Sorafenib in Advanced Hepatocellular Carcinoma
Hypertension as a Potential Surrogate Marker for Efficacy

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Background: Advanced hepatocellular cancer (HCC) is an incurable disease with limited options for systemic treatment. Sorafenib was approved for advanced HCC based on trials in patients with Child-Pugh class A. We reviewed our experience retrospectively in patients with HCC who were treated with sorafenib with a focus on Child-Pugh B (CP-B) liver cirrhosis and effect of hypertension (HTN) on survival.

Methods: We retrospectively reviewed medical charts of patients with documented advanced HCC who received sorafenib since 2007. Survival data were plotted according to Child-Pugh class and HTN.

Results: Results of 41 patients 39% had CP-B. Eighty-five percent were male and 67% had HCC due to viral hepatitis. Fifty-six percent received localized treatment before sorafenib. Five percent had a partial response and 39% had stable disease. Time to progression and overall survival (OS) for all patients were 3.2 and 6.2 months, respectively. Time to progression and OS were 4 and 8.4 months in Child-Pugh class A patients and 2 and 3.2 months in CP-B patients, which were statistically significant. Patients who had documented HTN while on treatment according to Common Terminology Criteria for Adverse Events version 3.0 had significantly better OS (18.2 vs. 4.5 mo; $P = 0.016$).

Conclusions: Development of HTN with sorafenib seems to be associated with a favorable effect on prognosis. Future trials should examine this observation.

Key Words: sorafenib, advanced hepatocellular carcinoma, hypertension, Child-Pugh liver cirrhosis, survival

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Hepatocellular carcinoma (HCC) is the third leading cause of death worldwide and continues to rise.[1–3] Curative treatments for HCC include orthotopic liver transplantation (OLT), hepatic resection, and in select cases radiofrequency ablation and percutaneous ethanol injection. Management of advanced HCC includes several palliative options ranging from localized therapy (eg, transarterial chemoembolization, radioembolization, and radiofrequency ablation) to systemic chemotherapy that has been associated with modest results.

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Sorafenib is a small molecule antiangiogenic tyrosine-kinase inhibitor. Earlier studies showed its activity against Raf-1, FLT3, and significantly against vascular endothelial growth factor receptors 2 and 3.[4] The interest in sorafenib for patients with HCC is based on early results from phase I and II trials indicating modest activity.[5,6]

Sorafenib was approved in November 2007 for advanced HCC based on results from the Sorafenib HCC Assessment Randomized Protocol trial.[7] The phase III Sorafenib HCC Assessment Randomized Protocol trial randomized patient with unresectable HCC, 95% of which had Child-Pugh A (CP-A) liver cirrhosis, to either placebo or sorafenib 400 mg twice daily. Overall survival (OS) and time to symptomatic progression were the primary endpoints. Time to symptomatic progression was similar, but OS and time to objective progression were significantly longer with sorafenib (10.7 vs. 7.9 mo and 5.5 vs. 2.8 mo, respectively).[7]

Treatment of patients with Child-Pugh B (CP-B) liver cirrhosis is challenging. Use of locoregional treatment options may be limited due to compromised liver function, and sorafenib has largely been studies in CP-A liver cirrhosis. Label indication for sorafenib does not specify hepatic functional status, and it remains one of the limited options available in CP-B patients but with little data to support its efficacy.

In several observations, the development of hypertension (HTN) with antiangiogenic agents has correlated with improved outcomes in renal cell carcinoma and lung cancer receiving sunitinib and bevacizumab (both antiangiogenic agents). Here, we analyze our experience with sorafenib in advanced HCC in patient with focus on CP-B liver cirrhosis and correlation of HTN and survival in our population.

METHODS

The study was approved by the Cleveland Clinic Institutional Review Board. This is a retrospective analysis of single institution electronic charts of patient with unresectable HCC receiving sorafenib. Patients were identified from electronic database by diagnosis and medication history. Patients were included if they had a diagnosis of HCC and evidence of receiving sorafenib. Those without pathologic diagnosis were evaluated based on the diagnostic criteria by the American Association for the Study of Liver Diseases.[8] Patients were excluded if they had OLT before or after initiation of sorafenib, had hepatectomy with curative intent, or had no evidence of taking sorafenib. Records were searched from January 2007 to April 2010. Analysis for OS and time to progression (TTP) was conducted in May 2010.

Data Collection

Demographics included age at time of sorafenib treatment, sex, and race. Staging and underlying causes of HCC were identified when known. We collected levels of alpha fetoprotein (AFP) and other laboratory values and clinical findings necessary

TABLE 1. Patient Characteristics

Variables	N (%)
Total no. patients	41
Age	
Median (range)	58 (28-92)
Mean ± SD	61 ± 13
Sex	
Male	35 (85)
Female	6 (15)
Ethnicity	
White	25 (61)
African American	13 (32)
Asian	2 (5)
Hispanic	1 (2)
Underlying cause	
HCV*	24 (59)
HBV	3 (8)
Alcohol*	10 (24)
Other/unknown	11 (27)
ECOG performance score	
0-1	20 (49)
2-3	3 (7)
Unknown	18 (44)
Portal vein thrombosis	11 (27)
AFP (ng/mL)	
Median (range)	146 (3.3-55313)
< 400 ng/mL	25 (61)
Child-Pugh class	
A	25 (61)
B	16 (39)
BCLC staging	
A	5 (12)
B	16 (39)
C	17 (42)

*Seven patients had both HCV and alcohol cirrhosis as a predisposing factor.

AFP indicates alpha fetoprotein; BCLC, Barcelona Cancer Liver Clinic; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus.

to classify patients according to Child-Pugh (CP) at the time of sorafenib initiation. We also collected information regarding types of therapy received before and after sorafenib.

Efficacy

When possible, we reviewed reports and images of dedicated liver or abdominal computed tomography scans before and serially after starting sorafenib. Response Evaluation Criteria In Solid Tumors criteria were used to assess objective responses to treatment and length of response when applicable. Clinical progression was noted when documented in clinic notes. OS was defined as the time from the first day on sorafenib until death from any cause or the last time the patient was known to be alive. TTP was defined as the time from the first day on sorafenib until radiologic or clinical progression. We censored those lost to follow-up or still on treatment and alive without progression.

Side Effects

HTN and hyperbilirubinemia were reported objectively and graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. Patients were divided into those who developed at least a grade 1 HTN while on sorafenib and those who did not. Proper evaluation of other side effects was not possible due to the retrospective nature of the study and may underrepresent the true incidence of side effects.

Statistical Methods

Categorical data were summarized as frequency counts and percentages. Quantitative data were summarized as means, standard deviations, medians, and ranges. Time to progression, OS, and duration of treatment were summarized using the method of Kaplan-Meier, and the log-rank test was used to compare these outcomes between patient groups. Data analysis was performed using SAS's JMP 8 statistical software (Cary, NC) and STATA (College Station, TX).

RESULTS

Between January 2007 and April 2010, we identified 51 patients with HCC who were prescribed sorafenib. Ten patients were excluded: 4 patients received OLT, 4 have received sorafenib as an adjuvant treatment after curative intent partial hepatectomy, and 2 had no evidence of taking sorafenib. One patient was lost to follow-up but had progressive disease while being followed; he is censored in survival analysis. Forty-one patients were included in the final analysis.

Demographics and Clinical Characteristics

Table 1 lists patients' characteristics at time of initiating sorafenib. Performance score data were occasionally missing. Male-to-female ratio was 6:1. Chronic viral hepatitis accounted for 67% of all cases. Eleven patients had no pathologic diagnosis, but all fulfilled diagnostic criteria according to American Association for the Study of Liver Diseases.[8] There were 25 (61%) patients with CP-A and 16 (39%) patients with CP-B.

Prior and Subsequent Therapy

Eighteen (44%) patients were started on sorafenib as the first therapeutic intervention after diagnosis; the rest received other localized interventions first. Eight (20%) patients received >1 local treatment modality before starting sorafenib.

TABLE 2. Retrospective Incidence of HTN and Hyperbilirubinemia With Sorafenib (CTCAE Version 3.0)

	All Patients (N = 41) (N [%])	Child-Pugh A (N = 25) (N [%])	Child-Pugh B (N = 16) (N [%])
Hypertension			
Grade 1	6 (15)	5 (20)	1 (6)
Grade 2	8 (20)	6 (24)	2 (13)
Grade 3	1 (2)	1 (4)	—
Hyperbilirubinemia			
Grade 1	6 (15)	5 (20)	1 (6)
Grade 2	8 (20)	4 (16)	4 (25)
Grade $\frac{3}{4}$	11 (27)	4 (16)	8 (50)

CTCAE indicates Common Terminology Criteria for Adverse Events; HTN, hypertension.

TABLE 3. Objective Best Response to Sorafenib

	CP Class		Hypertension		
Subgroup (N)	**A (25)**	**B (16)**	**Yes (15)**	**No (24)**	**All (41)**
PR (%)	2 (8)	—	2 (8)	—	2 (5)
SD (%)	11 (44)	5 (31)	7 (47)	8 (33)	16 (39)
PD (%)	9 (36)	3 (19)	5 (33)	6 (25)	12 (29)
CPD (%)	2 (8)	6 (38)	—	8 (33)	8 (20)
TTP (mo)	4	2	4	2.1	3.2
OS (mo)	8.4	3.2	18.2	4.5	6.2

CP indicates Child-Pugh; CPD, clinically progressive disease; DBP, diastolic blood pressure; N, number of patients; OS, overall survival; PD, progressive disease; PR, partial response; SD, stable disease; TTP, time to progression.

Eight patients received further localized treatment after sorafenib, and 13 (28%) received sorafenib as the only treatment for HCC. Chemoembolization was the most common localized therapy (19 procedures), followed by radioembolization (7 procedures). No patient received systemic chemotherapy before sorafenib; however, 1 patient received gemcitabine after progression on sorafenib.

Tolerance and Side Effects

Thirty-six (88%) patients were started on sorafenib 400 mg twice daily, whereas 5 (12%) started on 200 mg twice daily without intention to titrating up; 4 of them had CP-B. Toxicity led to treatment interruption in 10 (25%) patients (CP-A, 7; CP-B, 3) and dose reduction in 16 (39%) patients (CP-A, 10; CP-B, 6). Dose reduction was to a total daily dose of 400 mg in 9 patients and to 200 mg in 6 patients. Sorafenib was stopped due to radiologic progression in 16 (39%), clinical progression in 12 (29%), and toxicity in 7 patients (17%). At the time of analysis, 4 patients were still taking sorafenib (30, 31, 126, and 696 d) and 1 patient's status was unknown.

HTN data were available for 39 patients, and 2 patients did not have baseline blood pressure available for comparison. Fifteen patients had HTN while on sorafenib per CTCAE version 3.0 criteria; of those 6 had blood pressure >140/90 mm Hg at baseline and 13 were already taking antihypertensives. Median time to documented HTN was 30 days (range, 9 to 197). Sixty-one percent of those who had sorafenib >3 months had documented HTN per CTCAE guidelines. The Fisher exact test showed the difference in HTN between CP-A and CP-B to be statistically insignificant ($P = 0.1$). Although about 50% of those with CP-A had hyperbilirubinemia (mainly grade 1 to 2), almost all patients with CP-B liver cirrhosis developed some elevation in bilirubin, half of them had grade 3 to 4 toxicity. Table 2 lists the incidence of HTN and hyperbilirubinemia in those with CP-A and CP-B.

Efficacy

The median length of treatment with sorafenib was 77 days (range, 2 to 1029) and the mean was 190 ± 260 days

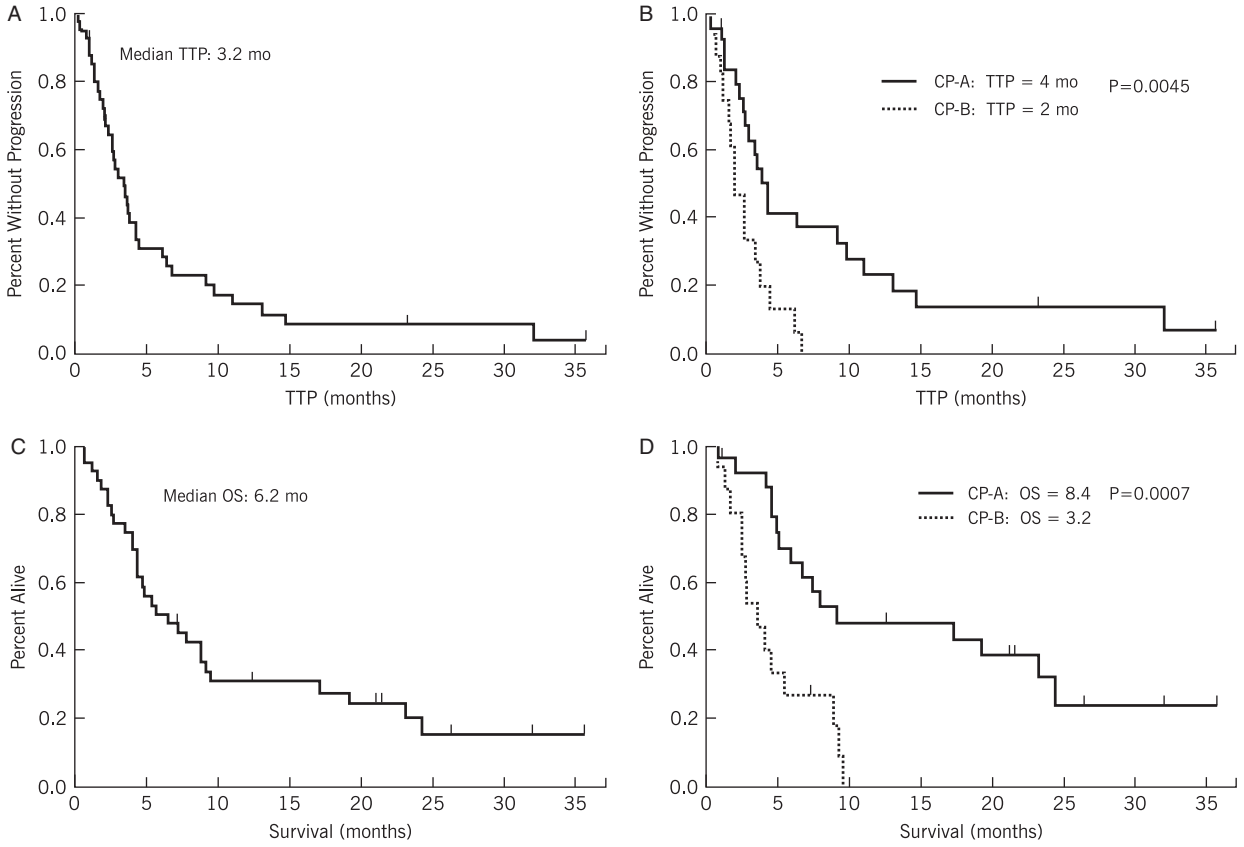

FIGURE 1. Time to progression (TTP) and overall survival (OS) Kaplan-Meier curves: A, TTP for all patients. B, TTP for patients with Child-Pugh class A (solid) and B (dotted). C, OS for all patients. D, OS for patients with Child-Pugh class A (solid) and B (dotted).

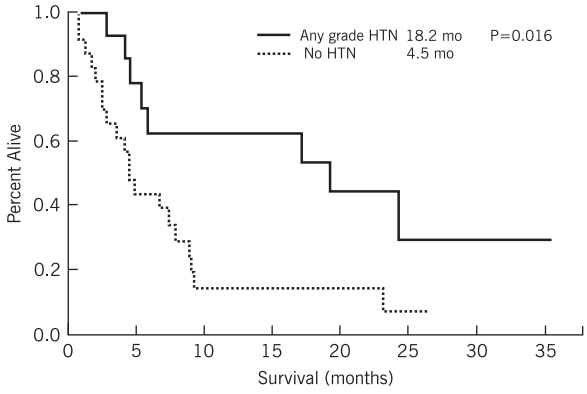

FIGURE 2. Overall survival for patient who had hypertension (HTN) while on sorafenib (solid) compared with those who did not (dotted).

[95% confidence interval (CI), 108-272]. CP-A patients had a median of 101.5 days (range, 3 to 1029) compared with 46 days (range, 2 to 200) in CP-B ($P=0.0015$). Three patients took sorafenib for >10 days (range, 2 to 8 d) but were included in an intention-to-treat analysis of objective response (Table 3).

Radiologic evaluation was feasible in 30 patients. Eight had clinical progression and no further radiologic evaluation, and 3 were still on sorafenib at time of data analysis without interim evaluation yet. Only 2 (5%) had an objective response that was evident on the second radiologic evaluation but not the first. One had liver mainly disease, whereas the other had distant disease after partial hepatectomy. Sixteen (39%) had stable disease upon initial evaluation. The efficacy of sorafenib (partial response and stable disease) in CP-A was 52% compared with 31% in CP-B. Median time from starting sorafenib to radiologic evaluation was 2.5 months (range, 1 to 7).

Median TTP for all patients was 3.2 months (95% CI, 2.2-3.8). For CP-A and CP-B, median TTP was 4 months (95% CI, 2.6-9.1) and 2 months (95% CI, 1.1-3.4), respectively ($P=0.0045$ by log-rank test) (Figs. 1A, B).

At the time of analysis, 10 patients were alive and 1 was lost to follow-up. Median OS for all patients was 6.2 months (95% CI, 4.4-8.9) with a 1-year survival of 27% (Fig. 1C). OS for patient with CP-A and CP-B was 8.4 months (95% CI, 4.9-23.2) and 3.2 months (95% CI, 2.4-4.5) and 1-year survival was 44% and 0%, respectively, which was statistically significant ($P=0.0007$ by log-rank test) (Fig. 2D). In other subgroup analyses, there was no difference in survival in older versus younger patients (≥ 60 vs. <60 y), AFP ≥ 400 versus <400 ng/mL, AFP response to treatment, sorafenib as a first or subsequent antitumor therapy, or viral versus nonviral etiology. We analyzed subgroup of CP-B patient and found no difference between those with a CP score of 7 versus 8 to 9 ($P=0.8$) or 7 to 8 versus 9 ($P=0.5$).

Those with any grade HTN during treatment (15 of 39 evaluable patients) lived longer than those without HTN during treatment with a median OS of 18.2 months (95% CI, 4.5-35.7) and 4.5 months (95% CI, 2.4-7.3), respectively ($P=0.0165$ by log-rank test). One-year survival was 62% versus 15%, respectively (Fig. 2). Median TTP was 4 months (95% CI, 3.4-13) for patient with documented HTN compared with 2.1 months (95% CI, 1.3-2.7). The median duration of treatment for those with HTN was 4.2 versus 1.6 months ($P=0.002$). Of note, only 3 of 15 patients with HTN had CP-B.

TABLE 4. Sorafenib Efficacy From Prospective Trials in Advanced HCC

Trial	Type	Subgroups (%)	Patient Arms	Treatment	PR (%)	SD (%)	PD (%)	TTP	OS	1-y OS
Cheng et al[9] (Asia-Pacific)	Phase III	CP-A (97), CP-B (3) HCV (8), HBV (73)	150 76	Sorafenib Placebo	3 1	54 27	NR	2.8 mo 1.4 mo $P=0.0005$	6.5 mo 4.2 mo $P=0.014$	NR
Yau et al[10] (Asian)	Phase II	CP-A (70), CP-B (25) HCV (6), HBV (90)	51	Sorafenib	8	18	74	3 mo (PFS)	5 mo CP-A: 5.5 mo CP-B/C: 5 mo	NR
Richly et al[11] (Germany)	Phase I	NR	18	Sorafenib/ doxorubicin	6	63	31	NR	NR	NR
Llovet et al[7] (multinational)	Phase III	CP-A (97), CP-B (3) HCV (28), HBV (18)	297 302	Sorafenib Placebo	2 1	71 67	NR	5.5 mo 2.8 mo $P<0.001$	10.7 mo 7.9 mo $P<0.001$	44% 33% $P=0.009$
Furuse et al[12] (Japan)	Phase I	CP-A (50), CP-B (50) HCV (74), HBV (11)	13 14	200 mg BID 400 mg BID	4	79	11	4.9 mo	15.6 mo	59%
Abou-Alfa et al[5] (US)	Phase II	CP-A (72), CP-B (28) HCV (48), HBV (16)	137	400 mg BID	2	34	35	4.2 mo	9.2 mo	NR
Strumberg et al[6] (Germany)	Phase I	NR	9	400 mg BID	11	44	11	NR	NR	NR

CP-A indicates Child-Pugh class A; CP-B, Child-Pugh class B; HBV, hepatitis B infection; HCV, hepatitis C infection; NR, not reported; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; TTP, time to progression.

TABLE 5. Sorafenib Efficacy From Retrospective Trials in Advanced HCC

Trial	Patients/Subgroups (%)	Patients (n)	PR (%)	SD (%)	PD (%)	TTP	OS
Estfan 2010 (This study) (US)	CP-A (61), CP-B (39) HCV (56), HBV (7)	41	5	39	29	All: 3.2 mo CP-A: 4 mo CP-B: 2 mo	All: 6.2 mo CP-A: 8.4 mo CP-B: 3.2 mo
Shim et al[13] (Korea)	CP-A (60), CP-B (40) HCV (7), HBV(79)	57	5	35	35	9.1 wk	NA
Pinter et al[14] (Austria)	CP-A (44), CP-B (39), CP-C (17) HCV/HBV (25)	59	2	24	54	2.8 mo	All: 6.5 mo CP-A: 8.3 mo CP-B: 4.3 mo CP-C: 1.5 mo
Worns et al[15] (Germany)	CP-A (44), CP-B (44), CP-C (12) HCV (21), HBV (15)	34	3	24	26	—	CP-A: 7.2 mo CP-B/C: 3.3 mo
Kim et al[16] (Korea)	Metastatic HCC, second line CP-A (83), CP-B (17) HCV (4), HBV (79)	24	—	58	NR	2.3 mo (PFS)	7.1 mo
Balsom et al[17] (US)	CP-A (50), CP-B (50) HCV (19), HBV (8)	26	NR	50	NR	5.4 mo	7.3 mo
Lee et al[18] ASCO abstract	CP-A (70), CP-B (30)	97	5	41	—	2.2 mo (PFS)	6.6 mo

CP-A indicates Child-Pugh class A; CP-B, Child-Pugh class B; CP-C, Child-Pugh class C; HBV, hepatitis B infection; HCC, hepatocellular carcinoma; HCV, hepatitis C infection; NR, not reported; OLT, orthotopic liver transplant; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; TTP, time to progression.

We performed a multivariable Cox regression analysis to include CP status and HTN. Both CP-A (hazard ratio = 0.32 [0.14 to 0.7], $P = 0.005$) and presence of HTN (hazard ratio = 0.43 [0.19 to 0.97], $P = 0.04$) were found to be independent predictors of survival.

DISCUSSION

The use of sorafenib is justified for advanced HCC patients with preserved liver function test based on early results from phase I and II trials and 2 recent large randomized trials (Table 4).[4,5,7,9–12] Less is known about efficacy in those with decompensated liver function.

Outcome data from our study seem to be consistent with those reported in other retrospective analyses in regard to TTP (range, 2.2 to 5.4 mo) and OS (range, 5.4 to 7.3 mo) but falls short of those reported in prospective phase III trials (Tables 4 and 5).

Major randomized trials have included mostly patients with CP-A, which makes interpretation difficult in CP-B.[7,9] In practice, patients with advanced HCC with CP-B liver cirrhosis are being prescribed sorafenib, as other options are usually lacking. Our data showed that as expected, outcome of patients with CP-B was worse compared with CP-A. An OS of 3.2 months in our CP-B patients is very similar to analyses by Worns et al and Pinter et al with an OS of 3.3 and 4.3 months, respectively.[14,15] Our study is one of few reports retrospectively evaluating single institution experience with sorafenib in advanced HCC in patients with CP-B liver cirrhosis (Table 5).[13–18] Single institution experience in CP-B patients are very important, as it is highly unlikely that a placebo-controlled randomized trial will be conducted using sorafenib in this subset of population.

Tolerance of sorafenib was similar in CP-A and CP-B patients in our study. Thirty-seven percent of those with CP-B required dose reduction during treatment compared with 40% in CP-A patients. In the phase II study conducted by Abou-Alfa toxicity profiles, discontinuation and dose reductions of sorafenib were similar for CP-A and CP-B patients (31% and 21%, respectively), despite shorter course of therapy for CP-B patients.[19] Previous studies showed no pharmacodynamic difference of sorafenib between patients with CP-A and CP-B liver cirrhosis in 2 different studies.[5,20] However, worsening of hepatic dysfunction such as hyperbilirubinemia was more commonly seen in CP-B patients. Another phase II trial by Yau et al[10] also found no significant toxicity differences between those with CP-A and CP-B/C.

HTN is a common toxicity of tyrosine-kinase inhibitors such as sunitinib, sorafenib, and axitinib or monoclonal antibodies against vascular endothelial growth factor such as bevacizumab. Several investigators studied the possible correlation between outcome and HTN.[21–24]

For example, Rini and colleagues evaluated patients with renal cell carcinoma on sunitinib. Systolic blood pressure ≥ 140 mm Hg and diastolic blood pressure ≥ 90 mm Hg were associated with significantly better outcomes compared with those with lower systolic blood pressure and diastolic blood pressure (median OS of 30.5 vs. 7.8 mo and 32.1 vs. 15 mo, respectively).[23] Dahlberg et al used CTCAE criteria to evaluate HTN in patient with lung cancer receiving bevacizumab in the Eastern Cooperative Oncology Group 4599 trial.[21] OS and progression-free survival were significantly better in the bevacizumab arm.

Therefore in our study, we also investigated HTN as a potential predictive marker in patients receiving sorafenib. Our findings are consistent with other studies indicating that there is a correlation between HTN and overall outcome in patients receiving sorafenib. To our knowledge, this is the first case series to address this issue in HCC. This supports the notion that HTN due to antiangiogenesis agents is a potential predictive marker. Our analysis is limited by blood pressure measurements at irregular intervals as opposed to serial measurements in prospective trials. Although multivariable analysis showed HTN to be an independent variable, the results might have been affected by the relatively small sample number. Another point is that the time range to documented

HTN is very wide, possibly leading to identifying those doing well long enough to develop HTN. A retrospective analysis of data from major randomized clinical trials could answer this observation in a better manner, given a larger number of patients and regular documentation of blood pressure reading.

Our study is also limited by a number of factors including its retrospective nature and inherent difficulties to collect accurate information about side effects (especially in regard to HTN), patient compliance, and quality-of-life data.

In conclusion, advanced HCC remains an entity with poor prognosis despite the recent addition of sorafenib especially in CP-B patients. Our study clearly demonstrates feasibility of using sorafenib in HCC patients with CP-B liver cirrhosis, albeit not without toxicity and need for dose reduction. The efficacy of the drug in this subset of population is unclear; therefore, one must use extreme caution when treating HCC in CP-B liver cirrhosis. HTN may serve as a potential predictive marker to sorafenib. We believe that retrospective analyses of well-conducted large randomized trials may potentially highlight the value of this observation.

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