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ORIGINAL ARTICLE

# Sorafenib for hepatocellular carcinoma according to Child-Pugh class of liver function

**Jeong Eun Kim · Baek-Yeol Ryoo · Min-Hee Ryu · Heung-Moon Chang · Dong Jin Suh · Han Chu Lee · Young-Suk Lim · Kang Mo Kim · Yoon-Koo Kang**

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**Abstract**
*Purpose* We compared the efficacy and safety of sorafenib in patients with Child-Pugh (CP) class B and CP class A.
*Methods* Clinical data from 267 patients with HCC who had been treated with sorafenib were reviewed. Patients were grouped according to CP score (5–6, 7, and 8–9), and their tumor response, tolerance, and survival were assessed.
*Results* Median patient age was 55 years, and 87.6% were men. Gender, HCC etiology, and extrahepatic metastasis did not differ according to CP score. Of the 225 evaluable patients, 4 achieved partial response and 121 achieved stable disease, making the disease control rate 46.8%. DCR was higher in patients with CP A than CP B score, but did not differ between those with CP scores of 7 and 8–9. The incidence rates of grade 3/4 toxicities did not differ according to CP score. Many patients with CP score 8–9 (26.3%) had to stop sorafenib due to cirrhosis-related complications. At a median follow-up of 15.6 months, the median time to progression and overall survival of all patients were 2.6 and 7.9 months, respectively. OS was greater in patients with CP score 5–6 than in patients with CP scores of 7 or 8–9.
*Conclusions* Sorafenib efficacy and survival outcomes were worse in patients with CP B function. Patients with a CP score of 7 had the same incidence of adverse events and cirrhosis-related complications as those with CP A liver function, suggesting that the former can be included in clinical trials of new agents.

**Keywords** Hepatocellular carcinoma · Sorafenib · Child-Pugh class

## Introduction

Sorafenib is a newly developed, multi-tyrosine kinase inhibitor that has demonstrated significant survival benefits in phase III trials of Asian (Asia–Pacific trial) and European and American (SHARP trial) patients with advanced HCC [2, 5]. These large-scale trials have established sorafenib as the new standard first-line treatment for patients with advanced HCC not indicated for curative approaches.

Although sorafenib is widely used to treat HCC patients with Child-Pugh (CP) B cirrhosis in practice, there are insufficient data on the safety and efficacy of sorafenib in these patients because all patients included in the two registration phase III trials had CP A liver function [2, 5]. Previous small retrospective analyses have shown that the efficacy of sorafenib was worse in patients with CP B cirrhosis, with shorter time to progression (TTP) and overall survival (OS) [4, 6, 7]. However, the incidence of severe toxicities and events related to complications of advanced liver cirrhosis were not compared in patients with CP A and B liver function. Moreover, it has not been determined whether poor survival is related to liver cirrhosis or disease progression.

J. E. Kim and B.-Y. Ryoo contributed equally to this work.

J. E. Kim · B.-Y. Ryoo · M.-H. Ryu · H.-M. Chang · Y.-K. Kang (✉)
Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, 86 Asanbyeongwon-gil, Songpa-gu, Seoul 138-736, Korea
e-mail: ykkang@amc.seoul.kr

D. J. Suh · H. C. Lee · Y.-S. Lim · K. M. Kim
Department of Gastroenterology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Patients classified as having CP B cirrhosis have CP scores ranging from 7 to 9. Thus, comparisons of the efficacy and toxicity of sorafenib according to CP score are needed to determine whether patients with early CP B (CP score 7) have outcomes similar to those of patients with CP A cirrhosis. We therefore evaluated and compared the efficacy and safety of sorafenib according to CP score in patients with HCC.

## Patients and methods

### Patients

We identified a total of 267 patients with HCC, diagnosed according to AASLD criteria [1], who were treated with sorafenib as first-line systemic chemotherapy between January 2006 and June 2010 at the Asan Medical Center. Of these, 68 patients (25.5%) had CP B liver cirrhosis, 30 (11.2%) with CP score 7, and 38 (14.2%) with CP score 8–9.

### Treatment schedule and toxicity and response assessment

Most patients received the standard dose of sorafenib, 400 mg twice daily (800 mg/day), on a continuous dosing schedule. However, 24 patients, 10 with CP B liver cirrhosis, 9 with severe neutropenia and/or thrombocytopenia, and 5 with elevated alanine transaminase (ALT), received reduced doses of sorafenib (400 or 600 mg/day). In addition, 25 patients with risk factors for adverse events, including 6 with advanced liver cirrhosis, 5 with postliver transplantation (LT) status, and 14 with neutropenia and/or thrombocytopenia, were treated initially with 400 mg/day sorafenib (200 mg twice daily or 400 mg once daily) and ramped up to the standard dose according to each patient's tolerance.

Sorafenib doses were reduced or interrupted in patients who experienced drug-related grade 2–4 toxicities, or at the discretion of the treating physician, until recovery to grade 1 or less. Treatment was continued until disease progression or intolerable toxicities, or until a patient refused further treatment. Toxicities were initially assessed every 2 weeks and subsequently assessed every 4 weeks using the National Cancer Institute Common Terminology Criteria for Adverse Events Versions 3.0 (for patients treated between January 2006 and May 2009) and 4.0 (for patients treated between June 2009 and June 2010). Tumor response was assessed every 6–8 weeks according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria [3].

### Statistical analysis

Continuous variables were summarized as medians and ranges, and categorical variables as percentages. Between-group comparisons of parameters were performed using the Mann–Whitney U test for continuous variables and the chi-square test or Fisher's exact test for categorical variables. TTP and OS, calculated from the start of sorafenib treated until objective disease progression and death, respectively, were estimated using the Kaplan–Meier method and compared using the log-rank test. A Cox proportional hazards model was used to determine factors independently prognostic for TTP and OS, after adjustment for confounding factors. All reported $P$ values are two-sided, with $P$ values $< 0.05$ considered significant.

## Results

### Patient characteristics

Patient characteristics are described in Table 1. Most (87.6%) were men, and the median patient age was 55 years. Gender, HCC etiology, and extrahepatic metastasis did not differ significantly among patients with CP scores of 5–6, 7, and 8–9. Portal vein invasion by HCC was more frequent in patients with CP A liver function (72.9% vs. 40.0% vs. 44.7%, $P < 0.001$). Most patients had been treated with one or more other treatment approaches prior to treatment with sorafenib. Surgical methods, including hepatectomy, liver transplantation, and metastasectomy, were significantly more frequent in patients with CP scores of 5–6 than in those with CP scores of 7 and 8–9 (49.7% vs. 30.0% vs. 21.1%, $P < 0.001$).

### Treatment outcomes

Of the 225 evaluable patients, 4 (1.5%) achieved partial response (PR) and 121 (45.3%) achieved stable disease (SD), making the disease control rate (DCR) 46.8% (95% confidence interval [CI], 40.9–52.8%; Table 2). The DCR was significantly higher in patients with CP A than CP B liver function (53.3% vs. 27.9%, $P < 0.001$), but did not differ significantly between patients with CP scores of 7 (26.7%; 95% CI, 14.2–44.5%) and 8–9 (28.9%; 95% CI, 17.0–44.8%). Among patients with CP B liver function, however, the proportion without evaluable disease was lower for those with CP score 7 than those with CP score 8–9 (20.0% vs. 34.2%).

### Adverse events and reasons for sorafenib discontinuation

As shown in Table 3, hand–foot skin reaction (HFSR), diarrhea, and skin rash were common toxicities in all patients. Grade 3/4 HFSR was observed in 67 patients (25.1%) and Grade 3/4 diarrhea in 15 (5.6%).

**Table 1** Patient characteristics ($N = 267$)

| | All patients | CP A score 5–6 ($N = 199$) | CP B score 7 ($N = 30$) | CP B score 8–9 ($N = 38$) | *P* value |
|---|---|---|---|---|---|
| Age (years) | | | | | |
| Median (range) | 55 (20–82) | 55 (20–82) | 58 (30–76) | 53 (34–73) | 0.030 |
| Gender | | | | | |
| Male | 234 (87.6%) | 174 (87.4%) | 28 (93.3%) | 32 (84.2%) | 0.521 |
| Female | 33 (12.4%) | 25 (12.6%) | 2 (6.7%) | 6 (15.8%) | |
| Etiology of liver disease | | | | | |
| HBV | 235 (88.0%) | 175 (87.9%) | 27 (90.0%) | 33 (86.8%) | 0.585 |
| HCV | 11 (4.1%) | 8 (4.0%) | 1 (3.3%) | 2 (5.3%) | |
| Alcohol | 8 (3.0%) | 4 (2.0%) | 2 (6.7%) | 2 (5.3%) | |
| Others | 13 (4.9%) | 12 (6.0%) | 0 (0.0%) | 1 (22.6%) | |
| Portal vein invasion | | | | | |
| Present | 174 (65.2%) | 145 (72.9%) | 12 (40.0%) | 17 (44.7%) | <0.001 |
| Absent | 93 (34.8%) | 564 (27.1%) | 18 (60.0%) | 21 (55.3%) | |
| Extrahepatic metastasis | | | | | |
| No metastasis | 22 (8.2%) | 16 (8.0%) | 2 (6.7%) | 4 (10.5%) | 0.811 |
| Metastasis | | | | | |
| Lung | 177 (66.3%) | 132 (72.1%) | 21 (75.0%) | 24 (70.6%) | 0.700 |
| LN | 38 (14.2%) | 27 (14.8%) | 4(14.3%) | 7(20.6%) | |
| Bone | 14 (5.2%) | 13 (7.1%) | 0 (0.0%) | 1 (2.9%) | |
| Others* | 16 (6.0%) | 11 (6.0%) | 3 (10.7%) | 2 (5.9%) | |
| Previous treatment | | | | | |
| Surgery | 116 (43.4%) | 99 (49.7%) | 9 (30.0%) | 8 (21.1%) | 0.001 |
| TACE or TACI | 206 (77.2%) | 155 (77.9%) | 24 (80.0%) | 27 (71.1%) | 0.631 |
| RFA | 49 (18.4%) | 36 (18.1%) | 5 (16.7%) | 8 (21.1%) | 0.899 |
| RT | 95 (35.6%) | 71 (35.7%) | 11 (36.7%) | 13 (34.2%) | 0.977 |

*HBV* hepatitis B virus, *HCV* hepatitis C virus, *TACE* transcatheter arterial chemoembolization, *TACI* transcatheter chemoinfusion, *RFA* radiofrequency ablation

* Adrenal gland, brain, spleen, ovary, pleura

**Table 2** Response to sorafenib treatment ($N = 267$)

| | All patients | CP A score 5–6 ($N = 199$) | CP B score 7 ($N = 30$) | CP B score 8–9 ($N = 38$) | *P* value |
|---|---|---|---|---|---|
| CR | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | |
| PR | 4 (1.5%) | 2 (1.0%) | 1 (3.3%) | 1 (2.6%) | |
| SD | 121 (45.3%) | 104 (52.3%) | 7 (23.3%) | 10 (26.3%) | |
| PD | 100 (37.5%) | 70 (35.2%) | 16 (53.3%) | 14 (36.8%) | |
| Not evaluable | 42 (15.7%) | 23 (11.6%) | 6 (20.0%) | 13 (34.2%) | |
| DCR (95% CI) | 46.8% (40.9–52.8%) | 53.3% (46.3–60.1%) | 26.7% (14.2–44.5%) | 28.9% (17.0–44.8%) | <0.001 |

*CP* Child-Pugh, *CR* complete response, *PR* partial response, *SD* stable disease, *DCR* disease control rate, *PD* progressive disease, *CI* confidence interval

No statistically significant differences were observed in the incidence rates of grade 3/4 toxicities according to CP score.

The median durations of sorafenib treatment were 75 days (range, 4–686 days) in patients with CP score 5–6, 48 days (range, 3–154 days) in patients with CP score 7, and 38 days (range, 7–582 days) in patients with CP score 8–9 ($P = 0.002$). Of the 267 included patients, 172 (64.4%) discontinued sorafenib because of disease progression, 39 (14.6%) because of adverse events, 11 (4.1%) because of complications of liver cirrhosis, and 19 at each patient's discretion; in addition, 13 patients (4.9%) were lost to follow up (Table 4). Only one patient with CP score 5–6 and none with CP score 7 discontinued sorafenib due to cirrhosis-related complications, compared with 10 patients (26.3%) with CP score 8–9. Of the latter, 4 discontinued sorafenib because of uncontrolled ascites or spontaneous bacterial peritonitis

**Table 3** Grade 3/4 adverse events of sorafenib ($N = 267$)

| | All patients | CP A score 5–6 ($N = 199$) | CP B score 7 ($N = 30$) | CP B score 8–9 ($N = 38$) | *P* value |
|---|---|---|---|---|---|
| HFSR | 67 (25.1%) | 54 (27.1%) | 7 (23.3%) | 6 (15.8%) | 0.613 |
| Diarrhea | 15 (5.6%) | 13 (6.5%) | 1 (3.3%) | 1 (2.6%) | 0.298 |
| Skin rash | 12 (4.5%) | 10 (5.0%) | 1 (3.3%) | 1 (2.6%) | 0.944 |
| Fatigue | 4 (1.5%) | 2 (1.0%) | 1 (3.3%) | 1 (2.6%) | 0.485 |
| Hypertension | 2 (0.7%) | 2 (1.0%) | 0 (0.0%) | 0 (0.0%) | 0.831 |
| Elevated ALT | 4 (1.5%) | 4 (2.0%) | 0 (0.0%) | 0 (0.0%) | 0.551 |
| Neutropenia/thrombocytopenia | 8 (3.0%) | 8 (4.0%) | 0 (0.0%) | 0 (0.0%) | 0.842 |
| Alopecia | 1 (0.4%) | 1 (0.5%) | 0 (0.0%) | 0 (0.0%) | 0.876 |
| Abdominal pain | 6 (2.2%) | 4 (2.0%) | 1 (3.3%) | 1 (2.6%) | 0.783 |
| Nausea/vomiting | 7 (2.6%) | 5 (2.5%) | 1 (3.3%) | 1 (2.6%) | 0.745 |

*HFSR* hand–foot skin reaction, *ALT* alanine transaminase

**Table 4** Reason for sorafenib discontinuation ($N = 267$)

| | All patients | CP A score 5–6 ($N = 199$) | CP B score 7 ($N = 30$) | CP B score 8–9 ($N = 38$) |
|---|---|---|---|---|
| Progression | 172 (64.4%) | 133 (66.8%) | 21 (70.0%) | 19 (50.0%) |
| Adverse event | 37 (13.9%) | 29 (14.7%) | 4 (13.3%) | 4 (10.5%) |
| HFSR | 9 | 8 | 1 | 0 |
| Diarrhea | 6 | 6 | 0 | 0 |
| Elevated ALT | 7 | 6 | 1 | 0 |
| Abdominal pain | 3 | 2 | 0 | 1 |
| Neutropenia and/or thrombocytopenia | 3 | 2 | 0 | 1 |
| Nausea/vomiting | 2 | 1 | 1 | 0 |
| Uncontrolled hypertension | 2 | 0 | 0 | 1 |
| Fatigue | 2 | 2 | 0 | 0 |
| Infection | 2 | 1 | 0 | 1 |
| Skin rash | 1 | 1 | 1 | 0 |
| Cirrhosis-related complication | 11 (4.1%) | 1 (0.5%) | 0 (0.0%) | 10 (26.4%) |
| Uncontrolled ascites or SBP | 5 | 1 | 0 | 4 |
| Variceal bleeding | 3 | 0 | 0 | 3 |
| Hepatic encephalopathy | 3 | 0 | 0 | 3 |
| Patient's own will | 18 (6.7%) | 13 (6.5%) | 3 (10.0%) | 1 (2.5%) |
| Follow-up loss | 13 (4.9%) | 9 (4.5%) | 2 (6.7%) | 2 (5.3%) |
| On treatment | 16 (6.0%) | 14 (7.0%) | 0 (0.0%) | 2 (5.3%) |

*CP* Child-Pugh, *HFSR* hand–foot skin reaction, *ALT* alanine transaminase, *SBP* spontaneous bacterial peritonitis

(SBP), 3 because of variceal bleeding, and 3 because of hepatic encephalopathy.

### Survival analysis and prognostic factors

During a median follow-up duration of 15.6 months (range; 0.5–40.4 months), the median TTP was 2.6 months (95% CI, 2.4–2.8 months) and the median OS was 7.9 months (95% CI, 6.5–9.3 months) (Fig. 1a, b). Both OS and TTP were significantly longer in patients with CP score 5–6 than in those with CP scores of 7 or 8–9, but there were no differences in the latter two subgroups (Fig. 2a, b).

## Discussion

Our analysis of sorafenib treatment according to liver function showed that our patients with CP A cirrhosis had similar DCR (53.3%) and median TTP (2.8 months) as patients in the Asia–Pacific trial [2], whereas patients with CP B cirrhosis had lower DCR (27.9%) and TTP (1.8 months).

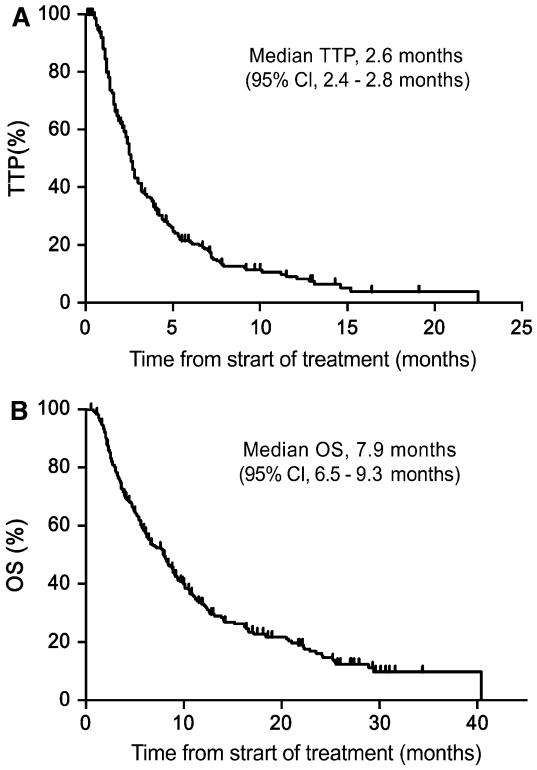


**Fig. 1** **a** Time to progression (TTP) of all patients. **b** Overall survival (OS) of all patients

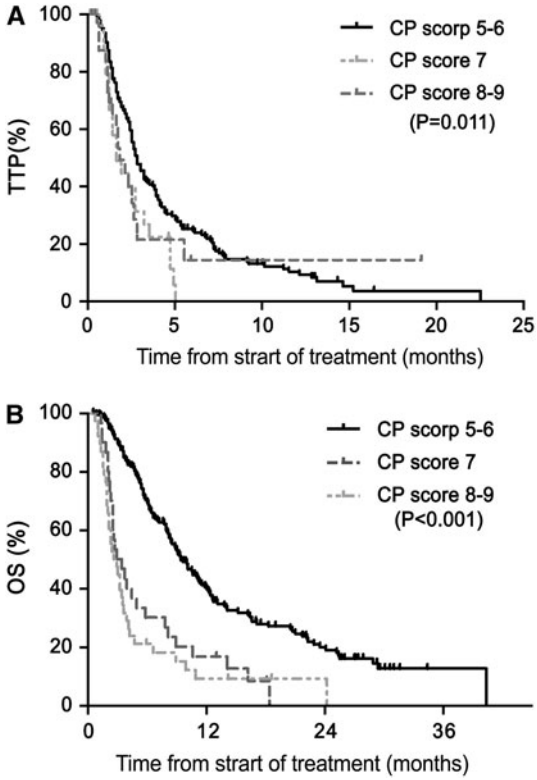


**Fig. 2** **a** Time to progression (TTP) according to Child-Pugh (CP) score. **b** Overall survival (OS) according to Child-Pugh (CP) score

Detailed comparisons of outcomes among CP B patients (score 7 vs. 8–9) showed no differences. In contrast, when we analyzed reasons for sorafenib discontinuation according to CP score, we found that a considerable number of patients with CP score 8–9, but none with CP score 7, experienced severe cirrhosis-related complications requiring interruption of treatment. These findings indicate that caution should be exercised in treating patients with CP score $\geq 8$ with sorafenib, due to the greater risks of cirrhosis-related complications rather than poorer efficacy.

Although studies have shown poorer survival in patients with CP B liver function [4, 6], others have shown no differences in survival relative to liver function [7]. Our results, showing that DCR and TTP were reduced, but that the incidence of adverse events and cirrhosis-related complications leading to sorafenib discontinuation was not altered, in CP B patients, even those with CP scores of 7, suggest that CP B liver function itself may be a marker of poor response to treatment with sorafenib. The incidence of sorafenib discontinuations due to cirrhosis-related complications was not described in detail in previous reports. In the Asia–Pacific trial [2], however, only four patients each (2.7%) discontinued sorafenib due to upper gastrointestinal hemorrhage and ascites, suggesting that the incidence of severe cirrhosis-related complications interrupting sorafenib treatment is low in patients with CP A liver function. We also observed that cirrhosis-related complications were a very rare cause of sorafenib discontinuation in patients with early CP B (CP score 7) as well as in patients with CP A liver function. However, 26.3% of patients with advanced liver cirrhosis (CP score 8–9) required sorafenib discontinuation because of cirrhosis-related complications. Thus, regardless of the lower efficacy of sorafenib in patients with advanced liver cirrhosis, the higher incidence of cirrhosis-related complications may be another limitation for their treatment with sorafenib.

Although patients with CP score 7 had a low incidence of adverse events and cirrhosis-related complication, their outcomes were poorer than in patients with lower CP scores. Thus, the poorer outcome in the former may be related to the limited efficacy of sorafenib itself in these patients. Thus, clinical trials with new agents, especially those challenging sorafenib, can include patients with CP score 7.

Our analysis represents a new approach, assessing sorafenib efficacy and safety relative to CP liver function, including comparisons of patients with CP scores of 7 and 8–9. This analysis enabled investigation of whether sorafenib can be a standard treatment in patients with advanced liver cirrhosis, who were not included in previous trials.

In conclusion, we have shown that sorafenib efficacy and survival outcomes were worse in patients with CP B than CP A liver function and that the incidence of

cirrhosis-related complications interrupting sorafenib treatment was higher in patients with CP scores $\geq 8$. Therefore, new therapeutic approaches are warranted for HCC patients with CP B liver function. Patients with a CP score of 7 can be included in clinical trials of new agents challenging sorafenib.

**Conflict of interest** None.

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