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Treatment strategies for advanced hepatocellular carcinoma: Sorafenib *vs* hepatic arterial infusion chemotherapy

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Abstract

Sorafenib is used worldwide as a first-line standard

systemic agent for advanced hepatocellular carcinoma (HCC) on the basis of the results of two large-scale Phase III trials. Conversely, hepatic arterial infusion chemotherapy (HAIC) is one of the most recommended treatments in Japan. Although there have been no randomized controlled trials comparing sorafenib with HAIC, several retrospective analyses have shown no significant differences in survival between the two therapies. Outcomes are favorable for HCC patients exhibiting macroscopic vascular invasion when treated with HAIC rather than sorafenib, whereas in HCC patients exhibiting extrahepatic spread or resistance to transcatheter arterial chemoembolization, good outcomes are achieved by treatment with sorafenib rather than HAIC. Additionally, sorafenib is generally used to treat patients with Child-Pugh A, while HAIC is indicated for those with either Child-Pugh A or B. Based on these findings, we reviewed treatment strategies for advanced HCC. We propose that sorafenib might be used as a first-line treatment for advanced HCC patients without macroscopic vascular invasion or Child-Pugh A, while HAIC is recommended for those with macroscopic vascular invasion or Child-Pugh A or B. Additional research is required to determine the best second-line treatment for HAIC non-responders with Child-Pugh B through future clinical trials.

Key words: Treatment strategy; Hepatic arterial infusion chemotherapy; Sorafenib; Hepatocellular carcinoma

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Core tip: In Japan, sorafenib and hepatic arterial infusion chemotherapy (HAIC) are described as treatment options for hepatocellular carcinoma (HCC). Although no randomized controlled trials have compared these treatments, retrospective analyses have shown similar survival between them. Sorafenib is generally used for Child-Pugh A, while HAIC is indicated for Child-Pugh A or B. Compared to sorafenib, HAIC shows better responses in cases exhibiting macroscopic vascular invasion. After reviewing treatment strategies for advanced HCC, we recommended sorafenib as first-line treatment for cases without macroscopic vascular invasion or Child-Pugh A, and HAIC for those with macroscopic vascular invasion or Child-Pugh A or B.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the second most

common cause of cancer related death worldwide^[1]. According to the Global Burden of Disease 2015 study of 195 countries, the number of liver cancer cases increased by 75% between 1990 and 2015, and hepatitis B virus (HBV) was responsible for 33% of global liver cancer mortality compared to 30% from alcohol, 21% from hepatitis C virus (HCV), and 15% from other causes^[2]. However, the incidence of both HBs antigen-negative and HCV antibody-negative HCC (non-B, non-C HCC) has recently increased in Japan^[3,4]. As there are not yet any established surveillance programs for non-B, non-C HCC patients, it is difficult to diagnose such patients at an earlier disease stage. Therefore, the number of advanced HCC patients at the time of diagnosis may be increasing in Japan. Additionally, even if an earlier disease stage of HCC is detected, many patients progress to an advanced stage because of frequent recurrence of the disease. Therefore, it is now more important than ever to develop a treatment for advanced HCC. In this review, we review the treatment strategies for advanced HCC, particularly sorafenib and hepatic arterial infusion chemotherapy (HAIC).

GUIDELINES FOR ADVANCED HCC

The results of the global investigation of therapeutic decisions in HCC and of its treatment with sorafenib (GIDEON) study show differences in the management of HCC, including diagnosis, treatment, and monitoring, among several regions. In consequence, there have been regional differences in patient outcomes^[5]. Although several guidelines for the clinical management of HCC have been established worldwide, there are some differences in the treatment algorithms among these guidelines. Table 1 shows the major recent guidelines from Asia, Europe and the United States^[6-13]. The Barcelona clinic liver cancer (BCLC) staging system, which stratifies patients by tumor stage and underlying liver disease, is widely accepted in clinical practice^[14]. Among the five HCC stages (BCLC 0, A, B, C and D), the advanced BCLC C stage includes symptomatic patients with performance status (PS) 1-2, vascular invasion, extrahepatic spread, or a combination thereof^[14]. For patients with BCLC C and good liver function (Child-Pugh A), sorafenib is the preferred first-line treatment according to guidelines from Europe and the United States^[11-13]. According to guidelines from Asia^[7-9], systemic therapy (molecular-targeted drugs) or transcatheter arterial chemoembolization (TACE) is recommended as standard treatment for such patients. However, HAIC is not generally recommended as a standard of care in the above-mentioned guidelines.

Whereas sorafenib and HAIC are indicated for the patients with minor portal vein invasion (so-called Vp1, 2) or portal invasion at the first portal branch (so-called Vp3) in the Japan Society of Hepatology and Liver Cancer Study Group of Japan (JSH-LCSGJ) Consensus-based Treatment Algorithm for HCC revised in 2014, HAIC, but not sorafenib, is recommended for portal invasion at the main trunk of the portal vein (so-called Vp4)^[6]. Fur-

Table 1 Guidelines for the clinical management of hepatocellular carcinoma

	Publishing year	Guidelines	Drafted by	Treatment algorithm for advanced HCC (BCLC C)	Ref.
Asia	2014	JSH-LCSGJ	Japan Society of Hepatology and Liver Cancer Study Group of Japan	HAIC (Vp1-4), Sorafenib (Vp1-3), TACE (Vp1, 2), Resection (Vp1, 2)	[6]
	2014	KLCSG-NCC	Korean Liver Cancer Study Group and National Cancer Center	TACE, Sorafenib	[7]
	2014	HKLC	Hong Kong Liver Cancer	Systemic therapy, Supportive care	[8]
	2017	APASL	Asian-Pacific Association for the Study of the Liver	Systemic therapy (sorafenib and regorafenib), TACE for patients with no extrahepatic metastasis	[9]
	2017	JSH	Japan Society of Hepatology	TACE, Resection, HAIC, Molecular targeted agents	[10]
Europe	2018	EASL	European Association for the Study of the Liver	Sorafenib (sorafenib, lenvatinib, regorafenib, and cabozantinib)	[11]
	2012	ESMO-ESDO	European Society for Medical Oncology and European Society of Digestive Oncology	Sorafenib	[12]
United States	2011	AASLD	American Association for the Study of Liver Disease	Sorafenib	[13]

HAIC: Hepatic arterial infusion chemotherapy; Vp1-4: Portal vein invasion according to JSH-LCSGJ; TACE: Transcatheter arterial chemoembolization; BCLC: Barcelona clinic liver cancer.

thermore, according to the most recent version (2017) of the Clinical Practice Guidelines for HCC proposed by JSH, TACE, resection, HAIC, and molecular-targeted agents are equally recommended for HCC patients with portal invasion. It has also been argued that the treatment should be selected after considering all of the patient's conditions as a whole^[10].

Finally, the 2017 version of the National Comprehensive Cancer Network (NCCN) Guidelines supports HAIC for unresectable HCC; however, its use in the context of a clinical trial is preferred^[15].

SORAFENIB FOR ADVANCED HCC

Current status of sorafenib

Sorafenib is an oral multi-targeted kinase inhibitor that suppresses tumor growth, and it was the first drug to demonstrate a survival benefit in patients with advanced HCC. In two large-scale Phase III trials, although the response rate of sorafenib was only 2%-3.3% according to the Response Evaluation Criteria in Solid Tumors (RECIST), sorafenib treatment significantly improved overall survival (OS) [sorafenib vs placebo median survival time (MST): 10.7 mo vs 7.9 mo, hazard ratio (HR): 0.69, $P < 0.001$ in the SHARP trial; and MST: 6.5 mo vs 4.2 mo, HR: 0.68, $P = 0.014$ in the Asia-Pacific trial] and the time-to-progression (TTP) (sorafenib vs placebo median TTP: 5.5 mo vs 2.8 mo, HR: 0.58, $P < 0.001$ in the SHARP trial; and TTP: 2.8 mo vs 1.4 mo, HR: 0.57, $P = 0.0005$ in the Asia-Pacific trial) in patients with advanced HCC^[16,17]. Therefore, sorafenib is utilized as a standard first line agent for the treatment of advanced HCC worldwide^[6-13]. Recently, Rimola *et al.*^[18] reported that 1% of patients treated with sorafenib (12/1119) exhibited complete response (CR), according to RECIST, and the MST for those patients was 85.8 mo.

For several years, antiangiogenic tyrosine-kinase

inhibitors other than sorafenib have failed in Phase III clinical trials^[19,20]. However, recent studies have demonstrated the efficacy of two oral multi-kinase inhibitors, the second-line agent regorafenib, which is used for sorafenib-resistant HCC, and the first-line agent lenvatinib, which has been shown to be non-inferior to sorafenib for OS^[21,22].

Regorafenib has been reported as a second-line agent following sorafenib because of improvement in OS (regorafenib vs placebo MST: 10.6 mo vs 7.8 mo, HR: 0.63, $P < 0.0001$) (RESORCE trial)^[21]. According to the results of this study, regorafenib was approved in the United States and Japan in 2017.

Lenvatinib is an oral multi-target inhibitor of vascular endothelial growth factor (VEGF) receptors 1-3, fibroblast growth factor receptors 1-4, platelet-derived growth factor receptor alpha, KIT, and RET^[23]. A comparative global Phase III trial of lenvatinib in the first-line setting (REFLECT trial) demonstrated non-inferiority to sorafenib in advanced HCC patients (lenvatinib vs sorafenib MST: 13.6 mo vs 12.3 mo, HR: 0.92)^[22]. In addition, the progression-free survival (PFS), TTP, and overall response rate (ORR) were significantly better in patients treated with lenvatinib than in those treated with sorafenib (lenvatinib vs sorafenib, median PFS: 7.4 mo vs 3.7 mo, HR: 0.66, $P < 0.0001$; median TTP: 8.9 mo vs 3.7 mo, HR 0.63, $P < 0.0001$; ORR: 24.1% vs 9.2%, $P < 0.0001$). Lenvatinib is approved for unresectable thyroid cancer and has been usable for HCC in Japan prior to it being approved in the rest of the world. However, HCC patients with 50% or higher liver occupation, bile duct invasion, or main portal invasion met the exclusion criteria of the REFLECT trial. Such HCC patients may be candidates for general usage of sorafenib.

Predictive factors for response and survival

Bruix *et al.*^[24] conducted analyses of two large trials

(827 patients, SHARP and Asia-Pacific trials) and reported prognostic factors. According to this report, vascular invasion, high alpha-fetoprotein (AFP), and high neutrophil-lymphocyte ratio (NLR) were prognostic factors for poorer OS, while lack of extrahepatic spread, HCV, and low NLR were predictive factors for greater sorafenib benefit^[24]. Among serum and plasma factors, VEGF^[25-27], angiopoietin-2 (Ang-2)^[25,26], AFP^[25,26,28-31], NLR^[32,33], TIE-2 expressing monocytes (TEMs)^[34], microRNA^[35-37], and circulating tumor cells (CTCs)^[38] have been identified as potential biomarkers (Table 2). The expression of phospho-ERK^[39-41], phospho-c-Jun^[42], and VEGFR-2^[41], and amplification of FGF3/FGF4^[43], have been identified as possible predictive biomarkers in tissues (Table 3). In studies of imaging biomarkers, it has been reported that decreased blood flow after sorafenib treatment^[44] and low pretreatment standardized uptake values of ¹⁸F-fluorodeoxyglucose (FDG) in positron emission tomography (PET)^[45] are associated with prolonged OS. Although there have been several reports of a correlation between adverse effects (hypertension, skin toxicity, diarrhea, etc.) and sorafenib efficacy, it has been difficult to establish conclusions because of difference in the frequencies of these adverse effects among patients of different races. However, Howell *et al.*^[46] reported that patients with sorafenib-related toxicity such as diarrhea, hypertension, and hand-foot syndrome, had good prognoses in a large, multicenter prospective cohort study. Furthermore, the potential of other biomarkers has been explored^[47]. Although several studies have investigated predictive biomarkers for response and survival associated with sorafenib, no such biomarkers have been established.

HAIC FOR ADVANCED HCC

Current status of HAIC

In HAIC, as it is theoretically possible to accumulate local concentrations of anti-cancer drugs in the liver and to reduce their systemic distribution, it is believed to have a stronger antitumor effect and lower incidence of adverse reactions compared with systemic chemotherapy. On the other hand, one disadvantage is the need to master the HAIC procedure, and several adverse effects are associated with HAIC including inflammation of blood vessels, arterial obstructions, peptic ulcers due to drug leakage, and infections or obstructions of reservoir catheters.

According to the 2017 version of the treatment algorithm for HCC produced by JSH^[10], HAIC is recommended as a second-line treatment for patients with ≥ 4 HCCs and an absence of portal invasion, while HAIC is considered a first-line treatment for those with portal invasion.

HAIC has become widely used in Asia, especially Japan, where the main HAIC regimens are low-dose cisplatin (CDDP) combined with 5-fluorouracil (5-FU) (low-dose FP)^[48-51], interferon (IFN) in combination with

5-FU (FAIT)^[50,52,53], and CDDP alone^[51,54-56] (Table 4). In both low-dose FP and FAIT regimens, the key drug is 5-FU. In addition, CDDP or IFN exert their own effects to amplify the effect of 5-FU, and they are therefore considered biochemical modulators of 5-FU. Moreover, one benefit of the CDDP alone regimen is that a catheter is inserted each time, making the troublesome implantation of a reservoir catheter unnecessary. The regimens using low-dose FP or FAIT have response rates of approximately 30%-40%, while the CDDP alone regimen has rates of approximately 20%-30% (Table 4)^[48-53,55-57]. Survival is significantly better in patients with radiological response [CR or partial response (PR)] (so-called responders) than in patients with radiological no-response (stable or progressive disease) (so-called non-responders).

The principal reasons for low clinical recognition of HAIC are the small sample size of almost all studies and the lack of large randomized trials. However, effective results have been demonstrated by previous studies. In a report comparing the FAIT regimen of HAIC with historical controls, HAIC was shown to significantly improve survival^[53]. A Japanese nationwide survey supported the efficacy of the low-dose FP regimen of HAIC for treating advanced HCC^[49]. After adjusting for known risk factors, survival benefits of this therapy were evident (HR: 0.48, 95%CI: 0.41-0.56, $P < 0.0001$). In a propensity score-matched analysis, the MST was longer in patients who received HAIC ($n = 341$, 14.0 mo) than in those who did not receive active treatment ($n = 341$, 5.2 mo) (HR: 0.60, 95%CI: 0.49-0.73, $P < 0.0001$). In cases of Child-Pugh A or B disease with more than three tumors (370 propensity score-matched patients), the MST was longer in patients treated with HAIC (13.9 mo) than in those with no therapy (3.7 mo) ($P < 0.0001$). In cases of Child-Pugh A or B disease with portal vein tumor thrombus (378 propensity score-matched patients), the MST was also longer in patients treated with HAIC (7.9 mo) than in those with no therapy (3.1 mo) ($P < 0.0001$).

Predictive factors for response and survival

As HAIC is selected for advanced HCC patients with poor prognoses, it is important to identify predictive factors for response and survival (Table 5)^[48,49,53,58-61].

The predictive factors for poor response to HAIC include the presence of vascular invasion^[58], the presence of extrahepatic metastasis^[58], $\text{NLR} \geq 2.87$ ^[58], a concentration of serum VEGF ≥ 100 pg/mL^[60], a negative HCV antibody test result^[61], and a platelet count $\geq 15 \times 10^4/\mu\text{L}$ ^[61], and a negative des-gamma-carboxy prothrombin (DCP) response [defined as a reduction of $< 20\%$ or an increase from baseline after a half course of HAIC (2 wk)]^[48].

Survival benefits for HAIC have been reported in HAIC responders^[53,60,61]. However, therapeutic effect is not an effective prognostic predictor. The poor prognostic predictors include not only tumor-associated factors,

Table 2 Serum and plasma biomarkers of sorafenib response and survival

Biomarkers	Ref.	Publishing year	Case number	Predictive factors for response	Predictive factors for survival	Others
VEGF	Llovet <i>et al</i> ^[25]	2012	299	No predictive value	Not prognostic value	
	Miyahara <i>et al</i> ^[26]	2013	120	No predictive value	Not prognostic value	
	Tsuchiya <i>et al</i> ^[27]	2014	63	No predictive value	VEGF response (a > 5% decrease during 8 wk of treatment): Better OS	
Ang-2	Llovet <i>et al</i> ^[25]	2012	299	No predictive value	Low Ang-2: Better OS	
	Miyahara <i>et al</i> ^[26]	2013	120	High Ang2: PD	Low Ang-2: Better OS	
Changes of AFP	Personeni <i>et al</i> ^[28]	2012	85	AFP response (a > 20% decrease during 8 wk of treatment): Better ORR, DCR	AFP response: Better OS	
	Yau <i>et al</i> ^[29]	2011	94	AFP response (a > 20% decrease during 6 wk of treatment): Better DCR	AFP response: Better PFS	
	Kuzuya <i>et al</i> ^[30]	2015	47	-	High AFP ratio (a > 1.2 at 2 wk relative to baseline): Poor OS	High poor prognostic score (the absence of disappearance of arterial tumor enhancement on CE-CT, AFP ratio of > 1.2, and two or more increments in CP score after 2 wk of Treatment): Poor OS and DCR
	Nakazawa <i>et al</i> ^[31]	2013	59	AFP increase (more than 20% from baseline during 4 wk of treatment): PD	AFP increase: Better OS and PFS	
AFP	Llovet <i>et al</i> ^[25]	2012	299	-	AFP > 200 ng/mL: Poor OS	
	Miyahara <i>et al</i> ^[26]	2013	120	-	Not prognostic value	
	Kuzuya <i>et al</i> ^[30]	2015	47	-	Not prognostic value	
NLR	Zheng <i>et al</i> ^[32]	2013	65	-	High NLR (> 4): Poor OS and TTP	
	Howell <i>et al</i> ^[33]	2017	175	-	High NLR (> 2.52): Poor OS	
TEMs	Shoji <i>et al</i> ^[34]	2017	25	High ΔTEMs (changes in TEMs before and at 1 mo after therapy): PD	High ΔTEMs (changes in TEMs before and at 1 mo after therapy): Poor OS	
	Stiuso <i>et al</i> ^[35]	2015	39	Upregulation of miR-423-5p after treatment: SD or PR	-	
MicroRNA	Yoon <i>et al</i> ^[36]	2017	24	-	Low miR-10b-3p: Poor OS	
	Nishida <i>et al</i> ^[37]	2017	53	High miR-181a-5p: PR + SD	High miR-181a-5p: Better OS	
CTCs	Li <i>et al</i> ^[38]	2016	59	pERK+/pAkt- CTCs: Better DCR	pERK+/pAkt- CTCs: Better DCR	

Ang-2: Angiopoietin-2; CE-CT: Contrast-enhanced computed tomography; NLR: Neutrophil to lymphocyte ratio; AFP: Alpha-fetoprotein; CTC: Circulating tumor cells; TEMs: TIE-2-expression monocytes; VEGF: Vascular endothelial growth factor; PD: Progressive disease; OS: Overall survival; DCR: Disease control rate; ORR: Overall response rate; PFS: Progression-free survival; CP: Child-Pugh; pERK: Phosphorylated extracellular signal-regulated kinase; PR: Partial response; SD: Stable disease; TTP: Time to progression.

such as more than three tumors^[49], large tumors (> 3 cm)^[49], the presence of vascular invasion^[49,53], the presence of extrahepatic metastasis^[49,58,61] and high AFP levels^[49,58,61], but also those associated with the patient, including dysfunction of the liver reserve^[48,49,53,58-61], ECOG PS 1-2^[58,61], and a positive HBs antigen test result^[49]. Additionally, poor prognostic predictors include negative responses of AFP or DCP^[48], high levels of inflammation-related markers such as NLR and CRP^[58], low transferrin levels (< 190 mg/dL)^[59] and high VEGF levels (\geq 100 pg/mL)^[60].

A new assessment score: Assessment for continuous treatment with HAIC

It is important to identify the effective benefit of early HAIC treatment in HCC patients. Therefore, we developed a new therapeutic assessment score to guide decisions regarding HAIC treatment, the Assessment for Continuous Treatment with HAIC (ACTH)^[48]. The ACTH score (range, 0-3) is calculated from simple three parameters: Child-Pugh score before HAIC (A = 0, B = 1), AFP response (yes = 0, no = 1), and DCP response (yes = 0, no = 1). The tumor markers' responses are

Table 3 Tissue biomarkers of sorafenib response and survival

Biomarkers	Ref.	Publishing year	Case number	Predictive factors for response	Predictive factors for survival
Expression of p-ERK	Abou-Alfa <i>et al</i> ^[39]	2012	33	-	High pERK: Longer TTP
	Chen <i>et al</i> ^[40]	2013	54	-	High pERK: Longer TTP
	Negri <i>et al</i> ^[41]	2015	77	-	High pERK: Shorter OS and PFS
Expression of p-c-Jun	Hagiwara <i>et al</i> ^[42]	2012	39	High p-c-jun: Poor response	High p-c-jun: Shorter TTP and OS
Expression of VEGFR-2	Negri <i>et al</i> ^[41]	2015	54	-	High VEGFR-2: Shorter OS and PFS
FGF3/FGF4 amplification	Arao <i>et al</i> ^[43]	2013	48	FGF3/FGF4 amplification: Responder	-

ERK: Extracellular signal-regulated kinase; FGF: Fibroblast growth factor; TTP: Time to progression; OS: Overall survival; pERK: Phosphorylated extracellular signal-regulated kinase; PFS: Progressive-free survival; VEGFR: Vascular endothelial growth factor receptor.

Table 4 Regimens of hepatic arterial infusion chemotherapy for advanced hepatocellular carcinoma

Ref.	Publishing year	Case number	Vascular invasion (%)	Regimens	Response rate (%)	Median survival time (mo)
Saeki <i>et al</i> ^[48]	2015	90	ND	Low-dose FP, including the combination of LV/IV or IV plus IFN	34.4	10.6
Nouso <i>et al</i> ^[49]	2013	476	44.1	CDDP + 5-FU	40.5	14.0 (341 patients)
Monden <i>et al</i> ^[50]	2012	34	90	IFN α , 5-FU	26.7	8.4
		35	90.3	Low-dose FP/CDDP	25.8	11.8
Yamashita <i>et al</i> ^[52]	2011	57	26.7	IFN α , CDDP, 5-FU	45.6	17.6
		57	50	IFN α , 5-FU	24.6	10.5
Nagano <i>et al</i> ^[57]	2011	102	100	IFN α , 5-FU	39.2	9
Obi <i>et al</i> ^[53]	2006	116	100	IFN α , 5-FU	52	6.9
Ikeda <i>et al</i> ^[54]	2013	25	100	CDDP powder (IA call)	28	7.6
Iwasa <i>et al</i> ^[55]	2011	84	31	CDDP powder (IA call)	3.6	7.1
Kim <i>et al</i> ^[51]	2011	41	83.3	CDDP	12.2	7.5
		97		CDDP, 5-FU	27.8	12
Yoshikawa <i>et al</i> ^[56]	2008	80	27.5	CDDP powder (IA call)	33.8	ND

ND: Not described; Low-dose FP: Low-dose 5-FU plus Cisplatin; LV: Leucovorin; IV: Isovornin; IFN: Interferon; CDDP: Cisplatin.

assessed as the difference between the baseline and 2 wk after HAIC induction (positive response: A reduction of $\geq 20\%$ from the baseline). ACTH score could stratify patients' survival (score ≤ 1 vs score ≥ 2 , 15.1 mo vs 8.7 mo; $P = 0.003$)^[48]. A validation study similarly showed that this score is useful for therapeutic assessment^[62]. Therefore, the ACTH score makes it possible to provide an early prediction of the prognosis of advanced HCC patients receiving HAIC, and can improve treatment efficiency by switching to other treatments, such as sorafenib or an experimental treatment in a clinical trial, for patients with a score ≥ 2 (Figure 1).

Modified HAIC and the combination approach

Nagamatsu *et al*^[63] developed a modified procedure for administering a low-dose FP regimen: HAIC using 5-FU after lipiodol-transcatheter arterial infusion chemotherapy (Lip-TAI) with CDDP; a multicenter phase II study showed that the MST and response rate were 27.0 mo and 75% for advanced HCC patients with portal vein thrombosis, respectively^[64]. Although this regimen produced a favorable outcome, it has not become widespread owing to the high level of proficiency needed for the procedure.

A multicenter open-labeled randomized Phase II

trial was conducted to evaluate the effect of combining the CDDP regimen of HAIC with sorafenib for treating advanced HCC. The results showed that survival was significantly better for patients receiving sorafenib plus HAIC (MST, 10.6 mo) than those receiving sorafenib alone (MST, 8.7 mo) (HR: 0.60, $P = 0.031$)^[65]; however, there was not a significant difference in survival between patients receiving sorafenib plus HAIC using low-dose FP and those receiving sorafenib alone^[66]. Therefore, further investigation is required.

Radiotherapy (RT) has become recognized as an optional treatment for HCC in the APASL and NCCN guidelines^[9,15], but it is not recommended in the AASLD and EASL guidelines^[11,13]. For advanced HCC patients with intravascular tumor thrombus, a combination of HAIC with RT is a reasonable approach. Compared to HAIC alone, a beneficial effect of 3-D conformal radiotherapy (3D-CRT) for major portal vein tumor thrombosis combined with HAIC has been demonstrated, although these results came from retrospective cohort studies^[67,68].

SORAFENIB VS HAIC

Sorafenib is recommended as a first-line treatment worldwide for advanced HCC patients (those with

Table 5 Predictive factors for response and survival of hepatic arterial infusion chemotherapy for advanced hepatocellular carcinoma

Ref.	Publishing year	Case number	Regimens	Poor predictive factors for response	Poor predictive factors for survival
Saeki <i>et al</i> ^[48]	2015	90	Low-dose FP with/without LV, IV, or IV plus IFN	DCP reduction or increase of < 20% from baseline to 2 wk after HAIC	Child-Pugh B, AFP reduction or increase of < 20% from baseline to 2 wk after HAIC, DCP reduction or increase < 20% from baseline to 2 wk after HAIC
Terashima <i>et al</i> ^[58]	2015	266	IFN α , 5-FU with/without CDDP	NLR \geq 2.87 (cut-off, median value), presence of vascular invasion, presence of extrahepatic metastasis	NLR \geq 2.87 (cut-off, median value), ECOG PS 1/2, Child-Pugh score 8-9, presence of extrahepatic metastasis, CRP \geq 0.8 mg/dL, AFP \geq 235.5 ng/mL
Zaitzu <i>et al</i> ^[59]	2014	44	Low-dose FP with/without IV, or IV plus IFN	ND	Child-Pugh B, serum transferrin < 190 mg/dL
Nouso <i>et al</i> ^[49]	2013	476	CDDP + 5-FU	ND	HBs antigen positive, Child-Pugh B, tumor number > 3, tumor size > 3 cm, presence of extrahepatic metastasis, Vp3/4, AFP > 400 ng/mL
Niizeki <i>et al</i> ^[60]	2012	71	Low-dose FP	VEGF \geq 100 pg/mL	Child-Pugh B, VEGF \geq 100 pg/mL, therapeutic effect SD + PD
Miyaki <i>et al</i> ^[61]	2012	249	Low-dose FP (106 patients); IFN α , 5-FU (143 patients)	HCV antibody negative, platelet count \geq 15 \times 10 ⁴ / μ L	ECOG PS 1-2, Child-Pugh score 8-9, presence of extrahepatic metastasis, AFP \geq 1000 ng/mL, absence of additional therapy, therapeutic effect SD + PD + DO
Obi <i>et al</i> ^[53]	2006	116	IFN α , 5-FU	Not detect	Vp4, Total bilirubin \geq 1.0 mg/dL, therapeutic effect PR + SD + PD

Low-dose FP: Low-dose 5-FU plus Cisplatin; LV: Leucovorin; IV: Isovornin; IFN: Interferon; CDDP: Cisplatin; DCP: Des-gamma-carboxy prothrombin; NLR: Neutrophil-to-lymphocyte ratio; ND: Not described; VEGF: Vascular endothelial growth factor; PS: Performance status; SD: Stable disease; PD: Progressive disease; DO: Drop-out; CR: Complete response.

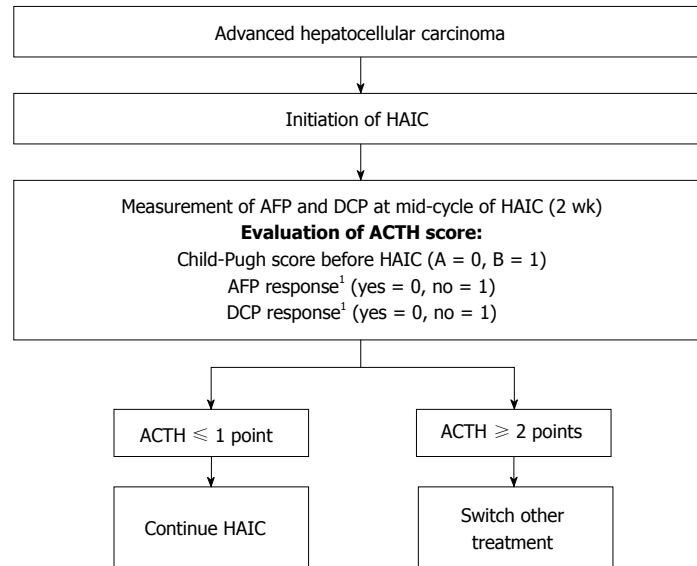


Figure 1 Treatment strategy for advanced hepatocellular carcinoma according to the hepatic arterial infusion chemotherapy score to assess continuous treatment. The score (range, 0-3) was calculated as follows: Child-Pugh score before hepatic arterial infusion chemotherapy (HAIC) (A = 0, B = 1), alpha-fetoprotein (AFP) response (yes = 0, no = 1), and des-gamma-carboxy prothrombin (DCP) response (yes = 0, no = 1). For patients with a score \leq 1, HAIC treatment would be continued, while for patients with a score \geq 2, a second-line therapy such as sorafenib and/or participation in a new clinical trial would be a better option. ¹The AFP and DCP responses were assessed 2 wk after HAIC induction; a positive response is defined as a reduction of \geq 20% from baseline. ACTH: Arterial infusion chemotherapy.

BCLC-C HCC)^[11-13]. Because of the low response rate to sorafenib, we suggest that maintaining the stability of HCC by suppressing tumor growth can significantly improve survival. Sorafenib therapy also worsens sur-

vival in patients with Child-Pugh B, unlike those with Child-Pugh A^[69]. Therefore, advanced HCC patients with Child-Pugh A are candidates for general usage of sorafenib.

Table 6 Clinical characteristics of three advanced hepatocellular carcinoma patients with complete response who have survived over 10 years

Age diagnosed as HCC	Sex	Etiology	Child-Pugh	Tumor stage ¹	Previous treatment	Maximum tumor size (mm)	Vascular invasion ¹	Regimen	Therapeutic effect	AFP (ng/mL)	DCP (mAU/mL)	HCC recurrence	Prognosis	Cause of death
67	Male	HCV	A (5)	IVA	None	110	Vp4, Vv0	Low-dose FP	CR	120700	260	62 mo	151 mo (dead)	Hepatic failure
66	Male	HCV	A (5)	III	None	50	Vp0, Vv0	Low-dose FP + IV	CR	6.4	2970	None	176 mo (dead)	Larynx cancer
44	Male	HBV	B (7)	III	None	150	Vp3, Vv3	Low-dose FP + IV + Peg IFN	CR	7145	233640	None	148 mo (alive ²)	-

¹According to the Liver Cancer Study Group of Japan; ²The follow-up period ended on January 31, 2018. HCC: Hepatocellular carcinoma; AFP: Alpha-fetoprotein; DCP: Des-γ-carboxyprothrombin; HCV: Hepatitis C virus; HBV: Hepatitis B virus; CR: Complete remission; Low-dose FP: Low-dose fluoropyrimidine combined with 5-FU; IV: Isovornin; Peg IFN: Pegylated interferon.

On the other hand, HAIC is not widely recommended as a standard of care for advanced HCC patients. As HAIC is thought to be one of the most effective treatment options for such patients, HAIC has become widely used in Asia, especially Japan. We propose that HAIC might be used as a treatment for achieving CR or PR. If patients with PR after HAIC receive additional therapies such as surgical resection, local ablation, or radiation, it is possible for those who show a disappearance of viable HCC to have a long survival time^[64]. In addition, although liver reserve dysfunction is a poor prognostic factor^[48,49,53,58-61], advanced HCC patients with Child-Pugh B are candidates for HAIC^[6,10].

Currently, no criteria have been established for selecting advanced HCC patients to receive either sorafenib or HAIC. According to the results of two largescale randomized controlled trials (RCTs), sorafenib indeed improved the survival of patients with macroscopic vascular invasion^[16,17]. However, these HCC patients with macroscopic vascular invasion have poorer prognoses than those without such invasion^[16,17,70,71]. Moreover, there have been no RCTs comparing sorafenib with HAIC. In a retrospective cohort study, while there was no significant difference in survival between the sorafenib group and the HAIC group, survival was significantly better in the HAIC group than in the sorafenib group among patients with macroscopic vascular invasion (14 mo vs 7 mo, $P = 0.005$)^[72]. A propensity score matched analysis also showed no significant differences in survival or disease progression between the two groups, while PFS was significantly longer in the HAIC group than in the sorafenib group, particularly for patients with portal vein invasion and/or without extrahepatic spread^[73]. On the other hand, survival was favorable in patients with HCC refractory to TACE treated with sorafenib rather than HAIC^[74]. Furthermore, it is important to preserve liver function during and after chemotherapy in advanced HCC patients. It has been reported that liver function after therapy was not significantly reduced in patients treated with HAIC compared with those treated with sorafenib^[75], and the Child-Pugh score of HAIC responders with deteriorated liver function was significantly improved after HAIC^[76]. According to our report^[62], most HAIC responders showed no deterioration of liver function. It was interesting to note that the Child-Pugh class of some responders with deteriorated live function improved from B to A after HAIC, but this did not occur in non-responders. Therefore, we conclude that HAIC may be well tolerated by advanced HCC patients with deteriorated liver function.

As of 2017, only 10 years have passed since sorafenib was first shown to be efficacious against advanced HCC. As such, it is impossible to assess survival longer than 10 years. However, we can examine survival rates from shorter-duration studies. As previously mentioned, Rimola *et al.*^[48] reported a CR rate and MST for CR patients under sorafenib of 1% and 85.8 mo, respectively. Shiba *et al.*^[77] reported that the CR rate was below 0.6% (18/3047 patients) in a nationwide study from Japan. By contrast, the CR rate for HAIC was 4.0% (19/476 patients) in a nationwide survey in Japan^[49]. According to our previous report^[78], the CR rate under HAIC using a low-dose FP-based regimen was 5% (6/114 patients), and overall 1-, 3-, 5-, 7-, and 10-year cumulative survival rates were 43.9%, 10.0%, 5.6%, 2.8%, and 2.8%, respectively (MST, 10.2 mo). Three of six CR patients from our study survived over 10 years, though 2 patients have since died and only one is still alive (Table 6 and Figure 2). Further investigations are

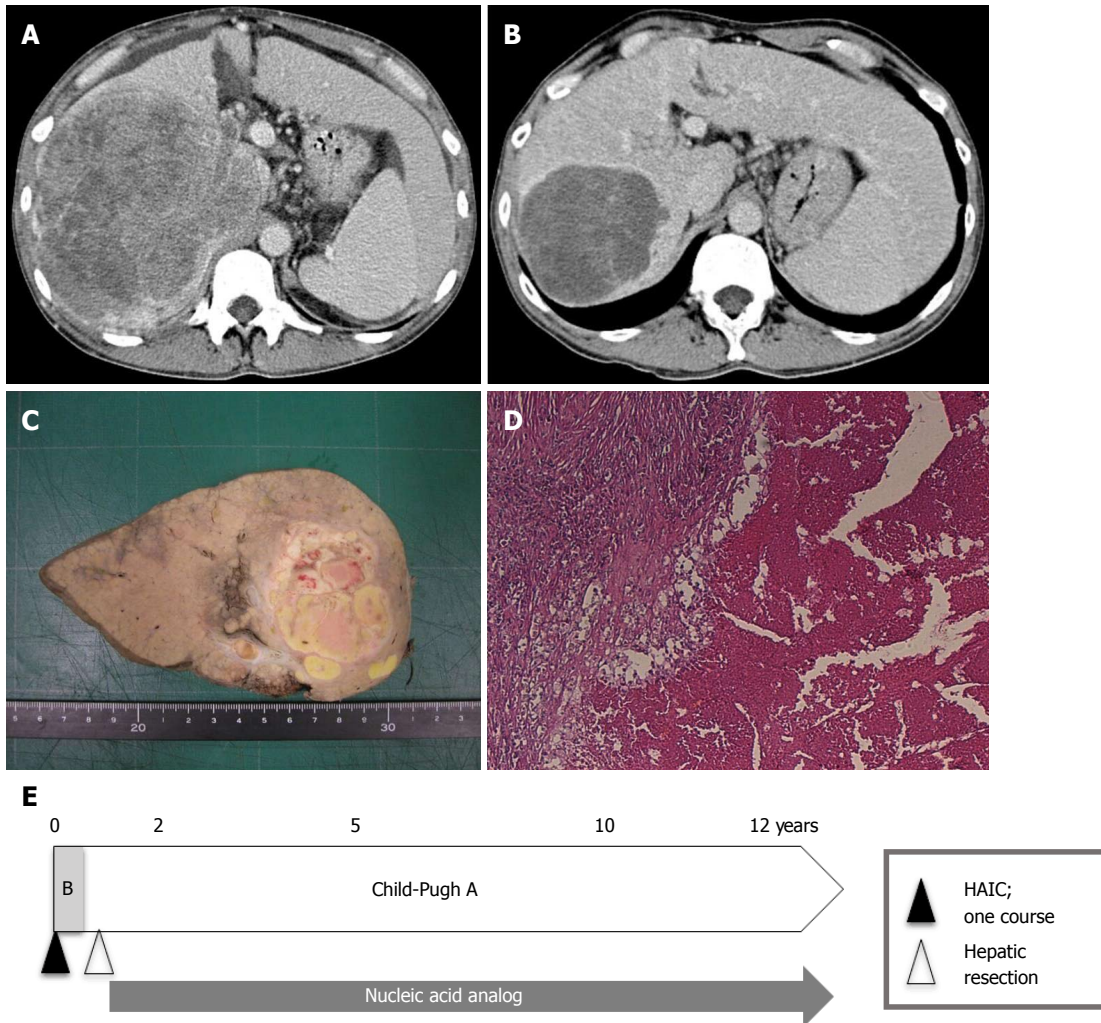


Figure 2 Patient with complete response treated with hepatic arterial infusion chemotherapy using low-dose cisplatin combined with a 5-fluorouracil (low-dose FP)-based regimen. A: This 44-year-old man had massive hepatocellular carcinoma (HCC) (16 cm in diameter) with tumor thrombosis in the right portal vein (Vp3) and the inferior vena cava (Vv3) on dynamic computed tomography; B: After one course of hepatic arterial infusion chemotherapy (HAIC), the liver tumor markedly decreased; however, as slight tumor vascularity remained, the patient was assessed as having partial response at that time; C, D: Three tumor markers [alpha-fetoprotein (AFP), des- γ -carboxyprothrombin (DCP), and AFP L3] decreased after HAIC (AFP from 7145 ng/mL to 12.7 ng/mL, DCP from 233460 mAU/mL to 51 mAU/mL, AFP L3 from 58.1% to 3.1%). The patient's Child-Pugh classification improved from B (8 points) to A (5 points). Thus, hepatic resection was performed, and histological findings showed no viable tumor cells (C, D). Finally, the patient was considered to have a complete response; E: The patient has been treated with nucleic acid analogs after the operation, and Child-Pugh A has been maintained. The patient is alive without HCC recurrence 148 mo after HAIC treatment.

required to compare long-term survival rates between sorafenib and HAIC.

Finally, we present a draft proposal of a treatment strategy for advanced HCC (Figure 3): (1) For advanced HCC patients without macroscopic vascular invasion and Child-Pugh A, the first-line treatment should be sorafenib, and second-line treatments should be either regorafenib^[21] or HAIC; (2) For advanced HCC patients with macroscopic vascular invasion and Child-Pugh A, the first-line treatment should be HAIC, and the second-line treatments should be either sorafenib or experimental treatment in clinical trials; (3) For advanced HCC patients with Child-Pugh B, the first-line treatment should be HAIC, and the second-line treatment should be clinical trials. Miyaki *et al.*^[79] reported that additional therapy with sorafenib improved the prognosis of HAIC refractory patients compared with that of patients not

treated with sorafenib therapy in a retrospective cohort study. Nonetheless, there have been no effective treatments for HAIC non-responders with deteriorated liver function (Child-Pugh B). We have shown the efficacy of an intra-arterial infusion therapy using the iron chelator deferoxamine for advanced HCC patients with deteriorated liver function^[78,80], and clinical trials are now ongoing^[81]. Because the best second-line treatment for HAIC non-responders with Child-Pugh B is to enroll in clinical trials, this remains an issue for future research.

CONCLUSION

We reviewed the current status and predictive biomarkers regarding the administration of sorafenib and HAIC for advanced HCC, and we have proposed a treatment strategy for patients with advanced HCC. The success

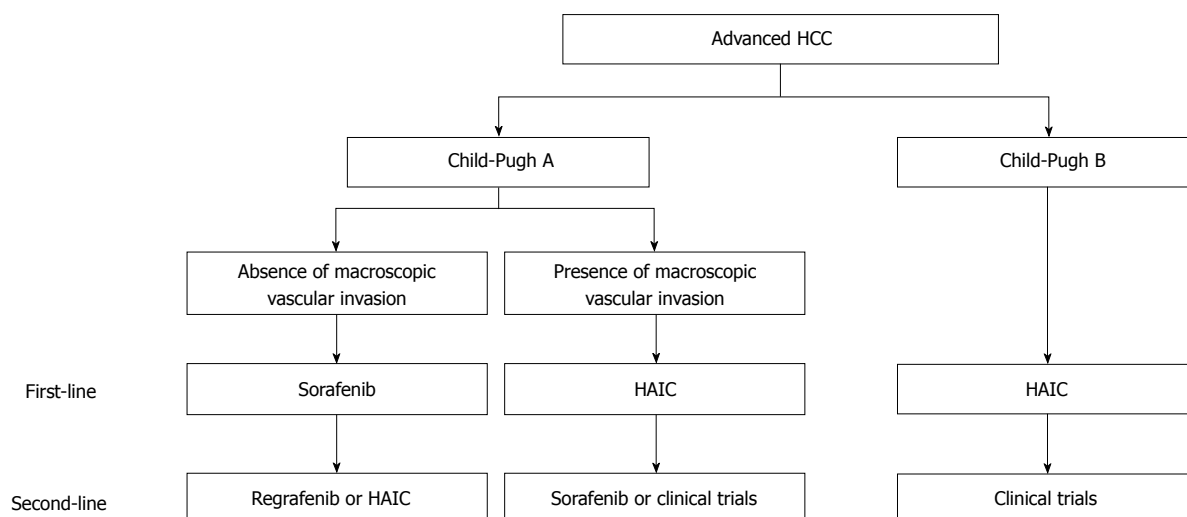


Figure 3 Draft proposal of a treatment strategy for advanced hepatocellular carcinoma. (1) For advanced hepatocellular carcinoma (HCC) patients without macroscopic vascular invasion and Child-Pugh A, the first-line treatment should be sorafenib, while second-line treatments should be either regorafenib or hepatic arterial infusion chemotherapy (HAIC); (2) For advanced HCC patients with macroscopic vascular invasion and Child-Pugh A, the first-line treatment should be HAIC, and the second-line treatments should be either sorafenib or experimental treatment in clinical trials; (3) For advanced HCC patients with Child-Pugh B, the first-line treatment should be HAIC, and the second-line treatment should be clinical trials.

of sorafenib, regorafenib, and lenvatinib in treating advanced HCC has shifted the treatment paradigm to molecular-targeted therapies. Furthermore, several immune-oncologic agents have been identified with potential for the treatment of advanced HCC^[82,83]. Thus, the chemotherapeutic interventions for advanced HCC have been kept up-to-date through several advances. However, alternative therapies will be required because of the high cost and ineffectiveness of these molecular agents for patients with deteriorated liver function.

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