Original Article

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Prediction of post-progression survival in patients with advanced hepatocellular carcinoma treated with sorafenib by using time-dependent changes in clinical characteristics

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Abstract

Aim: Sorafenib has been shown to improve time to tumor progression (TTP) and overall survival (OS) in patients with hepatocellular carcinoma (HCC); however, post-progression survival (PPS) has not been well characterized in these patients. This study aimed to evaluate the predictors of PPS by using time-dependent and dynamic changes in radiologic progression patterns, liver function, and performance status (PS) in patients with advanced HCC receiving sorafenib treatment.

Methods: We retrospectively analyzed the clinical characteristics of 128 advanced HCC patients with Child-Pugh scores ≤ 7 at the initiation of sorafenib treatment.

Results: The median TTP, OS, and PPS were 3.8, 15.6, and 9.9 months, respectively. At the time of confirmation of radiologic progressive disease (PD), a total of 46 (35.6%) patients showed impairments in their PS of ≥ +1 points over time. For the Child-Pugh score, 27 (21.1%) and 26 (10.9%) patients exhibited an impairment of ≥ +1 and ≥ +2 points, respectively. Multivariate analysis identified the following independent predictors of PPS: impairment in the PS score of ≥ +1 point [hazard ratio (HR) 1.81, 95% confidence interval (CI) 1.16-2.82], impairment in the Child-Pugh score of ≥ +2 points (HR 3.70, 95% CI 1.68-8.15), radiologic pattern of progression (target lesion growth and emergence of a new lesion) (HR 2.91, 95% CI 1.79-2.91), a TTP < 4 months

(HR 1.87, 95% CI 1.21-2.91), second-line treatment after radiologic confirmation of PD (HR 0.16, 95% CI 0.08-0.32), and continuous sorafenib treatment after radiologic confirmation of PD (HR 1.76, 95% CI 1.06-3.00).

Conclusion: PPS in patients with advanced HCC can be characterized by using time-dependent dynamic changes in clinical parameters.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the third common cause of cancer-related deaths worldwide. Surgical resection, liver transplantation, and ablation therapy are curative therapeutic treatments for early-stage HCC, and transcatheter arterial chemoembolization (TACE) is recommended for patients with intermediate-stage HCC who have preserved liver function[1,2]. However, most HCC patients are diagnosed during the advanced stage of the disease; their prognosis is poor, and treatment options are limited[1-3]. In patients who are not candidates for locoregional therapy, the oral multikinase inhibitor sorafenib has been the only systemic treatment option. Sorafenib inhibits tumor cell proliferation and tumor angiogenesis by inhibiting multiple signaling pathways. It has been shown to prolong both, progression-free survival and overall survival (OS) in patients with advanced HCC[4,5]. Since the Sorafenib HCC Assessment Randomized Protocol (SHARP) trial showed the efficacy of sorafenib for prolonging survival in HCC patients almost 10 years ago[4], all phase 3 trials of novel systemic drugs have failed to improve outcomes over sorafenib, both, as first-line[6-10] and second-line treatments (following sorafenib)[10-12]. Predicting the efficacy is difficult in sorafenib treatment, and no surrogate marker has been identified[11-13]. Since tumor progression is a dynamic process, it may be difficult to identify predictors for survival by analyzing clinical characteristic at one static data point. Using dynamic data might help clarify the predictors of survival.

A recent regorafenib for patients with HCC who progressed on sorafenib treatment (RESORCE) study[14] has revealed that regorafenib prolonged survival in patients with advanced HCC who were refractory to sorafenib treatment. The inclusion criteria in this study were a Child-Pugh score ≤ 6 and tolerability of sorafenib (≥ 400 mg daily for at least 20 of the 28 days before discontinuation). Based on this, the number of candidates for second-line treatment with regorafenib is likely very limited. Analyzing post-progression survival (PPS) after sorafenib treatment is desired to select candidates for second-line treatment.

In this study, we used dynamic and time-dependent data on the clinical characteristics of patients with advanced HCC, including progression patterns, impairments in liver function, and performance status (PS). Importantly, we assessed changes in these parameters by comparing them at the time of radiologic confirmation of progressive disease (PD) to baseline (the initiation of sorafenib treatment) to evaluate PPS.

METHODS
Patients
We reviewed data that were prospectively collected from 171 consecutive patients who received sorafenib (Nexavar; Bayer HealthCare Pharmaceuticals, West Haven, CT, USA) for the treatment of advanced HCC at the Department of Hepato-Biliary-Pancreatic Surgery at the National Hospital Organization Kyushu Medical Center between June 2009 and July 2016. Of these, 135 patients had radiologic PD, as assessed by the modified Response Evaluation Criteria In Solid Tumors (mRECIST)[15]. After excluding 7 patients with a Child-Pugh score ≥ 8, 128 patients were enrolled in the study.

HCC was diagnosed based on the results of a pathological examination or a combination of specific radiologic findings obtained via contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) according to the criteria of the American Association for the Study of Liver Diseases[2]. Of 128 patients, 116 were diagnosed with HCC based on the results of a pathological examination. The remaining 12 patients showed specific radiologic findings according to the criteria of the AASLD and elevated serum α-fetoprotein (AFP) levels. No patients with differentiated intracholangiocellular carcinoma and mixed-form liver cancer were included in this study.

Sorafenib was administered to patients with advanced HCC if: (1) they were not eligible for or their disease progressed after surgery, locoregional therapy, or TACE; (2) their ECOG PS was 0-1; (3) their liver function was classified as Child-Pugh A or B; and (4) they had adequate hepatic function (albumin > 2.5 g/dL, total bilirubin < 3.0 mg/dL, and alanine aminotransferase and aspartate aminotransferase levels < 5 times the upper limit of the normal range). Radiologic tumor progression was confirmed by contrast-enhanced CT or MRI. The starting dosage of sorafenib was 800 mg/day p.o. However, considering the possibility of having to discontinue sorafenib treatment at an early stage due to adverse events, the initial dosage for patients with comorbidities was reduced to 400 mg/day. Moreover, the initial dosage for patients aged ≥ 75 years, those with a body weight ≤ 40 kg, and those with a history of treatment for varices or ascites was 200-400 mg/day. The dose was increased to the standard dose according to each patient's tolerance. Treatment was continued until tumor progression, unacceptable toxicity associated with sorafenib, or withdrawal of consent. Second-line treatments after radiologic confirmation of PD included continuous sorafenib treatment, even in palliative patients upon their request. However, patients with Child-Pugh C or a PS > 2 at the time of confirmation of PD received best supportive care.

This study was approved by the Ethics Committee of the National Hospital Organization Kyushu Medical Center and performed in compliance with the Declaration of Helsinki. All patients provided written informed consent for sorafenib treatment.

Assessments
Tumor measurements were performed at baseline and every 2 months during treatment by contrast-enhanced CT or MRI. Patients visited the clinic every 2 to 4 weeks to assess treatment compliance and adverse effects. The survival status of the study participants was obtained from hospital records. Local response was determined by the mRECIST criteria[15]. We assessed the cause of progression (patterns of progression) based on the following: 20% increase in tumor size against a known baseline lesion or the emergence of a new lesion.

Follow-up
All patients were followed-up at our outpatient clinic according to a standardized protocol that included tumor marker tests every month and MDCT or MRI every 8 weeks until the patient's death or last visit.

Statistical analysis
Statistical analyses were conducted using the JMP version 11.0 software (SAS Institute, Cary, NC, USA). Categorical variables were analyzed with the Chi-square or Fisher's exact test, as appropriate. Continuous variables were analyzed using the Student's *t*-test or the Mann-Whitney *U* test, as appropriate. Time to tumor progression (TTP), OS, and PPS were evaluated through the Kaplan-Meier method, and comparisons between groups were performed using the log-rank test. Univariate and multivariate analyses were performed using a Cox proportional hazards model and the backward elimination procedure. A *P*-value of < 0.05 was considered significant.

RESULTS

Baseline characteristics of the patients
The average age of the 128 study participants (105 men and 23 women) was 68.9 years [Table 1]. Most (*n* = 100) had a PS of 0. Regarding the preservation of liver function, 71, 43, and 14 study participants had

Table 1: Characteristics at the initiation of sorafenib treatment

Variables		*n* = 128
Age, year		68.9
Gender	(male/female)	105/23
Etiology	HBV/HCV/NBNC	21/86/21
ECOG PS	0/1	100/28
Child-Pugh score	5/6/7	71/43/14
Extrahepatic spread		65 (51.2%)
Macrovascular invasion		29 (23.6%)
BCLC stage	B/C	34/94
Starting dose of sorafenib	800/600/400/200	26/0/83/16
AFP (ng/mL)	(median, IQR)	55.3 (8.4-469)
DCP (mAu/mL)	(median, IQR)	92.5 (22-1877)

HBV: hepatitis B virus; HCV: hepatitis C virus; NBNC: non B non C; ECOG: Eastern Cooperative Oncology Group; PS: performance status; BCLC: Barcelona Clinical Liver Cancer; AFP: α-fetoprotein; DCP: des-γ-carboxy prothrombin; IQR: interquartile range

Table 2: Change of clinical parameters at the time of confirmation of radiologic progressive disease compared with those of the initiation of sorafenib treatment

Variables		At the confirmation of radiologic PD
Impairment of PS score	≥ +1	46 (35.9%)
	≥ +2	14 (10.9%)
Impairment of Child-Pugh score	≥ +1	27 (21.1%)
	≥ +2	26 (20.3%)
Time to progression	≥ 4 months	60 (46.9%)
Radiologic progression pattern	Target lesion growth	63 (49.2%)
	New lesion	19 (14.8%)
	Target lesion growth and new lesion	46 (35.9%)

PD: progressive disease; PS: performance status

a Child-Pugh score of 5, 6, and 7, respectively. Whereas 65 patients presented with extrahepatic spread, 29 showed macrovascular invasion. At total of 34 and 94 study participants had Barcelona Clinical Liver Cancer (BCLC) stages B and C, respectively.

Second-line treatment after radiologic confirmation of PD
At the time of the radiologic confirmation of PD, 96 (75.0%) patients received subsequent second-line treatment. Of 96 patients who underwent subsequent treatment, 59 received continuous sorafenib treatment, 17 underwent TACE, 8 took part in clinical trials, 5 received hepatic arterial infusion chemotherapy, 5 underwent systemic chemotherapy, and 2 received radiotherapy.

TTP, OS, and PPS
The median TTP and OS were 3.8 months [95% confidence interval (CI), 3.2-4.4] and 15.6 months (95% CI, 12.4-18.5), respectively. The median PPS was 9.9 months (95% CI, 7.6-12.9). The TTP in this study was similar to those reported in the SHARP and AP trials.

Changes in clinical characteristics between baseline (the initiation of sorafenib treatment) and confirmation of radiologic PD
We then assessed the dynamic changes in the patients' clinical characteristics and compared them at baseline (the initiation of sorafenib treatment) to the confirmation of radiologic PD [Table 2]. A total of 46 (35.6%) and 14 (10.9%) patients showed impairments in their PS of ≥ +1 and ≥ +2 points over time, respectively. For the Child-Pugh score, 27 (21.1%) and 26 (20.3%) patients exhibited an impairment of ≥ +1 and ≥ +2 points, respectively. When we assessed the radiologic patterns of progression, 63, 19, and 46 patients showed target lesion growth only, emergence of a new lesion only, and both, target lesion growth and emergence of a new lesion, respectively. Of 34 patients with BCLC-B, 4 progressed to BCLC-C at the

Table 3: Predictive factors for post-progression survival

Variables		Univariate		Multivariate	
		HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age, year	≥ 75	1.11 (0.72-1.66)	0.64		
Gender	Male	1.07 (0.67-1.79)	0.79		
Hepatitis B infection	Yes	0.95 (0.56-1.53)	0.84		
Hepatitis C infection	Yes	0.87 (0.58-1.32)	0.5		
Impairment of PS	≥ +1 point	2.14 (1.45-3.17)	< 0.001	1.81 (1.16-2.82)	0.01
	≥ +2 points	8.54 (4.31-16.12)	< 0.001	1.12 (0.47-2.62)	0.79
Impairment of Child-Pugh score	≥ +1 point	2.21 (1.48-3.28)	< 0.001	1.10 (0.64-1.99)	0.73
	≥ +2 points	4.82 (2.93-7.68)	< 0.001	3.70 (1.68-8.15)	< 0.01
Extrahepatic spread	Yes	1.4 (0.94-2.08)	0.15		
Macrovascular invasion	Yes	2.01 (1.25-3.13)	0.03	1.08 (0.58-1.96)	0.80
BCLC stage	C	1.83 (1.19-2.90)	< 0.01	1.33 (0.80-2.23)	0.27
Radiological progression pattern	Growth + new	3.21 (2.09-4.91)	< 0.001	2.91 (1.79-4.76)	< 0.001
Time to tumor progression	< 4 months	2.25 (1.52-3.35)	< 0.001	1.87 (1.21-2.91)	0.01
Second-line treatment post-PD	Yes	0.12 (0.07-0.20)	< 0.001	0.16 (0.08-0.32)	< 0.001
Contiunuous sorafenib treatment post-PD	Yes	0.67 (0.45-0.98)	0.04	1.76 (1.06-3.00)	0.03
Decline of serum AFP level 2 weeks after starting sorafenib	> 20%	1.19 (0.72-1.89)	0.48		

BCLC: Barcelona Clinical Liver Cancer; AFP: α-fetoprotein; PD: progressive disease; PS: performance status; HR: hazard ratio; CI: confidence interval

time of confirmation of radiologic PD based on new extrahepatic spread (*n* = 3) or occurrence of a portal tumor thrombus (*n* = 1).

Prediction of PPS

Univariate analysis revealed a significant correlation between PPS and the following parameters in patients with radiologic PD: impairments in the PS score of ≥ +1 and ≥ +2 points, a Child-Pugh score of 8, impairments in the Child-Pugh score of ≥ +1 and ≥ +2 points, macrovascular invasion, radiologic patterns of progression, a TTP of ≤ 4 months, subsequent treatment post-PD, and continuous sorafenib treatment post-PD [Table 3]. Multivariate analysis identified the following independent predictors of PPS in patients with radiologic PD: impairment in the PS score of ≥ +1 point [hazard ratio (HR) 1.81, 95% CI 1.16-2.82], impairment in the Child-Pugh score of ≥ +2 points (HR 3.70, 95% CI 1.68-8.15), radiologic pattern of progression (target lesion growth and emergence of a new lesion) (HR 2.91, 95% CI 1.79-2.91), a TTP < 4 months (HR 1.87, 95% CI 1.21-2.91), second-line treatment after radiologic confirmation of PD (HR 0.16, 95% CI 0.08-0.32), and continuous sorafenib treatment after radiologic confirmation of PD (HR 1.76, 95% CI 1.06-3.00) [Table 3].

DISCUSSION

In our analysis of 128 patients with advanced HCC, we found impairment in the PS score of ≥ +1, impairment in the Child-Pugh score of ≥ +2, a TTP < 4 months, radiologic progression pattern, second-line treatment after radiologic confirmation of PD, and continuous sorafenib treatment after radiologic confirmation of PD were predictors of PPS. Time-dependent changes in these clinical parameters played an important role in predicting PPS.

PPS has been shown to be associated with OS in patients with lung[16], breast[17], and colorectal cancer[18]. Recently, a correlation between PPS and OS was also shown in patients with HCC[19,20]. However, to the best of our knowledge, few investigations have assessed the role of dynamic and time-dependent changes in clinical characteristics in the prediction of PPS.

Based on the findings of this study, patients with advanced HCC can be referred for second-line treatment at confirmation of PD during sorafenib treatment. Our findings also imply that observing disease

progression during sorafenib treatment is very important. A decrease in liver function or a worsening in the patients' general condition during sorafenib treatment should be detected early as these patients should be referred for second-line treatment as early as possible.

Our data revealed that an impairment in the Child-Pugh score of ≥ +2 points (and not ≥ +1 points) but was associated with a worse PPS. In previous studies, liver function impairment was defined as Child-Pugh score B or C. However, using this definition, an impairment in the Child-Pugh score of +1 point would be only defined as liver function impairment in patients with a Child-Pugh score of A6 at baseline, but not for those with a Child-Pugh score of A5 at baseline. Furthermore, the Child-Pugh score at the confirmation of PD may not accurately represent the development of the condition. In this study, we therefore focused on the changes in Child-Pugh scores over time to evaluate the effect on PPS of a change in the score of +1 point.

PS has been shown to correlate strongly with both, tumor and cirrhotic factors, and may predict survival outcomes in patients with advanced HCC[21,22]. In previous studies, liver function impairment was defined as a PS > 2[19,20]. In contrast, this study showed that even an impairment in PS of ≥ +1 point was associated with a worse PPS.

A recent study by Reig *et al.*[19] showed that the radiologic progression pattern affected both, OS and PPS in HCC patients receiving sorafenib treatment. The radiologic progression pattern in previous studies included intrahepatic growth, new intrahepatic lesion, extrahepatic growth, or new extrahepatic lesion. Patients with a new extrahepatic lesion, in particular, had a worse PPS[19,20]. When estimating a tumor response, radiologic examinations show a certain progression pattern in some patients; however, many patients have a complicated combination of progression patterns. Estimated all combination of these progression patterns, complicated combination may be difficult to comprehend. In this study, we adopted the progression pattern of target lesion growth and/or the emergence of a new lesion for a convenient and easily available approach in clinical practice.

Interestingly, a TTP of < 4 months was identified as an independent prognostic predictor in this study. A recent study reported that a TTP of < 4 months was an independent predictor of OS and PPS[20]. Earlier PD development predicts a poorer PPS after adjusting for other survival predictors. These patients should be referred for second-line treatment. It has been reported that continuous sorafenib treatment was a useful treatment option at the time of radiologic confirmation of PD. Moreover, our previous study showed that continuing sorafenib treatment after radiologic confirmation of PD may be a useful treatment strategy, especially in patients with a TTP of ≥ 4 months[23]. On the other hand, for patients with rapid PD, as defined by a TTP of < 4 months, alternative second-line treatments should be considered[24].

This study had some limitations. First, this study was a retrospective study. However, all patients underwent tumor evaluation by contrast-enhanced CT or MRI every 2 months during sorafenib treatment. Furthermore, no patient was lost to follow-up. Second, the study only enrolled patients with a Child-Pugh score of ≤ 7. Clinical trials of sorafenib showed the drug's efficacy in patients with a Child-Pugh score of ≤ 6. However, global[25] and Japanese[26] observational studies revealed that sorafenib treatment was often initiated in patients with a Child-Pugh score of 7 in clinical practice. Third, the target population of this study was heterogenous and included patients with BCLC-B and -C. However, sorafenib treatment is often used for HCC patients with BCLC-B who are refractory to TACE in clinical practice. Furthermore, predictors of PPS were analyzed after adjusting for BCLC staging. Fourth, 17 patients treated with TACE as a second-line treatment after the confirmation of radiologic PD were included in this study, as it is common practice to use a combination therapy of TACE and sorafenib to control disease progression. However, the efficacy of a combination therapy of TACE and sorafenib is still controversial and should

be confirmed in a randomized clinical trial[27]. Fifth, radiologic progression pattern, as mentioned before. Finally, the size of the study cohort was small. Therefore, further prospective studies with a larger number of subjects are required to confirm our findings.

In conclusion, we show that evaluating PPS in patients with advanced HCC by using time-dependent and dynamic changes in clinical parameters was extremely useful. Our findings may be useful for selecting second-line treatment at the time of PD. Furthermore, our data indicate that changes in liver function or worsening of a patient's general condition during sorafenib treatment should be observed carefully.

DECLARATIONS

Authors' contributions
All authors contributed equally to this work.

Data source and availability
The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Financial support and sponsorship
None.

Conflicts of interest
The authors declare no conflicts of interest associated with this manuscript.

Patient consent
All patients provided written informed consent for sorafenib treatment.

Ethics approval
This study was approved by the Ethics Committee of the National Hospital Organization Kyushu Medical Center and performed in compliance with the Declaration of Helsinki.

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