Original Paper

Novel Pretreatment Scoring Incorporating C-reactive Protein to Predict Overall Survival in Advanced Hepatocellular Carcinoma with Sorafenib Treatment

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Key Words

Hepatocellular carcinoma · Prognostic prediction · Systemic chemotherapy

Abstract

Objectives: This study aimed to build a prediction score of prognosis for patients with advanced hepatocellular carcinoma (HCC) after sorafenib treatment. **Methods:** A total of 165 patients with advanced HCC who were treated with sorafenib were analyzed. Readily available baseline factors were used to establish a scoring system for the prediction of survival. **Results:** The median survival time (MST) was 14.2 months. The independent prognostic factors were C-reactive protein (CRP) <1.0 mg/dL [hazard ratio (HR) =0.51], albumin >3.5 g/dL (HR =0.55), alpha-fetoprotein <200 ng/mL (HR =0.45), and a lack of major vascular invasion (HR =0.39). Each of these factors had a score of 1, and after classifying the patients into five groups, the total scores ranged from 0 to 4. Higher scores were linked to significantly longer survival ($p<0.0001$). Twenty-nine patients (17.6%) with a score of 4 had a MST as long as 36.5 months, whereas MST was as short as 2.4 and 3.7 months for seven (4.2%) and 22 (13.3%) patients with scores of 0 and 1, respectively. **Conclusions:** A novel prognostic scoring sys-

tem, which includes the CRP level, has the ability to stratify the prognosis of patients with advanced stage HCC after treatment with sorafenib.

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Introduction

Hepatocellular carcinoma (HCC) is the third most common cause of cancer-related death, with an age-adjusted worldwide incidence of 16 cases per 100,000 [1, 2]. Treating advanced HCC that is not amenable to surgery (liver resection or transplantation), locoregional therapy (radiofrequency ablation), or transcatheter arterial chemoembolization (TACE) remains a challenge in clinical practice. However, the Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) trial and the Asia-Pacific trial demonstrated the efficacy of sorafenib for unresectable advanced HCC, although the objective response rate was not optimal in both trials, and the survival benefit in clinical practice was limited [3–6]. Thus, because only a limited population can benefit from sorafenib therapy, there is an urgent need for pretreatment prediction of the response or prognosis. Several studies have reported prognostic factors for patients with unresectable HCC treated by sorafenib [7–12]. However, an adequate consensus on the prognostic factors has not been sufficiently established.

Recently, several studies have shown that a systemic inflammatory response is associated with a poor outcome in patients with many types of cancer [13]. Even in HCC, C-reactive protein (CRP) is one of the most important prognostic factors. Hashimoto et al. reported that preoperative CRP >1.0 mg/dL was associated with a poor prognosis and a high recurrence rate in operable patients with HCC [14]. Nagaoka et al. showed that patients with HCC and a high sensitivity CRP level ≥ 0.3 mg/dL had a poor prognosis [15]. Thereafter, CRP has been reported to be a useful prognostic factor in patients with HCC independent of treatment such as resection, orthotopic liver transplantation or transarterial approaches e.g. TACE [16–31]. In addition, Morimoto reported that the Glasgow Prognostic Score (including CRP and albumin) has significant prognostic value in patients undergoing sorafenib treatment for advanced HCC [32]. These findings encouraged us to establish a novel pretreatment prognostic scoring system for stratifying patients undergoing sorafenib treatment for advanced HCC, by using simple and readily available factors including inflammation, tumor factors and liver function.

Materials and Methods

Patients

This retrospective cohort study enrolled 165 consecutive patients with advanced inoperable HCC who had been treated with sorafenib at the Musashino Red Cross Hospital between December 2009 and October 2014, inclusive. The diagnosis of HCC was based on histology or characteristic radiological findings, such as typical arterial enhancement of the tumor followed by a washout pattern in the portal venous phase or the equilibrium phase according to dynamic spiral (CT) imaging or contrast-enhanced magnetic resonance imaging (MRI), in accordance with the guidelines of the American Association for the Study of Liver Diseases [33]. At enrollment, all patients had metastatic or locally advanced HCC, which was unresectable, and they were classified as stage B or C of the Barcelona Clinic Liver Cancer (BCLC) staging system. Patients were excluded with a clinically evident infection or those with a performance status of 3 or 4 according to the Eastern Cooperative Oncology Group classification [34]. This study was approved by the institutional ethical board in accordance with the Declaration of Helsinki.

Sorafenib Treatment

The initial daily dose of sorafenib was 800 mg in 82 patients, 400 mg in 70 patients and 200 mg in 13 patients. The lower initial doses were allowed for patients who had the following factors: advanced age (≥ 80 years), gastrointestinal varices with a risk of bleeding, low body weight (< 50 kg), and a poor performance status (≥ 2). Multiphase-multidetector CT imaging was performed before and one month after commencing sorafenib and every three months thereafter. Radiological responses to therapy were evaluated according to the modified Response Evaluation Criteria In Solid Tumors. In all patients, serial measurements of blood samples were performed before and monthly after receiving sorafenib treatment. Sorafenib was discontinued, and other palliative treatments or best supportive care was provided in cases of progressive disease or intolerable adverse events.

Survival Analysis

The endpoint of the current study was overall survival (OS). OS was calculated from the initial date of sorafenib treatment until death from any cause or until the last follow-up. The aim of the present study was to identify clinically useful factors that could predict OS before starting sorafenib treatment. Therefore, we analyzed factors that are simple and readily available in routine clinical practice, such as the clinical background of the patients, baseline biochemical data, and radiological findings related to tumors. The cut-off value for CRP was set at 1.00 mg/dL according to previous studies [14, 15, 17–22, 24–26, 28, 29], and we assigned patients with a serum CRP level ≥ 1.0 mg/dL to the high-CRP group and those with < 1.0 mg/dL to the low-CRP group.

Statistical Analysis

Categorical variables were analyzed using Fisher's exact test, and continuous variables were compared using an unpaired Student's *t*-test. *P* values < 0.05 was considered significant. OS was evaluated based on the Kaplan–Meier curve, and differences between the groups were assessed using the log-rank test. A Cox proportional hazards model was used to determine the factors associated with OS. All of the statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 18 (SPSS Inc., Chicago, IL, USA).

Results

Patient Characteristics

The patient characteristics are listed in table 1. Thirty-three patients received sorafenib as initial therapy for HCC. Forty-nine patients had evidence of extrahepatic metastases, and 29 had major vascular invasion. No patient was lost to follow-up in the present study. The median pretreatment serum CRP level was 0.25 mg/dL, with a range of 0.02–11.9 mg/dL, and 45 (27.3%) patients had a serum CRP level ≥ 1.0 mg/dL (high-CRP group). The high-CRP group mainly comprised males, and they had a higher body mass index (BMI), lower serum albumin, and higher des-r-carboxyprothrombin (DCP) compared to individuals in the low-CRP group (table 2).

Factors Associated with OS

The median survival time (MST) was 14.2 ± 0.65 months among all 165 patients enrolled in the study. The prognostic factors associated with OS were assessed in univariate and multivariate analyses. According to the univariate analysis of baseline factors, higher albumin ($p=0.0014$), lower CRP ($p=0.0067$), lower alpha-fetoprotein (AFP) (< 0.0001), lower DCP ($p=0.0084$), and a lack of major vascular invasion ($p<0.0001$) were associated with better OS (table 3).

The overall MST in the low-CRP group was significantly longer than that in the high-CRP group (15.7 ± 2.6 vs. 6.8 ± 1.1 months, $p=0.0067$) (fig. 1a). Similarly, the overall MST in patients with AFP < 200 ng/mL was significantly longer than those with AFP ≥ 200 ng/mL (24.1 ± 9.4 vs. 8.0 ± 1.5 months, $p<0.0001$) (fig. 1b). After stratification by AFP, MST was longer in the low-CRP group ($n=58$) than that in the high-CRP group ($n=20$) (figs. 1c and 1d). The dif-

Table 1. Patient characteristics

Variable	n=165
Age (years)	70.4 ± 10
Male n (%)	125 (76)
Height (cm)	161.5 ± 8.9
Body weight (kg)	60.2 ± 12
BMI (kg/m ²)	23 ± 3.3
Major vascular invasion n (%)	29 (18)
Distant metastases n (%)	49 (30)
Initial dose of sorafenib 200/400/800 (mg)	13/70/82
Child-Pugh score (5/6/7/8)	77/75/12/1
Prothrombin time (%)	89.9 ± 17
Albumin (g/dL)	3.5 ± 0.5
Total bilirubin (mg/dL)	0.9 ± 0.5
CRP (mg/dL)	0.25 (0.02–11.4)
AFP (ng/mL)	308 (2–98440)
AFP-L3 (%)	30.2 ± 27
DCP (mAU/mL)	358 (11–2160000)

AFP-L3=lectin lens culinaris agglutinin-bound fraction of AFP; AU=arbitrary unit.

Table 2. Comparison of the high-CRP group and low-CRP group

	High CRP group n=45	Low CRP group n=120	p-value
Age	68.7 ± 11.5	71.1 ± 9.4	0.171
Gender male/female	40/5	85/35	0.015
Height (cm)	163.9 ± 8.0	160.5 ± 9.1	0.030
Body weight (kg)	65.1 ± 12.3	58.3 ± 11.0	0.001
BMI (kg/m ²)	24.2 ± 3.6	22.5 ± 3.1	0.004
Etiology (HBV or HCV/NBNC)	15/30	28/92	0.485
Child-Pugh score (5/6/7/8)	17/21/6/1	60/54/6/0	0.077
Prothrombin time (%)	90.4 ± 20.3	89.7 ± 16.2	0.911
Albumin (g/dL)	3.3 ± 0.5	3.6 ± 0.5	0.001
Total bilirubin (mg/dL)	1.0 ± 0.6	0.9 ± 0.5	0.376
Major vascular invasion n (%)	12 (26.7)	17 (14.2)	0.069
Distant metastasis n (%)	16 (35.6)	33 (27.5)	0.340
AFP (ng/mL)	484.0 (2.3–70000)	266.0 (2–98440)	0.382
DCP (mAU/mL)	694.0 (12–2160000)	237.0 (11–305000)	0.008
Sorafenib dose (200/400/800 mg)	6/19/20	7/51/62	0.127
Sorafenib treatment duration (days)	184.0 (5–1622)	238.7 (5–1755)	0.312

HBV=hepatitis B virus; HCV=hepatitis C virus; NBNC=non-B non-C.

ference was statistically significant among patients with AFP <200 ng/mL (MST 30.7 vs. 14.1 months, p=0.03) and marginally significant among patients with AFP ≥200 ng/mL (MST 9.2 vs. 3.8 months, p=0.057). Similarly, MST was longer in the low-CRP group than that in the high-CRP group after stratification by albumin (p=0.0014 for patients with albumin ≤3.5 g/

Table 3. Factors associated with OS after sorafenib administration according to univariate and multivariate analyses

Variable	Univariate			Multivariate		
	p-value	HR	95% CI	p-value	HR	95% CI
Albumin >3.5 g/dL	0.0014	0.53	0.36–0.78	0.0032	0.55	0.37–0.82
Major vascular invasion (–)	<0.0001	0.28	0.18–0.45	0.0003	0.39	0.23–0.65
AFP <200 ng/mL	<0.0001	0.58	0.39–0.87	0.0002	0.45	0.3–0.68
DCP <200 mAU/mL	0.0084	0.58	0.39–0.86	0.12	0.73	0.49–1.09
CRP <1.0 mg/dL	0.0067	0.58	0.39–0.87	0.0014	0.51	0.34–0.77

95% CI=95% confidence interval.

dL and $p=0.745$ for patients with albumin >3.5 g/dL) or major vascular invasion ($p=0.0097$ for patients with major vascular invasion and $p=0.205$ for patients without major vascular invasion).

According to the multivariate analysis, CRP <1.0 mg/dL [hazard ratio (HR) =0.51, $p=0.0014$], albumin >3.5 g/dL (HR =0.55, $p=0.0032$), AFP <200 ng/mL (HR =0.45, $p=0.0002$), and lack of major vascular invasion (HR =0.39, $p=0.0003$) were identified as independent factors associated with OS (table 3).

Prognostic Scoring System Based on Simple and Readily Available Baseline Factors

We developed a prognostic scoring system based on the independent factors, where each of the following was scored as 1 and the total score was calculated: CRP <1.0 mg/dL, albumin >3.5 g/dL, AFP <200 ng/mL, and lack of major vascular invasion by CT or MRI. The score has been named the Baseline C-reactive protein Prognostic (BCP) score. Thus, the patients were classified into five groups with scores of between 0–4. Patients with higher scores had a significantly longer OS ($p<0.0001$) (fig. 2). Fifty-nine patients (35.8%) had prognostic scores of 3, and their MST was 19.4 months, which was longer than the overall MST of 14.2 months in all 165 patients. In particular, 29 patients (17.6%) had prognostic scores of 4, and their MST was as long as 36.5 months (table 4). In contrast, seven (4.2%) and 22 (13.3%) patients had prognostic scores of 0 and 1, and their MSTs were as short as 2.4 and 3.7 months, respectively (table 4). Thus, the prognosis of patients with advanced stage HCC treated by sorafenib was well stratified according to the BCP scoring system. To evaluate whether there was added benefit of combining the BCP score with the Cancer of the Liver Italian Program (CLIP) score, patients were stratified by the CLIP score and then further subdivided by the BCP score. Among patients with a CLIP score of 2, those with a BCP score of 3 or 4 had significantly better OS compared to those with a BCP score of 1 or 2 (MST 6.2 vs 19.4 months, $p=0.0002$, fig. 3). Among patients with a CLIP score of 3, those with a BCP score of 2 or 3 had a better OS compared to those with a BCP score of 0 or 1, which was of borderline significance ($p=0.057$, fig. 4).

Discussion

In the present study, we demonstrated that a lower pretreatment CRP level is associated with a more favorable prognosis after sorafenib treatment of advanced unresectable HCC, independent of well-characterized prognostic factors such as higher albumin concentration, lower AFP, and the absence of major vascular invasion. We showed that a novel prognostic scoring system based on these simple and readily available factors could stratify patients into

Fig. 1. OS of patients with advanced stage HCC treated with sorafenib stratified by baseline AFP and C-reactive protein (CRP). The Kaplan–Meier curve shows the OS stratified by (a) CRP [<1.0 vs. ≥ 1.0 mg/dL; MST = 15.7 vs. 6.8 months ($p=0.0067$)], (b) AFP [<200 vs. ≥ 200 ng/mL; MST = 24.1 vs. 8.0 months ($p<0.0001$)], (c) CRP [<1.0 vs. ≥ 1.0 mg/dL; MST = 30.7 vs. 14.2 months ($p=0.033$)] in the subgroup of patients with AFP <200 ng/mL, and (d) CRP [<1.0 vs. ≥ 1.0 mg/dL; MST = 9.2 vs. 3.8 months ($p=0.057$)] in the subgroup of patients with AFP ≥ 200 ng/mL.

subgroups with MSTs ranging from 2.4 to 36.5 months. Using this system, we could identify around 20% of patients with a MST longer than three years and another 20% of patients with an expected MST of only a few months. We consider that this scoring system may be useful in clinical decision making.

The serum CRP level has been reported to be a useful prognostic factor in patients with HCC who undergo surgical resection [14, 18–20, 28], liver transplantation [17, 21], multiple therapies [15, 22], and TACE [25, 26]. In patients with HCC BCLC stage-B, the selection for transarterial chemoembolisation treatment (STATE) score and the assessment for retreatment with TACE score combined with STATE (START) strategy, which include the CRP levels, are useful for determining the indications for TACE [26]. For sorafenib therapy, Morimoto et al. reported that the Glasgow Prognostic Score (including CRP and albumin) has significant prognostic value [32]. However, until now there has not been a comprehensive pretreatment scoring system including inflammation, tumor factors and liver function, for the stratification of the prognosis of advanced HCC in patients receiving sorafenib treatment. Our analysis also identified CRP as one of the independent prognostic markers which led to construction of a pretreatment scoring system based on CRP, AFP, albumin and major vascular invasion for the stratification of the prognosis of patients with advanced HCC treated by sorafenib. Several candidate biomarkers or genetic signatures have been reported for predicting the

Fig. 2. OS of patients with advanced stage HCC treated with sorafenib stratified by the proposed scoring system. This Kaplan–Meier plot shows the OS stratified by prognostic scores. The numbers of patients with prognostic scores of 0, 1, 2, 3, and 4 were 7, 22, 48, 59, and 29, respectively. The MSTs of patients with prognostic scores of 0, 1, 2, 3, and 4 were 2.4, 3.7, 9.0, 19.4, and 36.5 months, respectively.

Table 4. MST according to the prognostic scores

Score	Number of patients	MST (months)
0	7 (4.2%)	2.4
1	22 (13.3%)	3.7
2	48 (29.1%)	9.0
3	59 (35.8%)	19.4
4	29 (17.6%)	36.5

The score contains of AFP <200 ng/mL, albumin >3.5 g/dL, absence of major vascular invasion (Vp 3 or 4) and C-reactive protein <1.0 mg/dL. Each factor constitutes one point. The total score is calculated by adding each of the factors together.

prognosis [35–39], but they are costly and not readily available. In contrast, the serum CRP level is examined routinely in clinical practice, and it does not require invasive tissue collection.

The mechanism that underlies the association between CRP and the prognosis for cancer remains largely unknown. The causal relationship between these two may be explained by an aggressive cancer behavior resulting in a detrimental inflammatory reaction, thereby leading to elevated serum CRP levels. In addition, proinflammatory cytokine production, which is reflected by the serum CRP level, may promote the progression of tumors. In the latter case, the candidate proinflammatory cytokine may be interleukin (IL)-6, which is often highly expressed in the tumor microenvironment. In fact, elevated IL-6 and CRP levels are known to be associated with a higher risk of HCC [40]. The development of HCC is also dependent on the enhanced production of IL-6 [41, 42]. Another study showed that I κ B kinase-beta/nuclear factor-kappa-B activation controlled the development of liver metastases via IL-6 expression

Fig. 3. The patients with higher BCP scores had significantly better OS among patients with CLIP scores of 2 ($p=0.0002$). The OS of patients with prognostic scores of 1 or 2 v.s. 3 or 4 were 6.2 v.s. 19.4 months, respectively. CLIP 2=the Cancer of the Liver Italian Program score of 2.

[43]. Clearly, further basic and clinical studies are necessary to elucidate the mechanisms that underlie the association between CRP and the prognosis for HCC.

To date, sorafenib is the first-line treatment option for advanced HCC that is not amenable to surgery. However, the objective response rate is not optimal and only a limited number of patients experience a survival benefit. Sorafenib treatment is costly and it is accompanied by frequent adverse events. Therefore, there is a need for a clinically useful predictor of response during patient selection. Several studies have already reported prognostic factors for patients with unresectable HCC treated by sorafenib [7–12]. However, the advantage of our scoring system is that it uses factors that are simple and readily available in routine clinical practice without the need for tissue collection or specialized tests that may be costly. The variables included in our BCP score are included within the well established CLIP score, except for CRP. So it is relevant to know whether the BCP score added to the utility of the CLIP score. To analyze the additional value of the BCP score over the CLIP score, we stratified patients according to CLIP score and further subdivided patients into two groups by their BCP score. We found that patients with higher BCP scores had significantly better OS among patients with CLIP scores of 2 and better OS with borderline significance among patients with a CLIP score of 3. Thus, we believe that the BCP score has additional value over the established CLIP score.

We have shown that our scoring system can identify patients who are likely to have a prognosis that is better than average. Thirty-five percent of the patients had prognostic scores of 3, and their MST was 19.4 months, which was longer than the mean MST of 14.2 months found in all patients. In particular, 17.6% of patients had prognostic scores of 4, and their MST was as long as 36.5 months. Thus, patients with a score of 3 or 4, particularly a score of 4, may be the best candidates for sorafenib treatment. However, 4.2% and 13.3% of patients had a prognostic score of 0 and 1, respectively, and their MSTs were only a few months. Thus, alternative therapeutic options may be more appropriate for these patients.

Fig. 4. The patients with higher BCP scores had better OS among patients with CLIP scores of 3. That was marginally significant ($p=0.057$). The OS of patients with prognostic scores of 0 or 1 v.s. 2 or 3 were 3.5 v.s. 6.4 months, respectively. CLIP 3=the Cancer of the Liver Italian Program score of 3.

However, if such patients are treated by sorafenib, their response should be evaluated at earlier time points to assess the validity for treatment continuation.

There were some limitations in our present study. This study is a retrospective non-randomized observational study, and our scoring system needs to be validated in a prospective multi-center study.

In conclusion, the results of this study have demonstrated that the pretreatment CRP level is a widely applicable prognostic marker for patients with advanced stage HCC when treated by sorafenib. We also established a novel prognostic scoring system that includes the CRP level, which may help to stratify the prognosis of patients with advanced stage HCC, whereby those patients with higher BCP scores may show more favorable response and better OS when treated by sorafenib. This scoring system is simple and readily available, and it may be useful in clinical decision making as well as facilitating better risk-adjusted follow-up.

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Conflicts of Interest and Financial Disclosures

None reported.

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Study design: HN, MK, and NI

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Data analysis: HN, MK, and NI

Data interpretation: HN, MK, and NI

Manuscript writing: HN

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