

Sorafenib for Survival Post-progression in Advanced Hepatocellular Carcinoma Unresponsive to Hepatic Arterial Infusion Chemotherapy

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Received: November 14, 2012 Revised: December 31, 2012

Accepted: January 2, 2013

Published online: April 21, 2013

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Key words: Carcinoma; Hepatocellular; Cisplatin; Sorafenib; Survival Post-progression

Kondo M, Morimoto M, Moriya S, Takizawa K, Nozaki A, Fukuda H, Numata K, Maeda S, Tanaka K. Sorafenib for Survival Post-progression in Advanced Hepatocellular Carcinoma Unresponsive to Hepatic Arterial Infusion Chemotherapy. *Journal of Gastroenterology and Hepatology Research* 2013; 2(4): 520-525 Available from: URL: <http://www.ghrnet.org/index./joghr/>

ABSTRACT

AIM: Hepatic arterial infusion chemotherapy (HAIC) has been used as a palliative treatment option for the treatment of advanced hepatocellular carcinoma (HCC) patients in Japan. However, no beneficial data regarding salvage options, including the use of sorafenib, are available for patients who are unresponsive to HAIC.

METHODS: We retrospectively enrolled 67 consecutive HCC patients who had undergone HAIC with a fine-powder formulation of cisplatin. The primary evaluation criterion was survival post-progression (SPP), a surrogate for overall survival, among patients with progressive disease (PD) who received various post-HAIC salvage options.

RESULTS: Among the 38 PD patients who had a Child-Pugh score 8 or less during HAIC, the median SPP was significantly longer for the 19 patients who received sorafenib, compared with those who received other salvage options (continuous HAIC for 5 patients; tegafur-uracil for 2; best supportive care for 12) (5.5 vs. 3.8 months; $P=0.041$). A multivariate analysis showed that sorafenib use ($P=0.010$) and the absence of ascites ($P=0.003$) had a superior statistical significance with regard to the SPP.

CONCLUSIONS: Sorafenib may be beneficial as a salvage option in patients with advanced HCC who were unresponsive to HAIC using cisplatin powder. A further prospective study will be needed to validate these results in larger populations of patients.

INTRODUCTION

Hepatocellular carcinoma (HCC) is a frequent cause of death from cancer worldwide^[1]. At present, most patients can be effectively treated using several modalities including surgical resection^[2], liver transplantation^[3], transarterial chemoembolization (TACE)^[4], percutaneous ethanol injection^[5], microwave coagulation therapy^[6], and radiofrequency ablation (RFA)^[7]. However, HCC has a high recurrence rate^[8,9] and is also associated with a high risk of vessel involvement; the presence of portal vein tumor thrombosis (PVTT) correlated with an extremely poor prognosis. The modified Barcelona Clinic Liver Cancer (BCLC) staging classification and treatment schedule recently recommended that, during the intermediate stage, TACE should be the standard treatment option, and patients with vascular invasion should be treated with sorafenib, an orally active multikinase inhibitor^[10].

Sorafenib is the current standard option for the first-line systemic treatment of advanced HCC patients, since the median survival time of patients treated with sorafenib is 3 months longer than that of patients receiving a placebo^[10]. Although sorafenib can be gradually tolerated by Japanese patients, the majority of patients require a dose reduction, and the discontinuation rate because of intolerance is relatively high^[11,12]. On the other hand, hepatic arterial infusion chemotherapy (HAIC), which increases the local concentrations of antitumor agents and reduces systemic side effects, has been used as a palliative treatment with some reported efficacy^[13-15]. Although the efficacy of HAIC with conventional cisplatin alone has been limited^[14,16], HAIC with cisplatin combined with systemic

interferon- α therapy^[14] and HAIC with cisplatin combined with 5-fluorouracil (5-FU) therapy^[13,17] have been consistently beneficial. In 2004, a fine-powder formulation of cisplatin (cisplatin powder) was approved for use in Japan for the treatment of HCC via a transarterial approach without any lipiodol or embolic material. Cisplatin powder is readily soluble and is more suitable for the preparation of high-concentration aqueous solutions (1.4 mg/mL) than conventional cisplatin formulations (0.5 mg/mL). HAIC with cisplatin powder is potentially useful for the treatment of patients with advanced HCC^[18], PVTT^[19], or TACE-refractory HCC^[20]. However, a salvage option for advanced HCC patients who were unresponsive to HAIC using cisplatin powder has never been established.

Recently, survival post-progression (SPP), a surrogate for overall survival, has been used for analyzing the survival benefit of second-line chemotherapy in some malignancies^[21,22]. In the present study, we evaluated the survival duration of patients receiving HAIC with cisplatin powder and analyzed SPP among PD patients receiving post-HAIC salvage options, including sorafenib.

MATERIALS AND METHODS

Patients

This was a retrospective study of 67 consecutive HCC patients [50 men and 17 women; age range, 33-84 years (mean, 70.4 years)] who had PVTT or were TACE-refractory and who were treated with HAIC with cisplatin powder between April 1, 2005, and August 31, 2011. A diagnosis of HCC was made histopathologically or clinically based on imaging studies, such as contrast-enhanced multidetector-row CT and/or MRI. This study was performed according to the guidelines of the Helsinki Declaration, and the protocol was approved by the ethics committee at our institution. Written informed consent was obtained from all the patients and/or a relative.

Table 1 shows the baseline characteristics for all the patients. The etiology of the HCC was associated with infection with hepatitis B virus in 7 (10.4%) patients, infection with hepatitis C virus in 47 (70.1%) patients, and alcohol abuse in 5 (7.5%) patients. Forty-nine (73.1%) patients presented with Child-Pugh grade A liver cirrhosis, and the remaining patients (26.9%) presented with Child-Pugh grade B disease. The median serum AFP and DCP values before the initiation of HAIC treatment were 690 ng/mL and 1098 mAU/mL, respectively. Forty-four patients (65.7%) had PVTT. The tumor stage was graded according to the TNM classification of the Liver Cancer Study Group of Japan^[23] and the BCLC staging system.

HAIC procedure

The Seldinger technique was used to gain access to the right femoral artery. A 5-Fr or 4-Fr shepherd hook catheter (Terumo Clinical Supply Co., Gifu, Japan) was advanced into the celiac artery, and a 2-Fr microcatheter (Terumo Clinical Supply Co., Gifu, Japan) was then advanced through the first catheter into the proper hepatic artery, where it was used to intra-arterially infuse the cisplatin powder solution. Cisplatin powder (IA call[®]; Nippon Kayaku Co., Ltd. Tokyo, Japan) was dissolved in saline that had been heated to 50°C and was administered as a dose of 65 mg/m² over a period of about 30 min using a mechanical infusion pump. To prevent cisplatin-induced renal damage, 3 000 mL of infusion solution was infused intravenously during the first day of HAIC, and 1 500 mL was infused on each of the next 3 days. The treatment was repeated at an interval of 4 to 6 weeks if an adequate performance status, renal function, and hepatic reserve capacity were maintained or if disease progression was not confirmed using an imaging-based diagnosis.

Clinical response and toxicity evaluation

The efficacy of HAIC with cisplatin powder was evaluated according to the Response Evaluation Criteria for Solid Tumors (RECIST)^[24] using dynamic CT or MRI at 4 weeks after each HAIC session. The observed toxicity was assessed according to the Common Terminology Criteria for Adverse Events (CTCAE version 3.0).

Table 1 Patient characteristics at baseline.

Variables		n=67
Sex	Male/Female	50/17
Mean age (years)	Mean (range)	70.4 (33-84)
Etiology	HBs-Ag/HCV-Ab/Alcohol/other	7/47/5/8
TNM stage	II/III/IVA/IVB	3/22/39/3
BCLC stage	B/C	13/54
Performance status	0/1+2	45/22
Initial treatment	Resection/RFA or PEI/TACE/TACE+RFA/None	6/14/29/7/11
Child-Pugh grade	A/B	49/18
ALT (U/L)	Median (range)	54 (16-332)
Total bilirubin (mg/dL)	Median (range)	0.8 (0.2-2.0)
Prothrombin activity ratio (%)	Median (range)	95 (65-137)
Albumin (g/dL)	Median (range)	3.7 (2.3-4.6)
Platelet count (10 ⁴ /L)	Median (range)	12.0 (3.5-47.1)
AFP (ng/mL)	Median (range)	690 (6-584820)
	>500 ng/mL (n)	37
DCP (mAU/mL)	Median (range)	1098 (12-75000)
	>500 mAU/mL (n)	39
Ascites	yes/no	19/48
Portal vein thrombosis	yes/no	44/23
Tumor distribution	Unilateral/Bilateral	19/48
Tumor numbers	< 4/≥4	19/48
Maximum tumor size	< 50mm/≥ 50mm	40/27

TNM: tumor-node-metastasis staging revised by the Liver Cancer Study Group of Japan in 2008; BCLC: Barcelona Clinic Liver Cancer staging system; RFA: radiofrequency ablation; PEI: percutaneous ethanol injection; TACE: transcatheter arterial chemoembolization; ALT: alanine aminotransferase; AFP: alpha-fetoprotein; DCP: des-gamma-carboxy prothrombin.

Post-HAIC regimens

After every session of HAIC with cisplatin powder, we assessed the response to therapy in all the patients. In principle, patients assessed as having a partial response (PR) or stable disease (SD) continued to receive HAIC with cisplatin powder. However, for patients with progressive disease (PD), the subsequent therapeutic approach altered with one of the following options: sorafenib, continuous HAIC with cisplatin powder, tegafur-uracil (UFT[®]; Taiho Pharmaceutical Co., Ltd, Tokyo, Japan), or best supportive care (BSC). Before the approval of sorafenib in Japan (from 2004 to 2008), we principally recommended repeated HAIC with cisplatin powder or tegafur-uracil. BSC was undertaken for patients who refused receiving either of these two treatment options. After the approval of sorafenib (from 2009), we principally recommended sorafenib except for Child-Pugh grade C patients. For patients who refused to receive sorafenib, one of the three options, repeated HAIC with cisplatin powder, tegafur-uracil, or BSC, was undertaken. Sorafenib was started at a dose of 400 mg twice daily; however, out of concern regarding the possibility of having to discontinue sorafenib treatment at an early stage because of adverse events, the initial dosage was reduced to 200 mg twice daily for patients with an advanced age, low body weight, or a high Child-Pugh score.

Statistical analysis

The end-points of this study were overall survival, as calculated from the date of the first HAIC session with cisplatin powder, and survival post-progression (SPP), as calculated from the date of the first sign of radiological progression after the administration of HAIC, until death

arising from any cause or the last clinical follow-up examination. The Kaplan-Meier method was used to plot the estimated survival curves, and the statistical significance of the difference in survival between the two groups was evaluated using the log-rank test. Variables that reached a *P* value of <0.05 in a univariate analysis were entered into a multivariate analysis. The multivariate analysis was performed using a Cox proportional hazard regression model. Student's *t*-test was used to statistically compare continuous variables, and the Fisher exact test or the chi-square test was used for categorical variables. All the data analyses were performed using a statistical software package (SPSS version 17.0; SPSS Inc., Chicago, IL, USA).

RESULTS

The patients underwent a total of 136 HAIC sessions using cisplatin powder, and the average number of sessions per patient was 2.0 (range, 1-9 sessions). The number of HAIC sessions was 1 in 29 patients (43.3%), 2 in 19 patients (28.4%), 3 in 8 patients (11.9%), 4 in 4 patients (6.0%), 5 in 3 patients (4.5%), 6 in 2 patients (3.0%), 7 in 1 patient (1.5%), and 9 in 1 patient (1.5%). No complications arising from the procedure or from the chemoinfusion occurred during the treatments.

HAIC with cisplatin powder was discontinued because of a rash in only one patient. Grade 3 non-hematological toxicities consisted mainly of nausea and diarrhea (1.5% each); Grade 3 or 4 hematological toxicities consisted of an elevated serum bilirubin level (6.0%), an elevated serum aspartate aminotransferase level (16.4%), an elevated serum alanine aminotransferase level (10.4%), an elevated serum alkaline phosphatase level (1.5%), an elevated serum gamma glutamyl transferase level (19.4%), hyperglycemia (7.5%), thrombocytopenia (10.4%), anemia (7.5%), and/or neutrocytopenia (6.0%). All the manifestations of toxicity returned to their basal levels within 2 weeks after treatment.

During HAIC treatment, a complete response (CR), PR, and SD were achieved in 5, 9, and 5 patients, and the disease-control rate was 28.4%. PD was observed in 41 patients, and the remaining 7 patients were not evaluated. The survival rate calculated from the start of HAIC administration was 41.7% at 1 year, 27.1% at 2 years, and 19.2% at 3 years, and the median survival time was 7.8 months. The median survival times for the disease-control group (CR+PR+SD) and the PD patients were 47.4 months and 5.4 months, respectively; these values were significantly different ($P<0.001$).

Among the 41 PD patients, 3 patients developed a Child-Pugh score 9 or more during HAIC treatment and were excluded from the subsequent SPP analysis (Figure 1).

Among the remaining 38 patients, the possible candidates for sorafenib treatment, 19 patients received sorafenib (since 2009) and the remaining 19 patients underwent one of the following salvage options: continuous HAIC with cisplatin powder ($n=5$), tegafur-uracil ($n=2$), and BSC ($n=12$). Among the 12 BSC patients, 6 received this regimen before the approval of sorafenib in Japan, and the remaining 6 received this regimen after the approval of sorafenib but did not consent to undergo sorafenib treatment. Table 2 shows the characteristics of the patients who received sorafenib after HAIC and of those who received other salvage options; the characteristics were observed at the point of radiological progression after HAIC. No significant differences were observed between the two groups. The cumulative overall survival and SPP for the groups that received sorafenib or the other salvage options are shown in figure 2. The median overall survival of the patients that received sorafenib tended to be longer than those of the patients that received other salvage

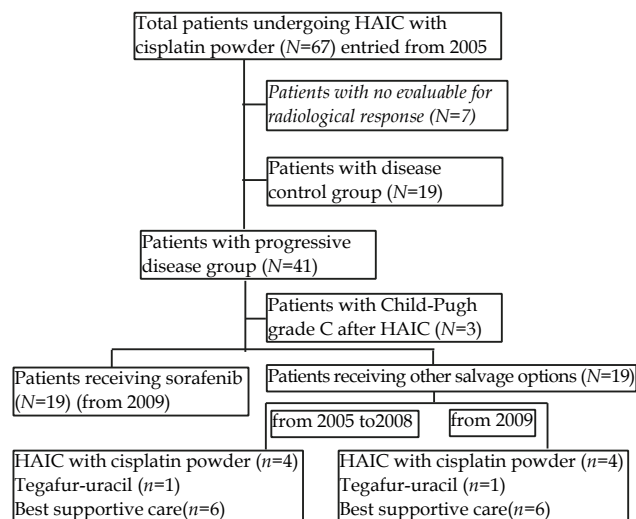


Figure 1 Design of the present exploratory analysis of survival post-progression among patients with progressive disease after hepatic arterial infusion chemotherapy (HAIC) using cisplatin powder.

Table 2 Patient characteristics at the time of radiological disease progression.

Characteristics	Sorafenib (N=19)	Other salvage therapies (N=19)	<i>P</i>
Sex			
Male/Female	14/5	14/5	1.000
Age (years) ¹	75 (50-84)	73 (56-79)	0.403
Performance status			
0/1+2	10/9	9/10	1.000
Ascites			
yes/no	6/13	8/11	0.737
Portal vein thrombosis			
yes/no	12/7	16/3	0.269
Tumor distribution (Unilateral/Bilateral)	4/14	6/12	0.714
Tumor numbers (<4/≥4)	4/14	2/16	0.660
Maximum tumor size (<50mm/≥50mm)	11/7	9/10	0.515
ALT (U/L) ¹	44 (14-100)	39 (9-302)	0.156
AST (U/L) ¹	80 (35-142)	95 (16-291)	0.233
Total bilirubin (mg/dL) ¹	1.0 (0.7-2.3)	1.0 (0.5-2.8)	0.436
Albumin (g/dL) ¹	3.9 (3.0-4.4)	3.6 (2.4-4.7)	0.273
Prothrombin activity ratio (%) ¹	97 (74-119)	94 (76-140)	0.759
Platelet count (×10 ⁴ /L) ¹	13.0 (5.1-22.8)	11.2 (4.0-44.6)	0.403
AFP (ng/mL) ¹	2003 (11-275577)	2277 (18-409606)	0.369
DCP (mAU/mL) ¹	1217 (27-221900)	4110 (39-54356)	0.988

ALT: alanine aminotransferase; AST: aspartate aminotransferase; AFP: alpha-fetoprotein; DCP: des-gamma-carboxy prothrombin. ¹Expressed as median (range).

options, but the difference was not statistically significant ($P=0.069$) (Figure 2A). However, the median SPP among the patients who received sorafenib treatment was significantly longer than that among the patients who received other salvage options, as shown using a univariate analysis (5.5 vs. 3.8 months, $P=0.041$) (Figure 2B). In a multivariate analysis, patients who received sorafenib ($P=0.010$) and the absence of ascites ($P=0.003$) were shown to have a superior statistical significance with regard to the SPP among prognostic variables (Table 3).

DISCUSSION

In the present study, we found that the median SPP for patients unresponsive to HAIC with a fine-powder formulation of cisplatin was significantly longer for patients receiving sorafenib salvage therapy than for those receiving other salvage options, as shown

Table 3 Prognostic factors for survival post-progression using univariate and multivariate analyses for patients with progressive disease.

Variables	Survival post-progression			
	Univariate analysis	Multivariate analysis		
	P-value	P-value	HR	95% CI
Age (<70 vs. ≥70 years)	0.325	-	-	-
Sex (male vs. female)	0.312	-	-	-
PS (0 vs. 1+2)	0.211	-	-	-
Platelet count (<12.5 × 10 ⁴ vs. ≥12.5 × 10 ⁴ /μL)	0.889	-	-	-
Albumin (<3.8 vs. ≥3.8 g/dL)	0.107	-	-	-
Total bilirubin (<1.0 vs. ≥1.0 mg/dL)	0.031	0.152	1.884	0.793-4.476
Prothrombin activity ratio (%) (< 94 vs. ≥94%)	0.206	-	-	-
ALT (< 50 vs. ≥50 U/L)	0.977	-	-	-
AST (< 84 vs. ≥84 U/L)	0.324	-	-	-
AFP (< 2000 vs. ≥2000 ng/mL)	0.361	-	-	-
DCP (<1800 vs. ≥1800 mAU/mL)	0.160	-	-	-
Ascites (yes vs. no)	0.001	0.003	0.283	0.104-0.769
Portal vein thrombosis (yes vs. no)	0.278	-	-	-
Sorafenib (yes vs. no)	0.041	0.010	2.481	1.120-5.497

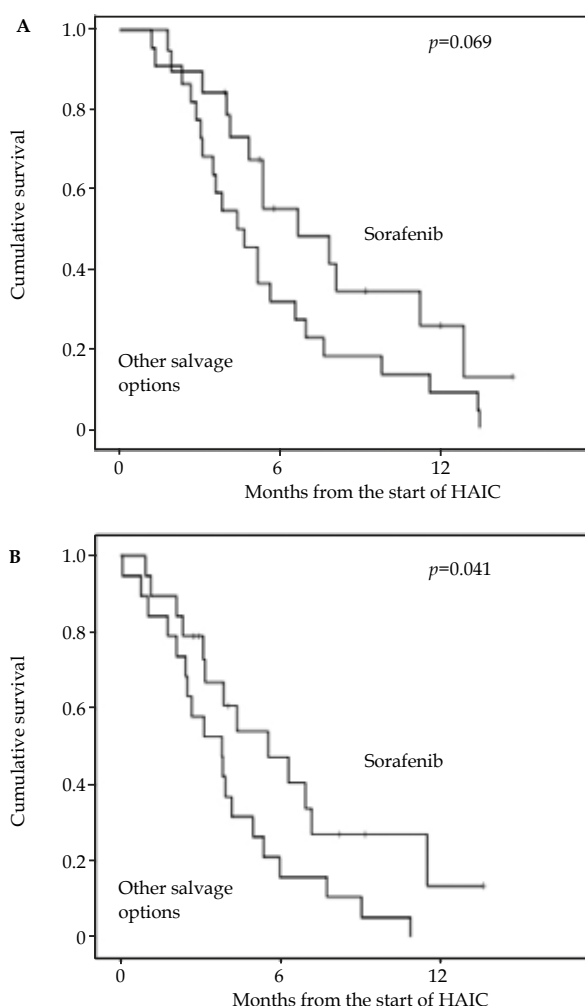


Figure 2 Comparison of overall survival and survival post-progression in hepatic arterial infusion chemotherapy (HAIC)-refractory patients receiving sorafenib and other salvage options. A: Overall survival, as calculated from the date of the first HAIC session with cisplatin powder. Progressive disease patients receiving sorafenib tended to survive longer than patients receiving other salvage options, but the difference was not significant ($P=0.069$). B: Survival post-progression, as calculated from the date of the first sign of radiological progression after the administration of HAIC. Progressive disease patients receiving sorafenib survived significantly longer than patients receiving other salvage options ($P=0.041$).

using univariate and multivariate analyses. These observations suggest a survival benefit of sorafenib as a salvage option among the various post-HAIC options available for patients with PD after having received HAIC.

Sorafenib is the current global standard therapeutic regimen for advanced HCC patients with PVTT or extrahepatic metastasis. In a phase III study (SHARP), the median survival time of patients with advanced HCC treated with sorafenib was 3 months longer than that of patients receiving a placebo^[10], but its use was associated with a low tumor response rate. Sorafenib has also been shown to provide a clinical benefit in subgroup analyses of patients with macroscopic vascular invasion^[10,25]. The modified BCLC staging classification and treatment schedule recently recommended that HCC patients with vascular invasion and those who fail to respond to TACE should receive sorafenib^[9,26,27]. In Japan, sorafenib was approved in May 2009, and some cases with a CR or a PR have been observed relatively frequently^[28]. However, sorafenib treatment also produces toxicities that may significantly affect patients' quality of life. High rates of dermatologic adverse effects are commonly reported in association with sorafenib treatment, the most clinically relevant being hand-foot skin reaction (HFSR)^[25], especially among Asian patients. In a Japanese study, the rate of treatment discontinuation because of sorafenib-induced adverse events, including HFSR, was reportedly as high as 22%^[29], and for the majority of patients, especially elderly patients, a high discontinuation rate because of intolerance and the need for dose reduction has been reported^[11].

In contrast, the Japanese evidence-based guidelines for the diagnosis and treatment of HCC and the consensus-based treatment algorithm for HCC recommend HAIC as a treatment option for patients with intermediate-stage or advanced-stage HCC, based on tolerability and efficacy^[30]. In this setting, sorafenib was recommended for use in HAIC-refractory HCC patients, even though the actual survival benefit of sorafenib after HAIC had not been established. In the present study, we did not confirm a survival benefit of sorafenib using overall survival, the traditional primary end-point for assessing the efficacy of first-line chemotherapy; when the SPP, a surrogate for overall survival, was used to assess the efficacy of second-line chemotherapy, however, sorafenib was found to elongate the SPP among patients receiving sorafenib after HAIC. To the best of our knowledge, the survival benefit of a salvage option after HAIC has never before been published.

SPP, which represents the survival period after disease progression, was defined as the median overall survival minus the median progression-free survival^[31]. Recent chemotherapy regimens are available for effective subsequent-line therapies, thereby contributing to the prolongation of survival time after disease progression occurring after first-line therapy. Such contributions are likely to have a large impact on increasing the SPP. The probability of a statistically significant benefit has been shown in second-line chemotherapy for patients with advanced non-small-cell lung cancer^[21] and breast cancer^[22]. Hereafter, as novel molecular-targeted agents or anticancer drug regimens for HCC become more varied, the SPP is likely to be further lengthened and may become a more statistically significant tool for analyzing the survival benefit of second-line chemotherapy. Furthermore, the median SPP accounted for about 80% of the median overall survival period (data not shown) among sorafenib-treated patients. Since the elongation of the SPP is closely associated with the overall survival of sorafenib-treated patients, the SPP may be a suitable surrogate for overall survival among patients receiving various salvage options after HAIC.

Our study had some limitations, such as its small sample size

and retrospective design, which may have allowed potential biases such as selection and recall biases. The retrospective nature of our analysis also raises potential limitations in the accuracy and complete documentation of the survival benefit of sorafenib among patients with PD after undergoing HAIC. Despite these limitations, our data may have some impact, especially as this report is the first to discuss the efficacy and safety profiles of sorafenib for HAIC-refractory HCC patients. Further studies are needed to confirm whether HAIC with cisplatin powder is a suitable first-line treatment option prior to sorafenib treatment for patients with advanced HCC patients with PVTT or TACE-refractory lesions. Although various clinical trials examining combinations of sorafenib and cytotoxic chemotherapeutic agents for patients with advanced HCC are currently ongoing^[29,32,33], trials involving these agents in a sequential setting are limited. We are currently conducting a randomized phase II study for advanced HCC patients who had PVTT or who were TACE-refractory to investigate the clinical efficacy and tolerability of sequential HAIC with cisplatin powder followed by sorafenib, compared with sorafenib monotherapy. The protocol has been registered at the web site of the University Hospital Medical Information Network (UMIN), Japan (protocol ID UMIN000006147).

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