

## Original Article

# Cyproheptadine significantly improves the overall and progression-free survival of sorafenib-treated advanced HCC patients

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## Abstract

**Objective:** Sorafenib is a recommended treatment for advanced hepatocellular carcinoma. The study is to evaluate the efficacy of sorafenib plus cyproheptadine compared with sorafenib alone in patients with advanced hepatocellular carcinoma.

**Methods:** A retrospective cohort study reviewed all consecutive advanced hepatocellular carcinoma cases with Child-Pugh Class A disease starting sorafenib treatment at our hospital from August 2012 to March 2013. They were followed up until 31 December 2013. A total of 52 patients were enrolled: 32 patients in the combination (sorafenib–cyproheptadine) group and 20 patients in the control (sorafenib alone) group. The response to treatment, overall survival and progression-free survival were compared.

**Results:** The median overall survival was 11.0 months (95% confidence interval: 6.8–15.1 months) in the combination group compared with 4.8 months (95% confidence interval: 3.1–6.6 months) in the control group (crude hazard ratio = 0.45, 95% confidence interval: 0.22–0.82). The median progression-free survival time was 7.5 months (95% confidence interval: 5.1–10.0 months) in the combination group compared with 1.7 months (95% confidence interval: 1.4–2.1 months) in the control group (crude hazard ratio = 0.43, 95% confidence interval: 0.22–0.86). Kaplan–Meier survival analysis revealed that both overall survival and progression-free survival in the combination group were significantly longer than that in the control group. The multivariate model found patients in the combination group were 76% less likely to die (adjusted hazard ratio = 0.24, 95% confidence interval: 0.10–0.58) and 82% less likely to have progression (adjusted hazard ratio = 0.18, 95% confidence interval: 0.08–0.44) during the 17 months of follow-up.

**Conclusion:** Cyproheptadine may significantly improve survival outcomes of sorafenib-treated advanced hepatocellular carcinoma patients.

**Key words:** cyproheptadine, hepatocellular carcinoma, sorafenib, survival

## Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the third most common cause of cancer-related death in the world (1,2). Surgical resection, various local ablative therapies and liver transplantation are the main curative treatment options, but these options are only suitable for early-stage cancer patients. Unfortunately, many HCC patients are diagnosed at an advanced stage with only a few months of median survival time. Although several therapeutic strategies, such as surgery, radiation and chemotherapy, have been developed, the prognosis of advanced HCC remains unfavorable (3,4).

The efficacy and safety of sorafenib, a multikinase inhibitor, has been tested and approved for advanced HCC patients given that it can prolong median survival and the time to radiologic progression for ~3 months (5). Sorafenib is currently considered the standard treatment for patients with advanced HCC and Child-Pugh Class A disease (3,4,6–8). Furthermore, some studies have found additional benefit from combining sorafenib with some other treatment strategy such as TACE (9,10), doxorubicin (11) and cisplatin (12). These sorafenib-based combination therapies may provide a prospective future for the treatment of advanced HCC.

Cyproheptadine (trade name: Periactin) is a first-generation antihistaminic drug that is often used to treat allergic reactions and common cold symptoms, such as rhinorrhea. We reported two advanced HCC cases with lung metastasis that experienced complete remission upon treatment with a combination of cyproheptadine and thalidomide (13). One patient, who is no longer receiving thalidomide but continues cyproheptadine, remained tumor-free for >22 months. *In vitro* cell line studies further confirmed that cyproheptadine itself has a cytotoxicity effect in HCC cell lines in a time- and dose-dependent manner (13). We had also demonstrated that cyproheptadine inhibits proliferation of HCC cells by blocking cell cycle progression through the activation of P38 MAP Kinase (14). Since 2012, some hepatologists and oncologists in our hospital have added cyproheptadine to primary chemotherapeutic agents for HCC, such as sorafenib or thalidomide. However, the outcomes of the combination of sorafenib and cyproheptadine in patients with advanced HCC have not been evaluated thoroughly (15). Therefore, we conducted this pilot study to evaluate the efficacy of sorafenib plus cyproheptadine compared with sorafenib alone in patients with advanced HCC and Child-Pugh Class A disease.

## Patients and methods

### Ethical approval

The study protocol was approved by our institution's Ethics Review Board (CYCH-IRB No. 102028).

### Recruitment of cases

This investigation is a retrospective study. We reviewed all consecutive advanced HCC cases with Child-Pugh Class A disease given sorafenib treatment at our hospital from August 2012 to March 2013. They were followed up until December 2013. All of the patients fulfilled the AASLD and BCLC Stage C criteria. Baseline demographic characteristics, including age, sex and history of HCC including duration of HCC, stage, metastasis, macroscopic vascular invasion, Child-Pugh class and Eastern Cooperative Oncology Group Performance Status (ECOG PS) were collected and analyzed. The date that a patient was first prescribed sorafenib was recognized as the study entry date. Patients were divided into two groups according to their history of cyproheptadine administration. The 'combination group' was defined

as sorafenib-treated advanced HCC cases simultaneously administered cyproheptadine for >4 weeks. Whether adding cyproheptadine or not was individual doctor's decision. Some doctors like to add cyproheptadine because of our previous successful experience (13), but there was no consensus or assignment among all doctors. The dose of cyproheptadine ranged from 8–12 mg per day (4 mg two or three times). The weighted mean daily dose of cyproheptadine was 11.1 (1.8) mg per person and the mean (standard deviation, SD) of duration was 155.7 (112.7) days. The 'control group' was defined as sorafenib-treated advanced HCC patients who had not used cyproheptadine after being prescribed sorafenib. The study subjects were followed up from the date of study entry until a patient's death, withdrawal or loss to follow-up, whichever occurred first.

### Sorafenib use and evaluation

The Bureau of National Health Insurance, Taiwan (BNHI) began paying for sorafenib on 1 August 2012. Eligible HCC cases should fulfill the criteria of the American Association for the Study of Liver Diseases (AASLD) with Barcelona-Clinic Liver Cancer (BCLC) classification Stage C and Child-Pugh Class A. An expert committee of the BNHI will evaluate the initial and continuous use of sorafenib. Initially, 400 mg of sorafenib was administered orally twice daily, and one course of administration consisted of 2 months. The cases were reassessed by computed tomography or magnetic resonance imaging near the end of each 2 month period. According to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) (16), the patients were examined for three possible outcomes: partial response, stable disease or progressive disease. If the images indicated progressive disease, the BNHI would end payment for sorafenib. If the images indicated stationary disease or improved results, an additional 2 months of sorafenib would be prescribed. Patients can continue sorafenib therapy until death or disease progression. Given the high cost of sorafenib (up to USD \$5000 per month), patients are unable to use sorafenib if the BNHI does not cover its payment. If unacceptable adverse effects resulted from the treatment, the medication dose was reduced or treatment was withdrawn. For drug-related toxicity, the dose was reduced from 400 to 200 mg twice daily and then 200 mg once daily, where necessary.

### Evaluation of outcomes

The date of the last patient's follow-up was 31 December 2013. The primary endpoint was overall survival (OS) and the secondary endpoint was progression-free survival (PFS). The mean weighted daily dose and the treatment duration of sorafenib and cyproheptadine were calculated.

### Statistical analysis

Baseline characteristics were described and compared between the combination and control groups. Mann-Whitney *U* test was performed to compare the differences of continuous variables between the two groups; Fisher's exact test was employed for the categorical variables. Treatment outcomes, including OS (i.e. time to death) and PFS, were assessed by using survival analysis. Kaplan-Meier survival curves were constructed for the two groups, and the log-rank test was performed to detect significant differences. To eliminate the confounding effects that result from the unbalanced distribution of other survival determinants, the adjusted hazard ratio (HR) and its 95% confidence interval (95% CI) were estimated from the regression coefficient of the Cox proportional hazard regression model.

## Results

### Demographic and clinical features of the two groups

In total, 52 patients were enrolled in the study. Of them, 32 subjects were placed in the combination (sorafenib–cyproheptadine) group, and 20 subjects were placed in the control (sorafenib alone) group. We observed 5 partial responses (9.6%), 11 stable diseases (21.2%) and 36 progressive disease (69.2%) cases. Patients receiving cyproheptadine were more likely to possess the following characteristics: young, increased risk of lymph node and adrenal gland metastasis, macroscopic vascular invasion and hepatitis B infection, but were less likely to have bone metastasis, hepatitis C infection and prior ascites (for Child A class, the ascites is minimal amount). However, these differences between the two groups were not statistically significant (Table 1).

### Overall and PFS of the two groups

Kaplan–Meier survival analysis revealed that both the OS and PFS in the combination group were significantly longer than the control group (Figs 1 and 2). The median OS was 11.0 months (95% CI: 6.8–15.1 months) in the combination group compared with 4.8 months (95% CI: 3.1–6.6 months) in the control group. The median

PFS time was 7.5 months (95% CI: 5.1–10.0 months) in the combination group compared with 1.7 months (95% CI: 1.4–2.1 months) in the control group.

The 90-day OS was 87.5% (76.1–98.9%) for the combination group and 70.0% (50.0–90.0%) for the control group. The 180-day OS was 75.0% (59.9–90.1%) for the combination group and 35.0% (14.0–56.0%) for the control group. The 90-day PFS was 78.9% (63.5–92.5%) for the combination group and 31.6% (11.0–53.0%) for the control group. The 180-day PFS was 54.3% (36.2–71.8%) for the combination group and 31.6% (11.0–53.0%) for the control group.

After adjusting for other factors associated with survival, patients received the combination group were 76% less likely to die than those who received control group during the follow-up period with an adjusted HR of 0.24 (95% CI: 0.10–0.58;  $P = 0.002$  as summarized in Table 2). And the PFS were also significantly better in those patients treated with combination group than those treated with control group with an adjusted HR of 0.18 (95% CI: 0.08–0.44;  $P < 0.001$  as summarized in Table 3).

### Dosage and duration of sorafenib

The occurrence rate, severity of hand–foot skin reaction (HFSR) and causes of sorafenib dose reduction in both groups were summarized in Table 4. The control group had higher rate of HFSR than the combination group (60.0 vs. 40.6%,  $P = 0.255$ ). In total, 7 patients (21.9%) in the combination group and 8 patients (40.0%) in the control group underwent sorafenib dose reductions due to intolerable adverse effects such as HFSR, diarrhea and nausea ( $P = 0.213$ ). The mean weighted daily dose of sorafenib was 775.9 (SD = 54.1) mg in combination group compared with 715.3 (136.5) mg in control group ( $P = 0.066$ ). The mean treatment duration of sorafenib was 169.7 (118.8) days in combination group compared with 110.7 (85.9) days in control group ( $P = 0.042$ ). It showed that the combination group could tolerate higher dose as well as longer use of sorafenib.

## Discussion

Our results indicate that cyproheptadine in combination with sorafenib prolonged the OS and PFS of sorafenib-treated advanced HCC cases. The percentage of patients with partial response or stable disease in the combination group was almost twice that in the control group. In contrast, the probability of sorafenib dose reduction was reduced by approximately half in the combination group compared with the sorafenib control group. The sorafenib–cyproheptadine combination may provide a prospective future for advanced HCC. However, this study was only a retrospective study. A prospective clinical trial with a larger sample size is needed for further investigation.

According to the sorafenib study of advanced HCC patients in the Asia-Pacific region (8), the median OS and time to progression of patients administered with sorafenib was 6.5 and 2.8 months, respectively, which were longer than the median OS and PFS of control group in our study, 4.8 months and 1.7 months, respectively. Some factors might explain such discrepancy. First, in the study of the Asia-Pacific region, the minimal life expectancy of the enrolled patients was 12 weeks (8), but we did not apply such criteria for our patients. If we excluded the patients who survived <12 weeks after starting sorafenib treatment, the median OS of the sorafenib-alone group was 178 days, closer to 6.5 months in the Asia-Pacific study. Second, our patients in the control group were older than in the Asia-Pacific study with a mean age of 66.1 vs. 51 years. Third, our patients had more

**Table 1.** Baseline demographic and clinical features of two groups patients

	Cyproheptadine		P value <sup>a</sup>
	Without (n = 20)	With (n = 32)	
Age, mean (SD)	66.1 (12.9) <sup>b</sup>	64.6 (10.2) <sup>b</sup>	0.498 <sup>c</sup>
Male, n (%)	16 (80.0)	29 (90.6)	0.408
ECOG PS, n (%)			
0	6 (30.0)	8 (25.0)	0.923
1	11 (55.0)	19 (59.4)	
2	3 (15.0)	5 (15.6)	
Macroscopic vascular invasion, n (%)	16 (80.0)	27 (84.4)	0.719
Extra-hepatic spread sites, n (%)			
Any one site	9 (45.0)	18 (56.3)	0.570
Lung	3 (15.0)	5 (15.6)	1.000
Bone	7 (35.0)	6 (18.8)	0.208
Lymph node	1 (5.0)	7 (21.9)	0.132
Adrenal gland	1 (5.0)	5 (16.1)	0.384
Positive hepatitis status, n (%)			
Hepatitis B	6 (31.6)	18 (56.3)	0.146
Hepatitis C	12 (63.2)	16 (50.0)	0.398
Prior ascites, n (%)	5 (25.0)	5 (15.6)	0.480
AFP			
≤20	4 (20.0)	7 (21.9)	1.000
>20	16 (80.0)	25 (78.1)	
Treatment outcomes			
Partial response	1 (5.0)	4 (12.5)	0.490
Stable disease	3 (15.0)	8 (25.0)	
Progressive disease	16 (80.0)	20 (62.5)	
Mortality, n (%)	16 (80.0)	18 (56.3)	0.133
Dose reduction, n (%)	8 (40.0)	7 (21.9)	0.213

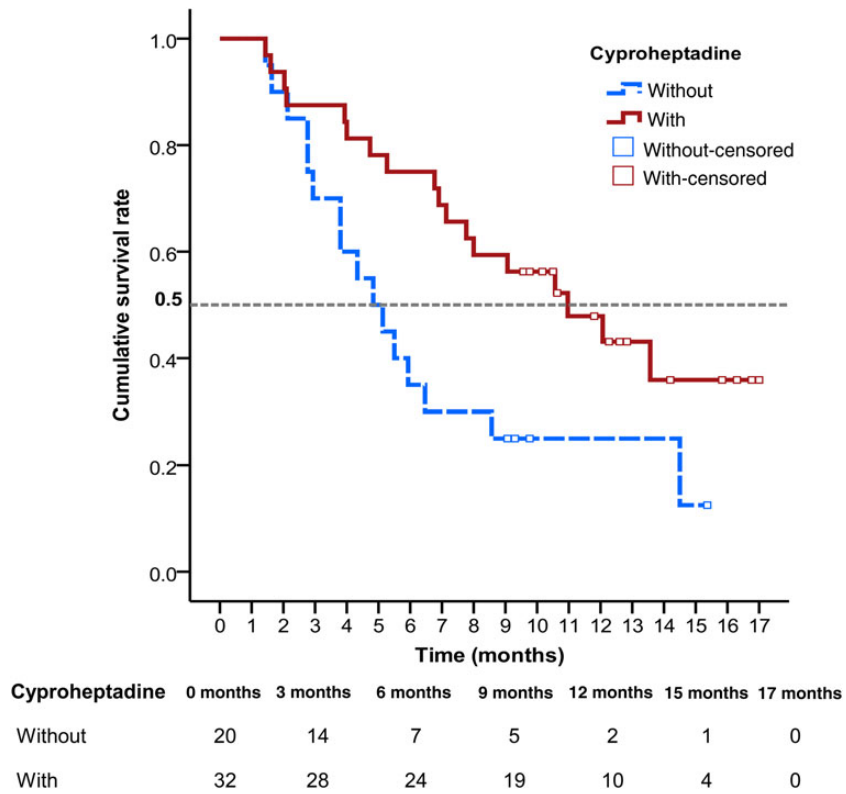
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AFP,  $\alpha$ -fetoprotein; SD, standard deviation.

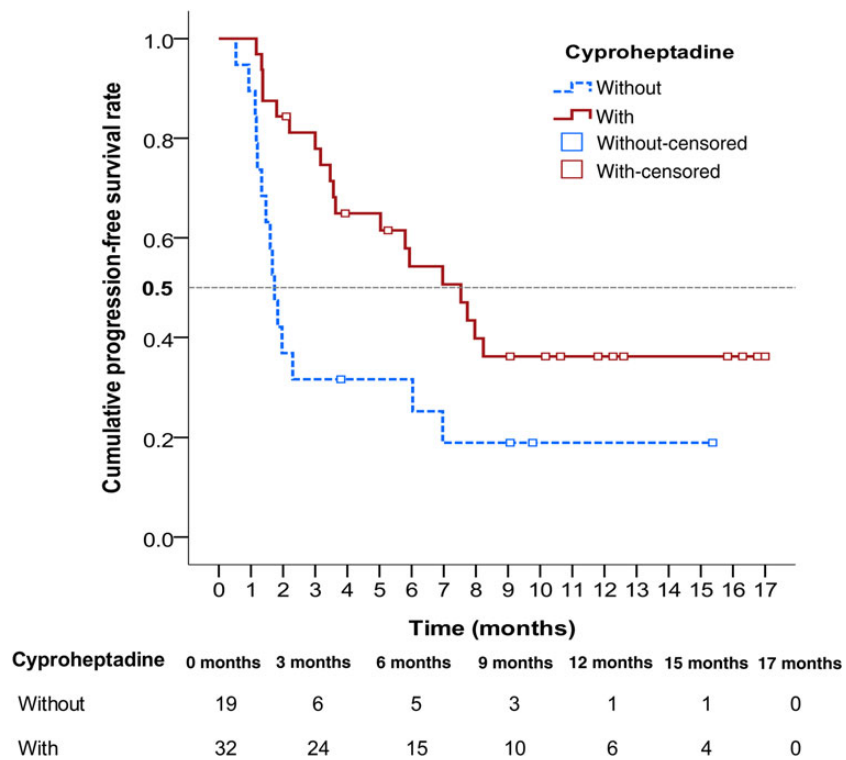
<sup>a</sup>Exact test, unless otherwise specified.

<sup>b</sup>Mean (SD).

<sup>c</sup>Mann–Whitney *U* test.



**Figure 1.** Overall survival curves for the two study groups. The solid line indicates the patients who received cyproheptadine; the dotted line indicates the patients who did not receive cyproheptadine ( $P=0.017$ , log-rank test).



**Figure 2.** Progression-free survival curves for the two study groups. The solid line indicates the patients who received cyproheptadine; the dotted line indicates the patients who did not receive cyproheptadine ( $P=0.004$ , log-rank test).

**Table 2.** Hazard ratio from Cox proportional hazard model for overall survival ( $n=51$ )

Characteristics	Univariate analysis		Multivariate analysis	
	HR (95% CI)	<i>P</i> value	aHR (95% CI)	<i>P</i> value
Cyproheptadine + vs. -	0.45 (0.22–0.822)	0.021	0.24 (0.10–0.58)	0.002
Age Per 1 year increase	1.01 (0.98–1.04)	0.691	1.01 (0.97–1.05)	0.755
Sex M vs. F	1.08 (0.41–2.83)	0.872	0.65 (0.19–2.31)	0.570
Macroscopic vascular invasion + vs. -	1.12 (0.54–2.35)	0.763	1.21 (0.39–3.73)	0.736
Extra-hepatic spread + vs. -	0.81 (0.41–1.59)	0.534	0.63 (0.25–1.57)	0.320
Hepatitis B + vs. -	0.88 (0.44–1.75)	0.719	2.08 (0.41–10.61)	0.381
Hepatitis C + vs. -	1.20 (0.60–2.39)	0.610	1.80 (0.38–8.46)	0.456
Prior ascites + vs. -	2.68 (1.21–5.95)	0.016	1.55 (0.55–4.37)	0.403
ECOG 1 vs. 0	4.95 (1.48–16.58)	0.010	9.51 (2.46–36.80)	0.001
2 vs. 0	24.71 (6.06–100.71)	<0.001	43.87 (8.65–222.51)	<0.001
AFP >20 vs. ≤20	0.84 (0.37–1.88)	0.671	0.70 (0.26–1.85)	0.469

Multivariable Cox proportional hazard regression analysis.  
CI, confidence interval; aHR, adjusted hazard ratio.

**Table 3.** Hazard ratio from Cox proportional hazard model for progression-free survival ( $n=50$ )

Characteristics	Univariate analysis		Multivariate analysis	
	HR (95% CI)	<i>P</i> value	aHR (95% CI)	<i>P</i> value
Cyproheptadine + vs. -	0.43 (0.22–0.86)	0.017	0.18 (0.08–0.44)	<0.001
Age per 1 year increase	1.00 (0.97–1.03)	0.961	0.99 (0.95–1.03)	0.681
Sex M vs. F	0.89 (0.31–2.52)	0.820	0.58 (0.13–2.55)	0.471
Macroscopic vascular invasion + vs. -	0.96 (0.47–1.97)	0.909	0.64 (0.21–2.01)	0.446
Extra-hepatic spread + vs. -	0.69 (0.35–1.35)	0.272	0.31 (0.12–0.81)	0.016
Hepatitis B + vs. -	1.10 (0.55–2.17)	0.794	3.36 (0.72–15.72)	0.124
Hepatitis C + vs. -	1.17 (0.59–2.32)	0.660	3.04 (0.75–12.33)	0.119
Prior ascites + vs. -	2.69 (1.20–6.07)	0.017	5.06 (1.52–16.82)	0.008
ECOG 1 vs. 0	3.15 (1.27–7.86)	0.014	8.82 (2.78–28.00)	<0.001
2 vs. 0	6.31 (1.91–20.86)	0.003	13.77 (3.20–59.27)	<0.001
AFP >20 vs. ≤20	1.69 (0.66–4.38)	0.277	1.16 (0.41–3.24)	0.778

Multivariable Cox proportional hazard regression analysis.

macroscopic vascular invasion (80 vs. 36%) and higher ECOG PS 2 (15 vs. 5.3%). Although our patients had some disadvantages than the patients in the Asia-Pacific study, the median OS and PFS in our combination group, 11.0 and 7.5 months, respectively, were still much longer than that in the Asia-Pacific region, 6.5 and 2.8 months, respectively.

Anorexia or loss of appetite is pervasive among patients with advanced cancer and has been recognized as one of the most troubling symptoms (17). Cyproheptadine is considered an appetite stimulant for cancer patients with anorexia (18–20), though this study did not find a significant difference in body weight change before and after treatment in both groups. Various studies using animal models or

**Table 4.** Hand-foot skin reaction and dose reduction of sorafenib in two groups with or without receiving treatment of cyproheptadine

Adverse drug effects	Cyproheptadine		P value <sup>a</sup>
	Without (n = 20)	With (n = 32)	
Hand-foot skin reaction			
All	12 (60.0)	13 (40.6)	0.255
Grade 1	5	5	
Grade 2	4	5	
Grade 3	3	3	
Dose reduction of sorafenib, due to	8 (40.0)	7 (21.9)	0.213
Hand-foot skin reaction	6	5	
Diarrhea	1	2	
Nausea	1	0	

Digits in cells represent count (percentage).

<sup>a</sup>Exact test.

cancer cell lines have demonstrated the inhibitory effects of cyproheptadine in myeloma, leukemia and mantle cell lymphoma (21,22). Our previous cell line studies have also demonstrated that cyproheptadine reduces the cell viability of two HCC cell lines, HepG2 and Huh-7, in a time- and dose-dependent manner (13). Thus, we hypothesized that the contribution of cyproheptadine to enhanced survival outcome was due to its anti-cancer effect, not appetite stimulation (13). Someone may wonder other antihistaminic drug have the same anti-cancer effect. We carefully reviewed the literature and found, in light of tumor-inhibiting effects, three histamine H1-receptor antagonists, diphenhydramine (23), loratadine (24) and chlorpheniramine (25) have been reported for their inhibitory effects on acute lymphoblastic leukemia cells (23), human colon carcinoma cell line (HT29) (24) and human breast cancer cell line (MCF-7) (25), respectively. Cyproheptadine is the first antihistaminic drug being reported to have inhibitory effect on human HCC cell line (13), though its mechanism of tumor-inhibiting effects is still unclear. However, in considering the catastrophic characteristics of HCC and other malignant diseases, any possibility to improve the treatment outcome should be appreciated.

HFSR is the most frequently reported adverse effect of sorafenib treatment; this symptom often results in a sorafenib dose reduction (8). Given that the adverse effects were typically additive, the combination therapy may result in increased adverse effects. For example, HFSR syndrome appeared to be more frequent when sorafenib was combined with 5-FU (15). However, our results demonstrated that the frequency of sorafenib dose reduction was considerably less frequent in the combination group than in the sorafenib-alone group (22 vs. 40%, Table 1). We hypothesize that cyproheptadine, an antihistamine, could potentially alleviate the allergic symptoms of HFSR and helps patients tolerate the typical sorafenib dose. In addition, given that cyproheptadine is inexpensive with a daily cost of US \$0.2 in Taiwan, the addition of cyproheptadine to sorafenib would not result in an additional financial burden for the patients. With regard to cyproheptadine, a small proportion of cases may experience sleepiness or dizziness after taking cyproheptadine, but patients typically adapt to these effects within a few weeks. Thus, compared with other combination therapies, the addition of cyproheptadine to sorafenib could be more advantageous and cost-effective.

Previous studies have demonstrated that patients with HBV-associated HCC have a poorer prognosis than patients with HCV-related HCC (8). A systematic review has concluded that the

response to sorafenib treatment is poorer in patients with hepatitis B compared with patients with hepatitis C (15). In this study, the survival outcome was enhanced in the combination group compared with the sorafenib-alone group despite the combination group containing a higher percentage of HBV patients and fewer HCV patients (Table 1). In the multivariate model adjustment for all associated factors, cyproheptadine was the only factor, in addition to ECOG, significantly related to prolonged OS and PFS. In contrast, extra-hepatic spread, macroscopic vascular invasion, AFP and hepatitis B or C infection had no statistically significant impact on survival.

### Limitations

The limitations of this study should be mentioned. First, since this investigation was a retrospective chart-review study, not a prospective randomized clinical trial, selection bias was a concern. Fortunately, the baseline demographic and clinical features between two groups were not significantly different (Table 1). Second, this study was conducted at a single hospital with a small case number. However, we still observed a significant difference in survival outcomes between the two groups after 17 months of follow-up.

### Conclusions

This pilot study indicated that the addition of cyproheptadine to sorafenib results in enhanced improvements to OS and PFS of patients with advanced HCC and Child-Pugh Class A disease. The reduced frequency of dose reduction observed in the combination group could be explained by the possible alleviation of the adverse effects of sorafenib by cyproheptadine. Considering the cost and benefit, this combination may produce a more advantageous and much less adverse effects compared with sorafenib alone. Furthermore, we wonder the addition of cyproheptadine to early or intermediate-stage HCC treatments could also prove beneficial; we are planning a prospective randomized clinical trial to test this hypothesis. In addition, the mechanism of cyproheptadine in HCC also requires further investigation.

### Authors' contributions

Y.-M.F. conceptualized the study, drafted the manuscript and approved the final manuscript as submitted.  
 C.-W.F. conceptualized the study, critically reviewed the manuscript and approved the final manuscript as submitted.  
 C.-L.L. carried out data analysis, critically reviewed the manuscript and approved the final manuscript as submitted.  
 M.-Y.L. conceptualized the study, collected and checked the data and approved the final manuscript as submitted.  
 C.-Y.C. conceptualized the study, collected and checked the data and approved the final manuscript as submitted.  
 S.C.-C.C. conceptualized and designed the study, carried out data analysis, critically reviewed the manuscript and approved the final manuscript as submitted.

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### Conflict of interest statement

None declared.

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