0.53–0.80) versus those without (HR 0.87, 95% CI 0.79–0.96).[6]

Our present results showed findings consistent with the previous reports. Subjects with HCV infection had a better TTP and OS compared to those with HBV infection. Those with EHS also had a longer TTP and OS than those with MVI, although these differences did not reach statistical significant levels. For patients with HBV infection, the occurrence of MVI, was associated with a significantly poorer outcomes in TTP and OS when compared to the occurrence of EHS. On the contrary, such occurrence of MVI or EHS did not alter the final outcome of patients with HCV infection.

The pathogenesis of greater sorafenib efficacy to HCV-infected cases of HCC patients is not clear yet. Some in vitro studies suggested that sorafenib inhibits HCV viral replication directly.[14,15] Other reported that HCV upregulates C-RAF[16] or enhances the expression of microRNAs,[17] thereby influencing the sensitivity of HCC cells to sorafenib. Another probable explanation is that HCV-mediated hepatocarcinogenesis strongly mediated by type I and III IFN, through the induction of kinases phosphorylation.[18] Therefore, in this setting, the multikinase inhibitor sorafenib could be more efficacious. Inconsistently, HBV-positive HCC patients are reportedly characterized by an interleukin-6 dependent inflammatory process,[19] which is different from the pathogenesis sorafenib is working on.

Here are several limitations of our study. First, it is a retrospective analysis of patients treated at a single tertiary care center. Selection bias of samples cannot be ruled out. Second, we did not measure elements of patient medical history like viral hepatitis, such as nucleotide/nucleoside analogs, interferon or direct-acting antivirals. Third, neither the grade of MVI nor location of EHS, both of which might influence the treatment outcome, were recorded and analyzed. Finally, we only analyzed subjects diagnosed with cirrhosis Child-Pugh stage A and HCC BCLC stage C. Further prospective research involving analysis of more variables is needed.

In conclusion, our study showed that HCC patients with HCV infection or presence of EHS are associated with better sorafenib

treatment outcomes. The HBV-positive patients with MVI showed a poorer outcome to sorafenib therapy.

Author contributions

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Writing – review & editing: Shou Wu Lee, Teng-Yu Lee, Sheng-Shun Yang, Chi-Sen Chang.

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