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ORIGINAL ARTICLE

Sorafenib in Liver Function Impaired Advanced Hepatocellular Carcinoma

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Objective To explore the efficacy and safety of sorafenib in Child-Pugh class B to class C hepatocellular carcinoma (HCC).

Methods In this three-center open-label study from November 2011 to May 2013, we randomly assigned 189 patients with advanced Child-Pugh class B or C HCC patients into two groups, one group with 95 patients to receive sorafenib (400 mg a time, twice a day) and the other group with 94 patients to receive best supportive care. The primary end points were progression-free survival and overall survival.

Results The median progression-free survival was 2.2 months and 1.9 months in the sorafenib group and best supportive care group respectively (Hazard ratio in the sorafenib group, 0.55; 95% confidence interval, 0.40-0.75; $P=0.002$). The median overall survival was 4.0 months and 3.5 months in the sorafenib group and best supportive care group respectively (Hazard ratio in the sorafenib group, 0.48; 95% confidence interval, 0.35-0.68; $P<0.001$). The main adverse effect of sorafenib was rash and acne of the skin (in 51.7% patients). The incidences of severe rash, diarrhea, and dry skin were 5.6%, 5.6%, and 2.2% in the sorafenib group. One patient reached partial response in the sorafenib group.

Conclusions Sorafenib is safe in patients with liver function impaired advanced HCC. It is effective in terms of progression-free survival and overall survival compared with best supportive care. Liver functions are the important predictive factors.

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HEPATOCELLULAR carcinoma (HCC) is the third leading cause of cancer death, just behind lung cancer and stomach cancer globally, and behind esophagus and stomach cancers in

China. Despite tremendous efforts in diagnosis and new treatment regimens, the prognosis of HCC is still extremely poor, especially in advanced cases. The incidence is increasing, with more than 626 000 new cases every year worldwide and most of them died in one year.¹ Due to hepatitis B virus and hepatitis C virus infection, about 55% HCC cases happened in China, among whom only 10% can be diagnosed in early stage, compared with 30%-40% in Western countries.²

These early-stage HCC patients could be cured by locoregional intervention; however, patients in advanced stages usually have a long history of liver disease, impaired liver function, and poor performance status, thus the prognosis of advanced-stages patients is ominous for lack of effective therapies.³

Sorafenib (Nexavar, Bayer HealthCare Pharmaceuticals-Onyx Pharmaceuticals, Leverkusen, Germany) is a novel, small-molecule inhibitor of several tyrosine protein kinases [vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor (PDGFR)], and a RAF/MEK/ERK cascade inhibitor that inhibits cancer angiogenesis and cell proliferation.⁴ Cellular signaling mediated by the Raf-1 and vascular endothelial growth factor pathways has been implicated in the molecular pathogenesis of HCC,^{5,6} providing a rationale for investigating the application of sorafenib in HCC treatment. In preclinical experiments, sorafenib exhibits antiproliferative activity in liver-cancer cell lines, and it reduces tumor angiogenesis and tumor-cell signaling, and increases tumor-cell apoptosis in a mouse xenograft model of human HCC.⁴

Sorafenib was reported to increase overall survival (OS) and progression-free survival (PFS) in advanced HCC patients with liver function of Child-Pugh class A.¹ It is critically urgent to find an effective treatment for Child-Pugh class B to class C patients. We conducted a randomized study among patients with advanced HCC and liver function of Child-Pugh class B or C treated with sorafenib or best supportive care (BSC) to investigate the efficacy and safety of sorafenib.

PATIENTS AND METHODS

Study design and patient selection

This is a multi-center open-label randomized study. Study patients were pathologically or cytologically confirmed advanced HCC, with liver function at Child-Pugh class B or C, Barcelona-Clinic Liver Cancer (BCLC) stage B or C, and estimated life time of 2 months or longer. All patients failed to respond to or were ineligible to locoregional treatment (e.g. surgery, radiotherapy, hepatic arterial embolization, chemoembolization, radiofrequency ablation, percutaneous ethanol injection, or cryoablation). Previously treated lesions were not selected as target lesions. None of the patients had received previous target therapy. Local therapy must be completed at least 4 weeks prior to the baseline scan. All the patients were 18-80 years of age with Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 and adequate renal function (Table 1).

All eligible patients were randomly assigned into two groups, in a 1 : 1 ratio, one group receiving continuous oral sorafenib 800 mg/day, twice daily, and the other treated with BSC. Randomization was performed with dynamic balancing⁷ with respect to performance status, as assessed using the World Health Organization (WHO) performance scale measuring activity, sex, hepatitis B or C infection history, and BCLC stage.⁸ Sorafenib treatment was continued until: (1) the disease progression defined by Response Evaluation Criteria in Solid Tumors (RECIST) criteria 1.1 and symptomatic progression defined by the Functional Assessment of Cancer Therapy-Hepatobiliary Symptom Index 8 (FHSI-8) questionnaire⁹ for measuring patient's quality of life; (2) liver function worsened to Child-Pugh class C or ECOG performance status changed to grade 3; (3) requested by patients or physician; (4) uncontrollable serious adverse effects or death. Crossover of patients from the sorafenib group to the BSC group was permitted in the cases of disease progression defined by RECIST and symptomatic progression by FSHI-8. Patient crossover from the BSC group to the sorafenib group was not allowed unless ECOG performance status was 0-2 and liver function restored to Child-Pugh A. Two dose reductions of sorafenib were permitted, first to 400 mg once daily, then to 400 mg every 2 days. Patients were withdrawn from the study if further dose reductions were needed (Fig. 1).

Enrolled patients were required to have one or more evaluable target lesions that could be measured in one dimension according to RECIST criteria 1.1. Patients were excluded if they were pre-treated with any molecular target therapies.

This study was approved by the Ethics Committee of Qingdao Central Hospital, 2nd Affiliated Hospital of Qingdao University, performed in compliance with the provisions of Good Clinical Practice guidelines, the Declaration of Helsinki, and local laws. Informed consents were obtained from the selected patients before randomization.

Outcomes and assessment

The primary end-points of the study were PFS and OS, measured from randomization date to disease progression or death. The second end-points were response rates and symptomatic progression time. Response rates were assessed using RECIST criteria 1.1, observed during trial period, and classified into: complete response (disappearance of tumor lesions), partial response (a decrease of at least 30% in the sum of tumor lesion sizes), stable disease (steady state of disease), or progressive disease (an increase $\geq 20\%$ in the sum of tumor lesion sizes). Symptomatic

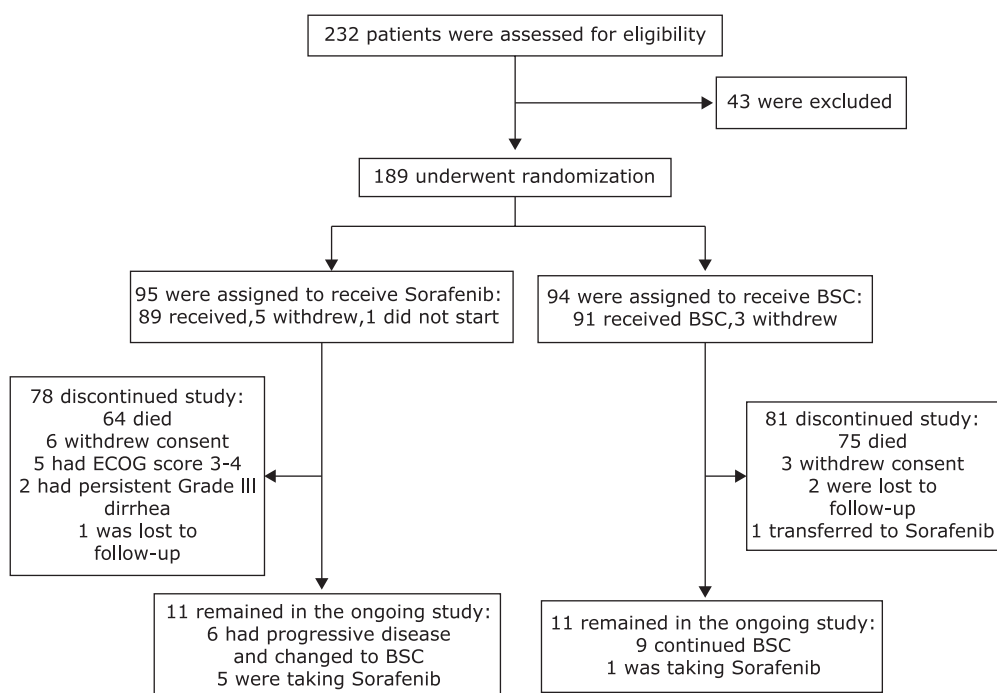


Figure 1. Screening, group assignment, and outcomes of the study patients.

BSC: best supportive care.

progression was defined as a decrease ≥ 4 from the baseline score 4 weeks later in the patients' responses to the FHSI-8 questionnaire.

Tumor measurements were performed at screening and every 4 weeks thereafter. Patient's compliance, treatment safety, and side effects were accessed at each check point, i.e. every 4 weeks.

Statistical analysis

PFS and OS curves were analyzed using Kaplan-Meiers log-rank test, and the hazard ratios (HR) using Cox proportional hazards model in the intention-to-treat principle to compare sorafenib with BSC, with BCLC stages, sex, and ECOG performance status as covariates. The 95% confidence interval for HR had to demonstrate no inferiority if the treatments were truly equal. The *P* value would be < 0.05 and the superiority could be concluded without statistical penalty if the 95% confidence interval for the HR was below 1. Covariates were used to identify predictive factors by assessing whether there was a significant difference in the treatment effect between subgroups.

The response rate, symptom reduction, and treatment-related adverse events were assessed with Fisher exact test.

RESULTS

Patient information

From November 2011 to May 2013, we screened 232

patients, of which 189 were enrolled for randomization. The remaining 43 patients were excluded from the study during screening for they did not meet the inclusion standard. The two groups were well balanced, with 95 patients randomly assigned to the sorafenib group, among them, 5 patients withdrew, 1 did not started, and 89 patients received sorafenib; 94 patients assigned to the BSC group with 3 patients withdrew.

All the patients were Chinese, recruited and resided in Chinese mainland. All the patients were in Child-Pugh class B or C, and over 80% were in stage C by BCLC staging system. Hepatitis B virus infection was the predominant cause of liver disease (159 cases), followed by hepatitis C virus infection (5 cases). Over 80% of the patients had extra-hepatic spread of HCC at baseline (Table 1).

Efficacy

The median PFS was 2.2 months and 1.9 months in the sorafenib group and the BSC group respectively (HR in the sorafenib group, 0.55; 95% confidence interval, 0.40-0.75; $P=0.002$). The median OS was 4.0 months and 3.5 months in the sorafenib group and the BSC group respectively (HR in the sorafenib group, 0.48; 95% confidence interval, 0.35-0.68; $P<0.001$) (Fig. 2).

The response rates were low in both groups. Without complete response, one patient reached partial response in the sorafenib group but none in the BSC group. The partial

Table 1. Baseline characteristics of the study patients

Groups	Age ($\bar{x} \pm s$, year)	Sex [n (%)]		Cause of disease [n (%)]			ECOG performance status [n (%)] [†]	
		Male	Female	Hepatitis B only	Hepatitis C only	Other	1	2
BSC (n=94)	58.6±12.2	78 (83)	16 (17)	78 (82)	2 (2)	14 (15)	27 (29)	67 (71)
Sorafenib (n=95)	59.4±11.9	81 (85)	14 (15)	81 (85)	3 (3)	11 (12)	24 (25)	71 (75)
Groups	Child-Pugh class [n (%)] [‡]		Bacelona stage [n (%)] [¶]		Extrahepatic spread [n (%)]			
	B	C	B	C	Regional lymph node	Metastasis		
BSC (n=94)	70 (74)	24 (26)	12 (13)	82 (87)	73 (78)	35 (37)		
Sorafenib (n=95)	72 (76)	23 (24)	11 (12)	84 (88)	78 (82)	37 (39)		

ECOG: Eastern Cooperative Oncology Group.

[†]The ECOG performance status assesses the daily living abilities of the patient, on a scale ranging from 0 (fully active) to 5 (dead).

[‡]The Child-Pugh system evaluates the severity of liver disease, divided into classes A to class C.

[¶]Bacelona stage denotes Barcelona-Clinic Liver Cancer staging system.

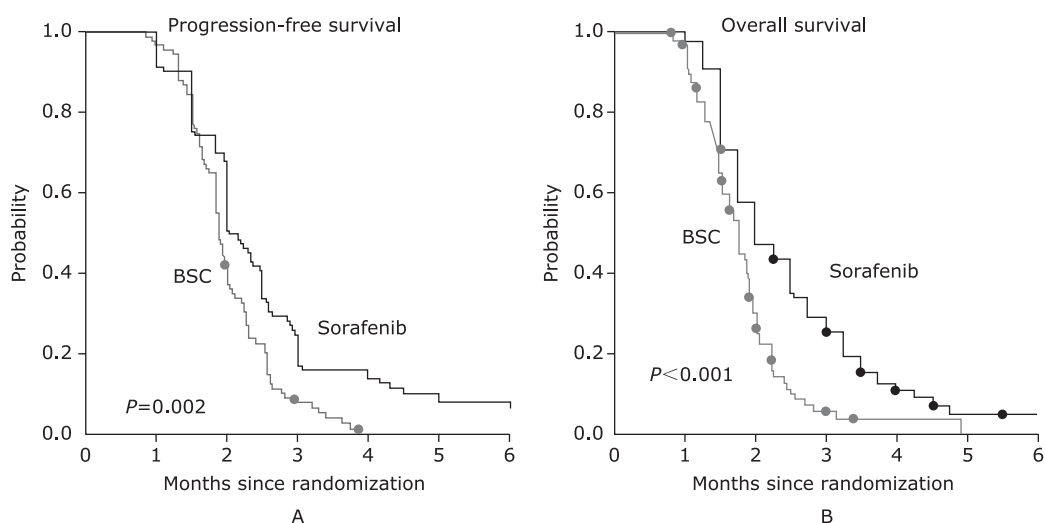


Figure 2. Kaplan-Meier analysis of the Progression-free Survival (PFS) and Overall Survival (OS) of 189 patients including 95 who received sorafenib and 94 who received BSC. The median PFS was 2.2 months in sorafenib group, compared with 1.9 months in the BSC group (hazard ratio for progression in the sorafenib group, 0.55; 95% CI, 0.40-0.75) (A). The median OS was 4.0 months in the sorafenib group, compared with 3.5 months in the BSC group (hazard ratio for death in the sorafenib group, 0.48; 95% CI, 0.35-0.68) (B).

response rate and stable disease rate were higher in the sorafenib group [1.1% (1/95) vs. 0% (0/94), $P=0.996$; 43.2% (41/95) vs. 28.7% (27/94), $P=0.055$]. The disease control rate (partial response + stable disease) was 44.2% in the sorafenib group, significantly higher than that in the BSC group (28.7%, $P=0.039$).

In the sorafenib group, the median PFS and OS were

significant longer in the patients at BCLC stage B and Child-Pugh class B liver function (Fig. 3).

Sorafenib prolonged PFS and OS in both BCLC stage B and stage C patients (Fig. 4A-D), also prolonged PFS and OS in patients with Child-Pugh class B liver function (Fig. 4 E-F) but not in patients with Child-Pugh class C liver function (Fig. 4G-H).

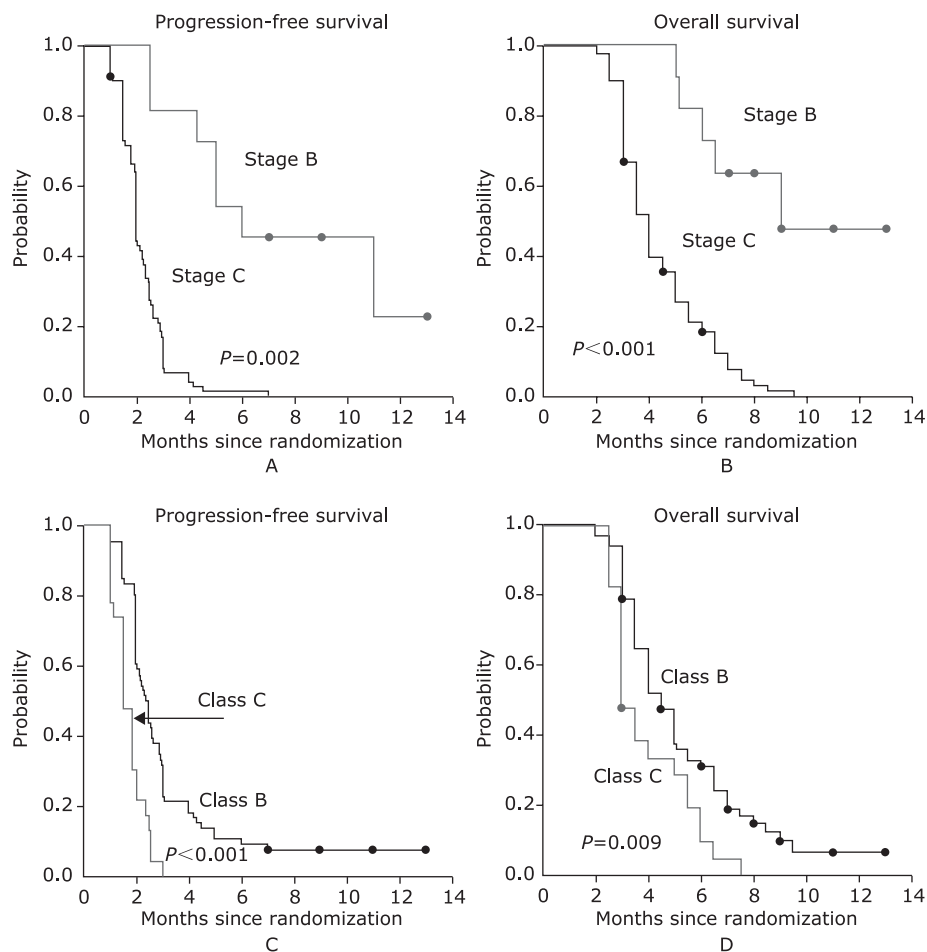


Figure 3. Kaplan-Meier analysis of the PFS and OS of the sorafenib-treated patients according to Bclerc stage (A and B) or liver function by Child-Pugh class (C and D).

Quality of Life

The quality of life of the 2 groups did not differ significantly at baseline or during the treatment, according to the response to the FHSI-8 questionnaire.

Adverse effects

The main adverse effect of sorafenib was rash and acne of the skin, happened in 51.7% patients in the sorafenib group, higher than the incidence in the BSC group (3.3%, $P<0.001$, Table 2). The incidences of diarrhea, dry skin, and anorexia were higher in the sorafenib group than in the BSC group (14.6% vs. 7.7%, 32.6% vs. 3.3%, 18.0% vs. 12.1%), but the differences were not significant. Grade III to grade IV rash, diarrhea, and dry skin rates were 5.6%, 5.6%, and 2.2% in the sorafenib group, higher than the rates in the BSC group (0%, 1.1%, 0%), but the differences were not statistically significant. Two patients discontinued sorafenib study for persistent Grade III diarrhea even through two times sorafenib dose reduction. There was no treatment-related death in either group (Table 2).

DISCUSSION

As shown by the results of this study, patients in the sorafenib group had 0.3 months longer median PFS than those in the BSC group did ($P=0.002$). The median OS was prolonged by 0.5 months in the sorafenib group compared with the BSC group ($P<0.001$), indicating the effect of sorafenib on OS. In this study, all the patients were in Child-Pugh class B or C, and over 80% of them were in stage C by BCLC staging system. Less persevered liver function with hepatic cirrhosis may contribute to the low treatment-related response rate. One patient reached partial response in the sorafenib group, and the rate of stable disease nearly doubled in the sorafenib group than in the BSC group (43.2% vs. 28.7%). Increased stable disease rate in patients with liver function-impaired HCC may result in prolongation of survival time.

In this study, liver functions were also important prognostic factors. Sorafenib significantly prolonged median PFS and OS in patients with Child-Pugh class B compared with

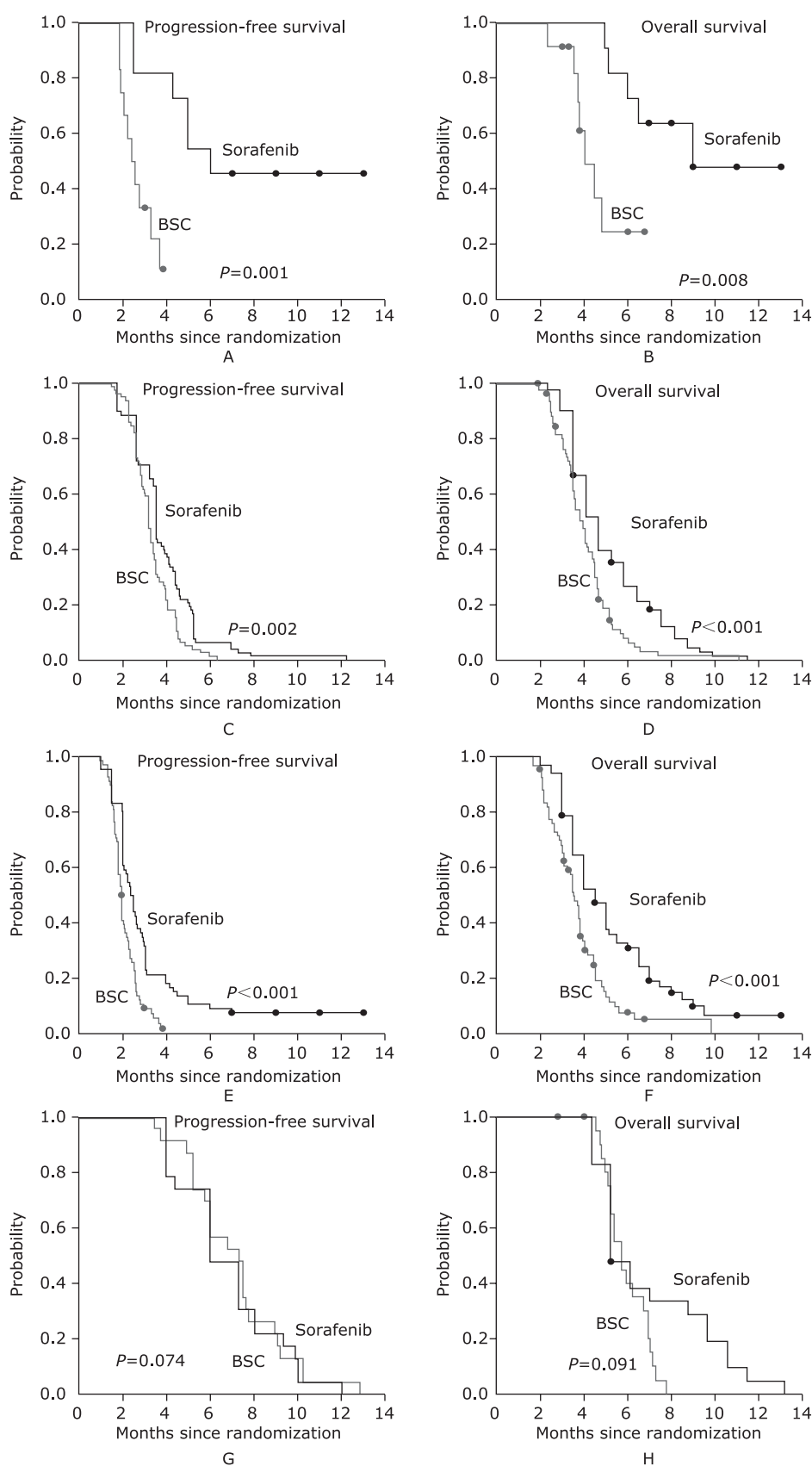


Figure 4. Kaplan-Meier analysis of the PFS and OS in Bcl-2 stage B (A and B) or stage C patients (C and D), or in Child-Pugh Class B (E and F) or Class C patients (G and H).

Table 2. Adverse events in the sorafenib group and the BSC group [n (%)]

Groups	Rash or acne		Diarrhea		Dry skin		Anorexia		Nausea		Vomiting		Constipation	
	All	Grade 3-4	All	Grade 3-4	All	Grade 3-4	All	Grade 3-4	All	Grade 3-4	All	Grade 3-4	All	Grade 3-4
BSC (n=91)	3 (3.3)	0	7 (7.7)	1 (1.1)	3 (3.3)	0	11 (12.1)	1 (1.1)	8 (8.8)	0	1 (1.1)	0	10 (11.0)	1 (1.1)
Sorafenib (n=89)	46 (51.7)	5 (5.6)	13 (14.6)	5 (5.6)	29 (32.6)	2 (2.2)	16 (18.0)	1 (1.1)	11 (12.4)	0	8 (9.0)	0	13 (14.6)	2 (2.2)
P	<0.001	0.072	0.274	0.218	<0.001	0.491	0.423	0.482	0.646	NA	0.042	NA	0.696	0.993

Groups	Alopecia		Neurotoxic effects		Myalgia		Arthralgia		Neutropenia		Anemia		Leukopenia		Epistaxis	
	All	Grade 3-4	All	Grade 3-4	All	Grade 3-4	All	Grade 3-4	All	Grade 3-4	All	Grade 3-4	All	Grade 3-4	All	Grade 3-4
BSC (n=91)	0	0	0	0	0	0	0	0	0	0	4 (4.4)	0	0	0	0	0
Sorafenib (n=89)	1 (1.1)	0	2 (2.2)	0	3 (3.4)	0	1 (1.1)	0	2 (2.2)	0	3 (3.4)	1 (1.1)	2 (2.2)	0	1 (1.1)	0
P	0.996	NA	0.482	NA	0.248	NA	0.996	NA	0.482	NA	0.989	NA	0.482	NA	0.996	NA

Adverse events were defined by the National Cancer Institute Terminology Criteria.

NA: not applicable.

patients with Child-Pugh class C. Compared with BSC, sorafenib prolonged PFS and OS in Child-Pugh class B patients but not in those with Child-Pugh class C. Because only 23 Child-Pugh class C patients were enrolled in the sorafenib group and 24 in the BSC group, and survival time of these liver function-impaired patients were short, the exact role of sorafenib in these patients needs further study. Patients' hepatitis history was not found to influence survival.

Hepatocellular cancer is a heterogeneous cancer with several active pathways.^{4,10} Invasive HCC can exhibit up-regulation of nuclear factor-kappaB (NF-kB) and epidermal growth factor receptor variant III. Sorafenib inhibits VEGF expression via suppressing the ERK/NF-kB pathway in HCC cells,^{11,12} prevents neoangiogenesis by inhibiting molecular components of the Raf-MEK-ERK signaling pathway, and suppresses tumor growth.⁴ Sorafenib is the standard choice for HCC patient with liver function Child-Pugh class A and with extensive liver tumor burden.^{1, 3, 13} This agent has PFS and OS benefits in HCC with liver function at Child-Pugh class A compared with doublets chemotherapy, while the results in patients with poor liver function were not clear.^{1, 4} Abou-Alfa et al¹⁴ and Chiu et al¹⁵ reported that sorafenib is safe and effective in a small number of patients with advanced HCC and Child-Pugh class B liver function. In this study, patients were in advanced stages and previously treated with locoregional methods, with liver function being Child-Pugh class B or C, which precludes aggressive treatment and maybe the reasons of short survival time.

Sorafenib was found safe in HCC patients with poorly

reserved liver function in this study. Liver function was not worsened by oral sorafenib compared with BSC. The main adverse events were I-II degree hand-foot skin reaction. Five patients suffered grade III diarrhea, three of whom resumed sorafenib by dose reduction, two withdrew from the study with persistent symptoms even with dose reduction and anti-diarrhea treatment. Anorexia and constipation were related to inactivity and analgesic medication, happening at equal rates in both groups. One patient developed mild epistaxis and one suffered grade III anemia. Lee et al¹⁶ reported ethnic differences in genetic polymorphisms of TNF- α , VEGF, and UGT1A9, especially serum TNF- α , after sorafenib therapy, which was related with the incidence of hand-foot skin reaction. We observed no severe hemorrhagic or cardiac events in this study.

In conclusion, sorafenib could prolong PFS and OS in patients with advanced-stage HCC. It also benefits patients with Child-Pugh class B liver function but not those with class C liver function. The effects of continuous sorafenib therapy in patients after disease progression need to be investigated by further studies.

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