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Original Article

History of Transcatheter Arterial Chemoembolization Predicts the Efficacy of Hepatic Arterial Infusion Chemotherapy in Hepatocellular Carcinoma Patients

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This study sought to identify factors that are predictive of a therapeutic response to hepatic arterial infusion chemotherapy (HAIC) by focusing on the number of prior transcatheter arterial chemoembolization (TACE) sessions. To determine the parameters predicting a good response to HAIC, we retrospectively analyzed 170 patients with hepatocellular carcinoma (HCC) who received HAIC regimens comprising low-dose cisplatin combined with 5-fluorouracil (LFP) or cisplatin (CDDP) for the first time. In both the LFP and CDDP regimens, the response rates were significantly lower in patients with three or more prior TACE sessions than in those with two or fewer prior TACE sessions (LFP 57% versus 28%; $p=0.01$, CDDP 27% versus 6%; $p=0.01$). Multivariable logistic regression analysis revealed that the number of prior TACE sessions (≥3) was significantly associated with non-responder status (odds ratio 4.17, 95% Confidence Interval (CI) 1.76-9.86) in addition to the HAIC regimen. Multivariable analysis using the Cox proportional hazards model revealed that a larger number of prior TACE sessions (≥3) was a significant risk factor for survival (hazard ratio 1.60, 95% CI 1.12-2.29) in addition to Child-Pugh class, serum alpha-fetoprotein concentration, and maximum diameter of HCC. HCC patients who receive fewer prior TACE sessions (≤2) were found to be better responders to HAIC.

Key words: hepatic arterial infusion chemotherapy, hepatocellular carcinoma, refractory, transcatheter arterial chemoembolization

Most treatment algorithms for hepatocellular carcinoma (HCC) recommend transcatheter arterial chemoembolization (TACE) as the standard-of-care for intermediate HCC [1-3]. Guidelines from the American Association for the Study of Liver Disease (AASLD) [1] and the European Association for the Study of the Liver (EASL) [2] recommend molecular-targeted agents as an alternative therapy when TACE is unsuitable or when patients are refractory to TACE.

In contrast, the Japanese clinical practice guideline for HCC [3] recommends the use of hepatic arterial infusion chemotherapy (HAIC) as well as molecular-targeted agents based on studies that have reported the anticancer effects of HAIC in some patients with intermediate or locally advanced HCC without distant metastasis. In a prospective phase 2 study with HCC patients, Ikeda *et al.* [4] found that sorafenib plus HAIC

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with cisplatin significantly prolonged overall survival when compared to sorafenib alone. In a prospective phase 3 trial, Kudo *et al.* [5] found that the combination therapy of sorafenib and HAIC with low-dose cisplatin plus 5-fluorouracil improved the median survival time of HCC patients with main portal vein invasion when compared to sorafenib monotherapy. Furthermore, in a large-scale nationwide propensity-score matched analysis, Nouso *et al.* [6] found that the median survival time was longer for patients who underwent HAIC with 5-fluorouracil and cisplatin than for patients who did not receive active treatment.

Because no definite biomarker has been established that predicts the response to HAIC and molecular-targeted agents, it has been difficult to establish whether use HAIC or molecular-targeted agents would benefit HCC patients. Patients with HCC that is refractory to TACE are known to exhibit a poorer response to HAIC compared with those who are not refractory to TACE [7,8]. We speculated that pretreatment TACE status might be a marker that predicts which patients may benefit from HAIC. Few previous studies have attempted to explore this relationship precisely.

Our study aimed to identify predictive factors that determine the therapeutic response to HAIC, especially focusing on the number of prior TACE sessions in a cohort of clinically consecutive patients.

Materials and Methods

Patients. Between 1999 and 2016, 271 patients with HCC who received HAIC at the Department of Gastroenterology and Hepatology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences were enrolled in this study.

The exclusion criteria for 101 patients are listed in Fig. 1, and the remaining 170 patients were analyzed. Of these patients, 97 patients received low-dose cisplatin combined with 5-fluorouracil (LFP) and 73 patients received cisplatin (CDDP).

The study protocol was approved by the Human Ethics Review Committee of Okayama University (#2007-013) and was conducted in accordance with the Declaration of Helsinki.

Diagnosis and eligibility criteria for HAIC. HCC was diagnosed by typical imaging findings using early-phase enhancement and late-phase contrast washout on dynamic computed tomography (CT) [9,10] or dynamic magnetic resonance imaging (MRI) [10] together with the elevation of serum alpha-fetoprotein (AFP) or des-gamma-carboxy prothrombin (DCP) concentration [11].

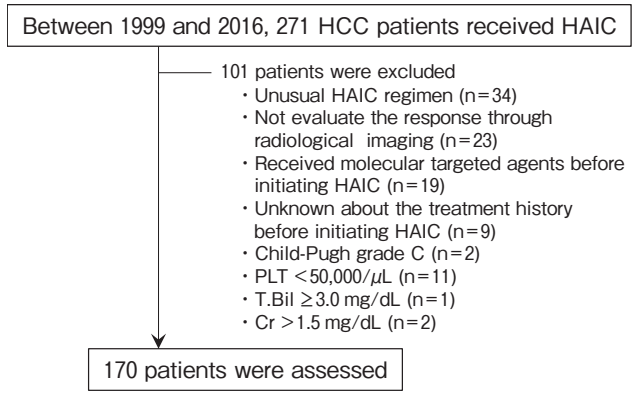

Fig. 1 Study profile. HCC, hepatocellular carcinoma; HAIC, hepatic arterial infusion chemotherapy; PLT, platelet; T.Bil, total bilirubin; Cr, creatinine.

The eligibility criteria for HAIC at our institution were as follows: 1) Child-Pugh A or B; 2) Eastern Cooperative Oncology Group (ECOG) performance status [12] 0-2; 3) ineligible for curative treatments such as hepatic resection and thermal ablation; 4) unsuitable for or refractory to TACE [13]; 5) no refractory ascites; 6) leukocyte count ≥1,500 /μL, platelet count ≥50,000 /μL, serum total bilirubin <3.0 mg/dL, serum creatinine ≤1.5 mg/dL; 7) lacking distant metastasis, or with distant metastasis if the intrahepatic tumor burden was estimated to be the critical prognostic factor.

Catheterization and treatment protocol. The treatment procedure of TACE was as follows: a mixture of iodized oil (Guerbet, Tokyo, Japan) and epirubicin (Pfizer, Tokyo, Japan, or Sawai Pharmaceutical, Osaka, Japan) were injected through a microcatheter located at the tumor feeder distal to the segmental or subsegmental hepatic artery, followed by gelatin sponge particles (Nippon Kayaku, Tokyo, Japan).

To deliver the LFP regimen, an intra-arterial catheter was inserted from the right femoral artery and its tip was placed in the gastroduodenal artery with a side hole at the common hepatic artery. The right gastric and the gastroduodenal arteries were embolized to avoid efflux of chemotherapeutic agents into the stomach and duodenum. In patients with a "replaced" right hepatic artery, *i.e.*, patients in whom this artery arises from the

superior mesenteric artery rather than the celiac artery, the right hepatic artery was embolized to alter the blood flow. An indwelling reservoir was implanted subcutaneously in the anterior right thigh. The treatment protocol for LFP was continuous hepatic arterial infusion with 5-fluorouracil (Kyowa Kirin, Tokyo, Japan, or Towa Pharmaceutical, Osaka, Japan) (250 mg/day, Monday-Friday for 4 weeks), and daily hepatic arterial infusion with cisplatin (Nippon Kayaku, Tokyo, Japan, or Yakult Honsha, Tokyo, Japan) (10 mg/body for 30 min, Monday-Friday for 4 weeks). [14, 15].

In the CDDP regimen, cisplatin (IA call®; Nippon Kayaku, Tokyo, Japan) was administered concurrently for 30 minutes at 65 mg/m^2/cycle via a catheter placed in the proper hepatic artery [16], or in the left and right hepatic artery when the patient had a replaced right hepatic artery.

After a drug washout period of 4-6 weeks to reduce chemotherapy-related toxicity, patients received periodic and repeated treatment until the radiological assessment of disease progression was performed or until intolerable severe adverse events occurred.

The HAIC regimen (LFP or CDDP) to be used was discussed by a cancer board comprising hepatologists belonging to our institution. In general, the response rate to the LFP regimen has been suggested to be higher than that to the CDDP regimen [16-20]. However, the LFP regimen is invasive, in that a reservoir must be implanted, and the course of LFP requires more time than the CDDP regimen to complete. Therefore, the cancer board recommended that only more advanced and younger HCC patients receive the LFP regimen.

Evaluation. To assess the response to HAIC within the intrahepatic HCC nodules, we used the Response Evaluation Criteria in Solid Tumors guidelines version1.1 [21] and applied them to radiological imaging (contrast-enhanced CT or MRI), which was performed one month after the end of 1 course of HAIC.

The number of TACE sessions performed before the first HAIC was counted as the number of prior TACE sessions. Those TACE procedures performed in combination with curative treatments such as surgical resection and thermal ablation were excluded from this count.

The survival duration was assessed from the date of the first HAIC to the date of death or the last follow-up day.

Statistical analysis. All statistical analyses were performed using the JMP statistical software package, version14.0 (SAS Institute, Cary, NC, USA). Continuous variables are expressed as medians and ranges. Statistical significance was assessed by a nonparametric test. Pearson's $\chi 2$ test was performed to compare categorical variables. Univariable and multivariable analyses were performed using logistic regression to determine the parameters predicting response to HAIC. In the univariable and multivariable analyses, cut-off values of continuous variables were adopted from previous reports [11, 22-25]. The results of univariable and multivariable analyses are presented as odds ratios (ORs) with corresponding 95% confidence intervals (CIs). Survival curves were generated by the Kaplan-Meier method and compared by the log-rank test. Univariable and multivariable analyses were performed using the Cox proportional hazards model to determine the parameters predicting survival. The results of univariable and multivariable analyses are presented as hazard ratios (HRs) with corresponding 95% CIs. *P* values less than 0.05 were considered statistically significant.

Results

Patient profiles. Demographic and clinical characteristics of the patients enrolled in this study are summarized in Table 1. Most of the patients presented with intermediate or locally advanced HCC without distant metastasis according to the Barcelona Clinic Liver Cancer staging system [26]. More patients received the LFP regimen than the CDDP regimen. The maximum diameter of the HCC was significantly greater, and the proportion of patients with tumor invasion to the main trunk or first-order branches of the portal vein was significantly higher in the LFP group than in the CDDP group. Median age and the number of prior TACE sessions in the CDDP group were significantly higher than those in the LFP group.

Treatment response. Of all the patients, 10 (6%) exhibited complete response, 50 (29%) exhibited partial response, 48 (28%) exhibited stable disease, and 62 (36%) exhibited progressive disease as the best overall response. The response rate (complete response and partial response) was 35%, and the disease control rate (complete response, partial response, and stable disease) was 64%. With respect to the HAIC regimen, the

Table 1 Demographic and clinical characteristics of the patients

	Total (n=170)	LFP Group (n=97)	CDDP Group (n=73)	*P*-value
Age, years†	69 (31–89)	65 (31–89)	73 (43–85)	<0.01
Gender (male)	137 (81%)	84 (87%)	53 (73%)	0.02
HBsAg (positive)	37 (22%)	24 (25%)	13 (18%)	0.27
Anti-HCV (positive)	100 (59%)	58 (60%)	42 (58%)	0.76
Child-Pugh class (B)	58 (34%)	29 (30%)	29 (40%)	0.18
WBC, /μL†	4290 (1960–13460)	5100 (2400–13460)	3820 (1960–10180)	<0.01
Hgb, g/dL†	12.3 (6.9–18.5)	12.7 (8.7–18.5)	11.9 (6.9–16.0)	0.01
PLT, $\times 10^4/\mu L$†	12.8 (5.0–65.3)	14.2 (6.0–65.3)	11.3 (5.0–27.7)	<0.01
T.Bil, mg/dL†	0.91 (0.21–2.88)	0.86 (0.38–2.73)	0.98 (0.21–2.88)	0.06
Alb, g/dL†	3.4 (2.3–4.6)	3.6 (2.3–4.6)	3.2 (2.4–4.6)	<0.01
Cr, mg/dL†	0.74 (0.39–1.43)	0.72 (0.39–1.17)	0.76 (0.39–1.43)	0.01
AFP, ng/mL†	163 (1.6–455560)	373 (2.1–455560)	77 (1.6–413400)	<0.01
DCP, mAU/mL†	902 (10–942700)	2306 (10–708400)	316 (10–942700)	<0.01
Maximum diameter of HCC, mm†	50 (7–200)	60 (10–200)	30 (7–179)	<0.01
No. of HCC (multiple)	146 (86%)	86 (89%)	60 (82%)	0.23
PVTT (Vp3 or Vp4)	46 (27%)	38 (39%)	8 (11%)	<0.01
Distant metastasis (presence)	23 (14%)	17 (18%)	6 (8%)	0.07
No. of prior TACE sessions†	1 (0–13)	0 (0–13)	2 (0–12)	<0.01

LFP, low-dose cisplatin combined with 5-fluorouracil; CDDP, cisplatin; HBsAg, hepatitis B surface antigen; anti-HCV, antibody against hepatitis C virus; WBC, white blood cell; Hgb, hemoglobin; PLT, platelet; T. Bil, total bilirubin; Alb, albumin; Cr, creatinine; AFP, alpha-fetoprotein; DCP, des-gamma-carboxy prothrombin; HCC, hepatocellular carcinoma; No., number.; PVTT, portal vein tumor thrombosis; Vp3, tumor invasion to the first-order branches of the portal vein; Vp4, tumor invasion to the main trunk of the portal vein; TACE, transcatheter arterial chemoembolization. †Data were expressed as median (range) unless otherwise noted.

response rate of LFP was significantly higher than that of CDDP (49% versus 16%; $p<0.01$).

Table 2 depicts the clinical background of the responders and the non-responders. When compared to responders, a significantly higher proportion of the non-responders received the CDDP regimen (55% versus 20%; $p<0.01$) and had ≥3 prior TACE sessions (47% versus 15%; $p<0.01$). On the contrary, the maximum diameter of HCC, number of HCC lesions, and presence of distant metastasis did not influence the response to HAIC.

Figure 2 demonstrates the relationship between the response rate to HAIC and the number of prior TACE sessions. In both regimens, the response rates to HAIC were significantly lower in the patients with three or more prior TACE sessions than in those with two or fewer prior TACE sessions (LFP 57% versus 28%; $p=0.01$, CDDP 27% versus 6%; $p=0.01$).

Among 15 pretreatment clinical parameters, the *p*-values of platelet count (≤12.0×10^4/μL), presence of tumor invasion to the main trunk or the first-order branches of the portal vein, HAIC regimen (CDDP), and number of prior TACE sessions (≥3) were less than 0.10 in the univariable analyses for non-responders. Multivariable logistic regression with these factors revealed that two were significant risk factors for non-responders: HAIC regimen (CDDP) (OR 4.21, 95% CI 1.86-9.53) and number of prior TACE sessions (≥3) (OR 4.17, 95% CI 1.76-9.86) (Table 3).

Survival. The median survival time and the cumulative survival rate at 12 months for all patients was 11.4 months and 50%, respectively (Fig. 3A). The patients who received two or fewer prior TACE sessions had significantly prolonged survival compared with those who received three or more prior TACE sessions ($p=0.02$) (Fig. 3B). In both HAIC regimens, responders had significantly prolonged median survival times compared with non-responders (LFP, 16.4 months versus 6.8 months, $p<0.01$; CDDP, 28.6 months versus 10.9 months, $p<0.01$) (Fig. 3C, D).

Among 15 pretreatment clinical parameters, the *p*-values of Child-Pugh class B, serum AFP concentration (≥200 ng/mL), maximum diameter of HCC (≥50 mm), presence of distant metastasis, and number of prior TACE sessions (≥3) were less than 0.10 in the univariable analyses for survival. Multivariable analysis with these factors revealed four as significant risk factors for survival: Child-Pugh class B (HR 1.94, 95% CI

Table 2 Clinical background of responders and non-responders

	responders (n = 60)		non-responders (n = 110)		*P*-value
Age, years †	66	(31–89)	70	(34–87)	0.22
Gender (male)	51	(85%)	86	(78%)	0.28
HBsAg (positive)	14	(23%)	23	(21%)	0.71
Anti-HCV (positive)	36	(60%)	64	(58%)	0.81
Child-Pugh class (B)	18	(30%)	40	(36%)	0.40
WBC, /μL †	4895	(2400–10970)	4135	(1960–13460)	0.05
Hgb, g/dL †	12.8	(8.3–18.5)	12.0	(6.9–17.9)	0.06
PLT, $\times 10^4/\mu L$ †	13.8	(6.0–46.4)	11.8	(5.0–65.3)	0.26
T.Bil, mg/dL †	0.86	(0.21–2.66)	0.94	(0.38–2.88)	0.50
Alb, g/dL †	3.5	(2.3–4.5)	3.4	(2.4-4.6)	0.17
Cr, mg/dL †	0.72	(0.48–1.08)	0.75	(0.39–1.43)	0.22
AFP, ng/mL †	141	(3.4–170910)	279	(1.6–455560)	0.81
DCP, mAU/mL †	320	(10–511100)	1372	(10–942700)	0.21
Maximum diameter of HCC, mm †	50	(8-200)	48	(7–180)	0.95
No. of HCC (multiple)	50	(83%)	96	(87%)	0.48
PVTT (Vp3 or Vp4)	22	(37%)	24	(22%)	0.03
Distant metastasis (presence)	6	(10%)	17	(15%)	0.32
HAIC regimen (CDDP)	12	(20%)	61	(55%)	< 0.01
No. of prior TACE sessions (≥ 3)	9	(15%)	52	(47%)	< 0.01

HAIC, hepatic arterial infusion chemotherapy

Other abbreviations were the same as indicated in the footnote of Table 1. †Data were expressed as median (range) unless otherwise noted.

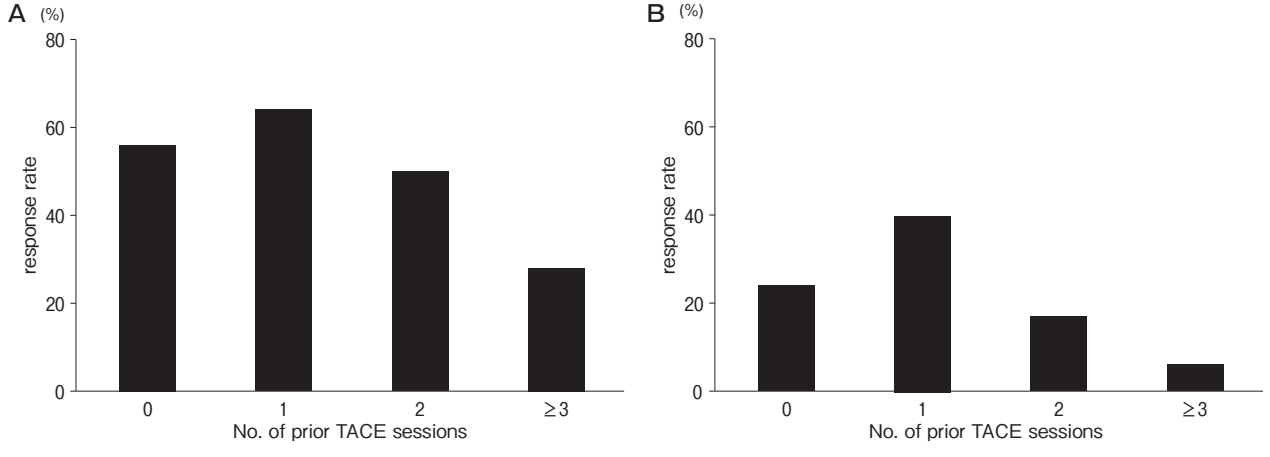

Fig. 2 Response rate according to the number of prior TACE sessions. For both the LFP regimen (**A**) and CDDP regimen (**B**), the response rates were significantly lower in the patients with three or more prior TACE sessions than in those with two or fewer prior TACE sessions (LFP 57% versus 28%; $p = 0.01$, CDDP 27% versus 6%; $p = 0.01$). TACE, transcatheter arterial chemoembolization; LFP, low-dose cisplatin combined with 5-fluorouracil; CDDP, cisplatin; No., number

1.37-2.74), serum AFP concentration (≥ 200 ng/mL) (HR 1.65, 95% CI 1.19-2.29), number of prior TACE sessions (≥ 3) (HR 1.60, 95% CI 1.12-2.29), and maximum diameter of HCC (≥ 50 mm) (HR 1.53, 95% CI 1.10-2.11) (Table 4).

Discussion

To the best of our knowledge, this is the first report that closely evaluates the relationship between the number of prior TACE sessions and the efficacy of HAIC.

Table 3 Risk factors for non-responders

Variables	Univariable OR (95% CI)	*P*-value	Multivariable OR (95% CI)	*P*-value
Age (≥65 yr)	1.05 (0.54–2.02)	0.87		
Gender (male)	0.63 (0.27–1.46)	0.28		
HBsAg (positive)	0.86 (0.40–1.84)	0.71		
Anti-HCV (positive)	0.92 (0.48–1.76)	0.81		
Child-Pugh class (B)	1.33 (0.67–2.61)	0.40		
Hgb (≤12.0 g/dL)	1.40 (0.74–2.64)	0.29		
PLT ($\leq 12.0 \times 10^4/\mu L$)	1.73 (0.91–3.28)	0.09	0.94 (0.44–1.97)	0.87
AFP (≥200 ng/mL)	1.26 (0.67–2.38)	0.46		
DCP (≥100 mAU/mL)	1.11 (0.54–2.29)	0.76		
Maximum diameter of HCC (≥50 mm)	0.90 (0.48–1.69)	0.74		
No. of HCC (multiple)	1.37 (0.56–3.30)	0.48		
PVTT (Vp3 or Vp4)	0.48 (0.24–0.96)	0.03	1.03 (0.47–2.26)	0.93
Distant metastasis (presence)	1.64 (0.61–4.42)	0.32		
HAIC regimen (CDDP)	4.97 (2.38–10.3)	<0.01	4.21 (1.86–9.53)	<0.01
No. of prior TACE sessions (≥3)	5.08 (2.27–11.3)	<0.01	4.17 (1.76–9.86)	<0.01

OR, odds ratio; CI, confidence interval.
Other abbreviations were the same as indicated in the footnote of Table 1 and Table 2.

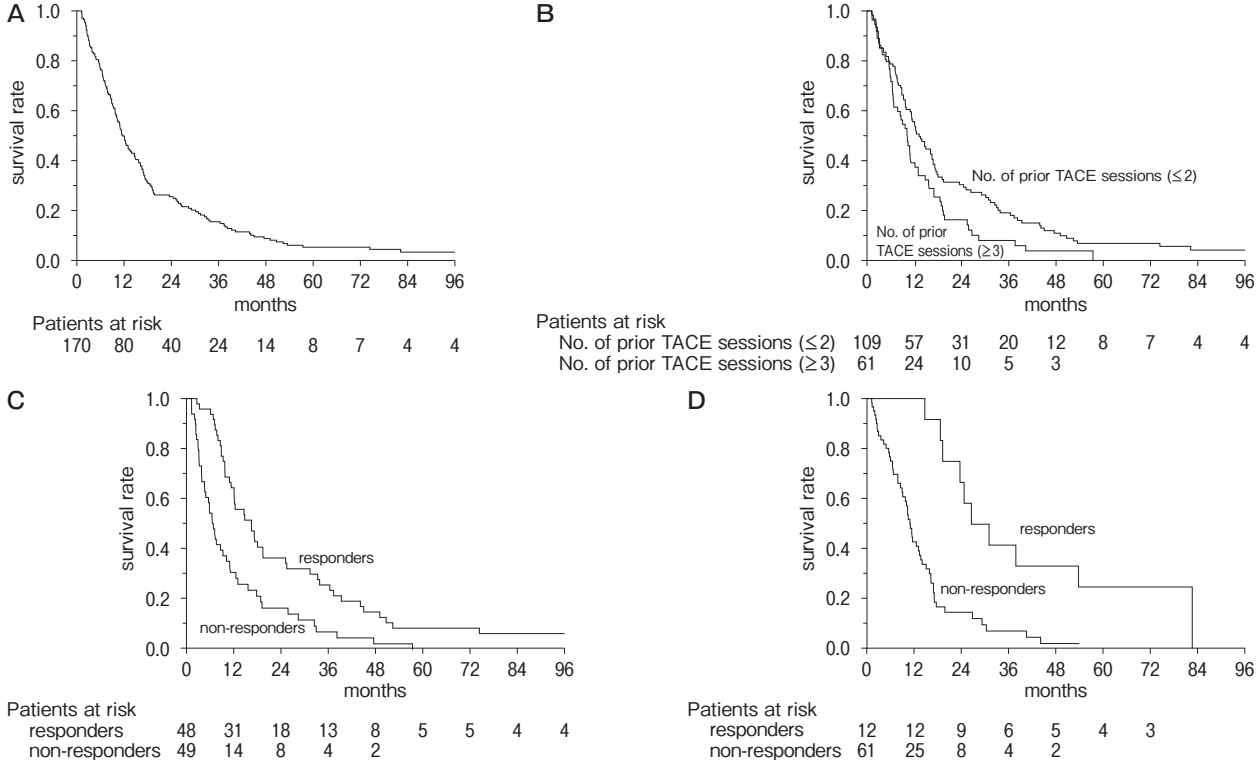

Fig. 3 Survival of patients. **A**, The median survival time and cumulative survival rate at 12 months of all patients were 11.4 months and 50%, respectively; **B**, The patients who received two or fewer prior TACE sessions had significantly prolonged survival compared with the patients who received three or more prior TACE sessions ($p=0.02$); **C**, For the LFP regimen, responders had a significantly prolonged median survival time compared with non-responders (16.4 months versus 6.8 months; $p<0.01$); **D**, For the CDDP regimen, responders had a significantly prolonged median survival time compared with non-responders (28.6 months versus 10.9 months; $p<0.01$). TACE, transcatheter arterial chemoembolization; LFP, low-dose cisplatin combined with 5-fluorouracil; CDDP, cisplatin.

Table 4 Risk factors for survival

Variables	Univariable HR (95% CI)	*P*-value	Multivariable HR (95% CI)	*P*-value
Age (≥65 yr)	0.80 (0.58–1.12)	0.20		
Gender (male)	0.72 (0.48–1.09)	0.13		
HBsAg (positive)	1.34 (0.92–1.96)	0.12		
Anti-HCV (positive)	0.81 (0.59–1.12)	0.21		
Child-Pugh class (B)	1.70 (1.22–2.37)	<0.01	1.94 (1.37–2.74)	<0.01
Hgb (≤12.0 g/dL)	1.11 (0.81–1.53)	0.50		
PLT (≤$12.0 \times 10^4/\mu$L)	1.28 (0.93–1.76)	0.12		
AFP (≥200 ng/mL)	1.51 (1.09–2.07)	0.01	1.65 (1.19–2.29)	<0.01
DCP (≥100 mAU/mL)	1.23 (0.85–1.79)	0.26		
Maximum diameter of HCC (≥50 mm)	1.30 (0.95–1.79)	0.09	1.53 (1.10–2.11)	0.01
No. of HCC (multiple)	1.26 (0.79–2.00)	0.32		
PVTT (Vp3 or Vp4)	1.05 (0.73–1.50)	0.77		
Distant metastasis (presence)	1.62 (1.02–2.55)	0.03	1.57 (0.98–2.53)	0.05
HAIC regimen (CDDP)	0.95 (0.69–1.32)	0.79		
No. of prior TACE sessions (≥3)	1.46 (1.05–2.05)	0.02	1.60 (1.12–2.29)	<0.01

HR, hazard ratio.
Other abbreviations were the same as indicated in the footnote of Table 1, Table 2, and Table 3.

Our study indicated that fewer prior TACE sessions was a favorable factor for good therapeutic response to HAIC, in addition to the absence of extrahepatic metastasis and good liver function, which have been reported in prior studies during the past decade [27,28]. Furthermore, the HAIC responders demonstrated prolonged survival compared with non-responders in our study. These findings suggest that efficacious HAIC can be anticipated in patients with fewer prior TACE sessions who were either refractory to TACE or unsuitable candidates for TACE.

Molecular-targeted agents are effective treatments for patients with a Child-Pugh class A score. Thus, unnecessary HAIC should be avoided to prevent the deterioration of liver function due to disease progression. Nouso *et al.* [6] reported that responders (those with complete response and partial response) undergoing HAIC with 5-fluorouracil and cisplatin displayed a longer median survival time compared to those with stable disease and progressive disease (25.8 months versus 9.5 months and 6.0 months, respectively; $p<0.0001$). Furthermore, Kudo *et al.* [29] suggested that patients who received a combination therapy comprising sorafenib and HAIC with low-dose cisplatin plus 5-fluorouracil displayed a median survival time that was significantly longer in responders than in non-responders (23.0 months versus 9.9 months; HR 0.28, 95% CI 0.16-0.49; $p<0.0001$). They also reported that objective response was an independent prognostic factor (HR 0.32, 95% CI 0.18-0.59; $p=0.0003$). Therefore, determining the pre-treatment simple and clinical factors that are predictive of response to HAIC is a critical problem that needs to be solved. However, despite efforts to predict the efficacy of HAIC over the past decade, little has been known about the factors that influence the response to HAIC.

In the present study, we found that those with a history of numerous (≥3) TACE sessions had a lower response rate to HAIC. Repetition of the TACE procedure for intrahepatic recurrences presumably increases the malignant potential of HCC, including the acquisition of resistance to chemotherapeutic agents. Supporting this hypothesis, Kojiro *et al.* [30] reported that among patients with various anticancer therapies, the incidence of HCC with sarcomatous appearance was most frequently observed in patients who received repeated TACE. They attributed this finding to phenotypic changes in HCC cells induced by anticancer therapy, or to some other factor(s) associated with therapy that might accelerate the proliferation of pre-existing sarcomatous cells in the original tumor.

Response rates to HAIC in HCC patients have varied from study to study, and should be carefully considered when trying to extrapolate its efficacy [7,8,16-20]. According to our results, a primary reason for the variability may be that most have not included the patients'

prior treatment history with TACE in their analyses. Indeed, the low response rate of the CDDP group in our study, which was comparable to that observed in a study reported by Iwasa *et al*. [7], might be related to the fact that a higher proportion these patients received repeated TACE. Moreover, the patients with two or fewer prior TACE sessions in the CDDP group in our study achieved a response rate equivalent to those of other studies reporting a good response (20.8-33.8%) [16, 20].

There are some limitations in our study. First, this study was a retrospective cohort study. The assignment of patients to HAIC or molecular-targeted agents as their first treatment in the clinical setting was not defined or controlled at the outset of the study. Therefore, an undefined selection bias might exist. Second, the HAIC regimen was not uniform; rather, two different regimens, LFP and CDDP, were utilized, and there were some differences in the demographic and clinical characteristics of the patients who received them. Moreover, the LFP regimen is not standardized; some differences exist among institutions, although the regimen used in our study was designed based on that used in the two original studies [14, 15]. Third, this study was conducted at 1 institution. Additional prospective studies with larger sample sizes spanning multiple institutions are warranted.

Nevertheless, we clearly demonstrated that HCC patients who received fewer prior TACE sessions were good candidates for HAIC treatment, especially when the number was twice or fewer. In summary, our study has the potential to guide effective therapeutic strategies for using HAIC in patients with intermediate or locally advanced HCC without distant metastasis.

References

1. Marrero JA, Kulik LM, Sirlin CB, Zhu AX, Finn RS, Abecassis MM, Roberts LR and Heimbach JK: Diagnosis, Staging, and Management of Hepatocellular Carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology (2018) 68: 723–750.
2. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol (2018) 69: 182–236.
3. Kokudo N, Takemura N, Hasegawa K, Takayama T, Kubo S, Shimada M, Nagano H, Hatano E, Izumi N, Kaneko S, Kudo M, Iijima H, Genda T, Tateishi R, Torimura T, Igaki H, Kobayashi S, Sakurai H, Murakami T, Watadani T and Matsuyama Y: Clinical practice guidelines for hepatocellular carcinoma: The Japan Society of Hepatology 2017 (4th JSH-HCC guidelines) 2019 update. Hepatol Res (2019) 49: 1109–1113.
4. Ikeda M, Shimizu S, Sato T, Morimoto M, Kojima Y, Inaba Y, Hagihara A, Kudo M, Nakamori S, Kaneko S, Sugimoto R, Tahara T, Ohmura T, Yasui K, Sato K, Ishii H, Furuse J and Okusaka T: Sorafenib plus hepatic arterial infusion chemotherapy with cisplatin versus sorafenib for advanced hepatocellular carcinoma: randomized phase II trial. Ann Oncol (2016) 27: 2090–2096.
5. Kudo M, Ueshima K, Yokosuka O, Ogasawara S, Obi S, Izumi N, Aikata H, Nagano H, Hatano E, Sasaki Y, Hino K, Kumada T, Yamamoto K, Imai Y, Iwadou S, Ogawa C, Okusaka T, Kanai F, Akazawa K, Yoshimura K, Johnson P, Arai Y, SILIUS study group: Sorafenib plus low-dose cisplatin and fluorouracil hepatic arterial infusion chemotherapy versus sorafenib alone in patients with advanced hepatocellular carcinoma (SILIUS): a randomised, open label, phase 3 trial. Lancet Gastroenterol Hepatol (2018) 3: 424–432.
6. Nouso K, Miyahara K, Uchida D, Kuwaki K, Izumi N, Omata M, Ichida T, Kudo M, Ku Y, Kokudo N, Sakamoto M, Nakashima O, Takayama T, Matsui O, Matsuyama Y, Yamamoto K; Liver Cancer Study Group of Japan: Effect of hepatic arterial infusion chemotherapy of 5-fluorouracil and cisplatin for advanced hepatocellular carcinoma in the Nationwide Survey of Primary Liver Cancer in Japan. Br J Cancer (2013) 109: 1904–1907.
7. Iwasa S, Ikeda M, Okusaka T, Ueno H, Morizane C, Nakachi K, Mitsunaga S, Kondo S, Hagihara A, Shimizu S, Satake M and Arai Y: Transcatheter arterial infusion chemotherapy with a fine-powder formulation of cisplatin for advanced hepatocellular carcinoma refractory to transcatheter arterial chemoembolization. Jpn J Clinc Oncol (2011) 41: 770–775.
8. Kirikoshi H, Yoneda M, Mawatari H, Fujita K, Imajo K, Kato S, Suzuki K, Kobayashi N, Kubota K, Maeda S, Nakajima A and Saito S: Is hepatic arterial infusion chemotherapy effective treatment for advanced hepatocellular carcinoma resistant to transarterial chemoembolization? World J Gastroenterol (2012) 18: 1933–1939.
9. Araki T, Itai Y, Furui S and Tasaka A: Dynamic CT densitometry of hepatic tumors. AJR Am J Roentgenol (1980) 135: 1037–1043.
10. Sangiovanni A, Manini MA, Iavarone M, Romeo R, Forzenigo LV, Fraquelli M, Massironi S, Corte CD, Ronchi G, Rumi MG, Biondetti P and Colombo M: The diagnostic and economic impact of contrast imaging techniques in the diagnosis of small hepatocellular carcinoma in cirrhosis. Gut (2010) 59: 638–644.
11. Nakamura S, Nouso K, Sakaguchi K, Ito YM, Ohashi Y, Kobayashi Y, Toshikuni N, Tanaka H, Miyake Y, Matsumoto E and Shiratori Y: Sensitivity and specificity of des-gamma-carboxy prothrombin for diagnosis of patients with hepatocellular carcinomas varies according to tumor size. Am J Gastroenterol (2006) 101: 2038–2043.
12. Sørensen JB, Klee M, Palshof T and Hansen HH: Performance status assessment in cancer patients. An inter-observer variability study. Br J Cancer (1993) 67: 773–775.
13. Kudo M, Han KH, Ye SL, Zhou J, Huang YH, Lin SM, Wang CK, Ikeda M, Chan SL, Choo SP, Miyayama S and Cheng AL: A Changing Paradigm for the Treatment of Intermediate-Stage Hepatocellular Carcinoma: Asia-Pacific Primary Liver Cancer Expert Consensus Statements. Liver Cancer (2020) 9: 245–260.
14. Kanayama M, Nagai H and Sumino Y: Influence of the etiology of liver cirrhosis on the response to combined intra-arterial chemotherapy in patients with advanced hepatocellular carcinoma. Cancer Chemother Pharmacol (2009) 64: 109–114.
15. Nagai H, Kanayama M, Higami K, Momiyama K, Ikoma A, Okano N,

Matsumaru K, Watanabe M, Ishii K, Sumino Y and Miki K: Twenty-four hour intra-arterial infusion of 5-fluorouracil, cisplatin, and leucovorin is more effective than 6-hour infusion for advanced hepatocellular carcinoma. World J Gastroenterol (2007) 13: 280–284.
16. Yoshikawa M, Ono N, Yodono H, Ichida T and Nakamura H: Phase II study of hepatic arterial infusion of a fine-powder formulation of cisplatin for advanced hepatocellular carcinoma. Hepatol Res (2008) 38: 474–483.
17. Okuda K, Tanaka M, Shibata J, Ando E, Ogata T, Kinoshita H, Eriguchi N, Aoyagi S and Tanikawa K: Hepatic arterial infusion chemotherapy with continuous low dose administration of cisplatin and 5-fluorouracil for multiple recurrence of hepatocellular carcinoma after surgical treatment. Oncol Rep (1999) 6: 587–591.
18. Ando E, Tanaka M, Yamashita F, Kuromatsu R, Yutani S, Fukumori K, Sumie S, Yano Y, Okuda K and Sata M: Hepatic arterial infusion chemotherapy for advanced hepatocellular carcinoma with portal vein tumor thrombosis: analysis of 48 cases. Cancer (2002) 95: 588–595.
19. Ueshima K, Kudo M, Takita M, Nagai T, Tatsumi C, Ueda T, Kitai S, Ishikawa E, Yada N, Inoue T, Hagiwara S, Minami Y and Chung H: Hepatic arterial infusion chemotherapy using low-dose 5-fluorouracil and cisplatin for advanced hepatocellular carcinoma. Oncology (2010) 78 (suppl 1): 148–153.
20. Kondo M, Morimoto M, Numata K, Nozaki A and Tanaka K: Hepatic arterial infusion therapy with a fine powder formulation of cisplatin for advanced hepatocellular carcinoma with portal vein tumor thrombosis. Jpn J Clin Oncol (2011) 41: 69–75.
21. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D and Verweij J: New response evaluation criteria in solid tumours: revised RECIST guideline (version 1. 1). Eur J Cancer (2009) 45: 228–247.
22. Obi S, Yoshida H, Toune R, Unuma T, Kanda M, Sato S, Tateishi R, Teratani T, Shiina S and Omata M: Combination therapy of intra-arterial 5-fluorouracil and systemic interferon-alpha for advanced hepatocellular carcinoma with portal venous invasion. Cancer (2006) 106: 1990–1997.
23. Xiaojie Li, Zhimin Ye, Sheng Lin and Pang H: Predictive factors for survival following stereotactic body radiotherapy for hepatocellular carcinoma with portal vein tumour thrombosis and construction of a nomogram. BMC Cancer (2021) 21: 701.
24. Piscaglia F and Ogasawara S: Patient selection for transarterial chemoembolization in hepatocellular carcinoma: importance of benefit/risk assessment. Liver Cancer (2018) 7: 104–119.
25. Kudo M, Matsui O, Izumi N, Iijima H, Kadoya M, Imai Y, Okusaka T, Miyayama S, Tsuchiya K, Ueshima K, Hiraoka A, Ikeda M, Ogasawara S, Yamashita T, Minami T, Yamakado K; Liver Cancer Study Group of Japan: JSH consensus-based clinical practice guidelines for the management of hepatocellular carcinoma: 2014 update by the Liver Cancer Study Group of Japan. Liver Cancer (2014) 3: 458–468.
26. Bruix J and Sherman M: Management of hepatocellular carcinoma: an update. Hepatology (2011) 53: 1020–1022.
27. Katamura Y, Aikata H, Kimura Y, Kawaoka T, Takaki S, Waki K, Hiramatsu A, Kawakami Y, Takahashi S, Ishikawa M, Hieda M, Kakizawa H and Chayama K: Intra-arterial 5-fluorouracil/interferon combination therapy for hepatocellular carcinoma with portal vein tumor thrombosis and extrahepatic metastases. J Gastroenterol Hepatol (2010) 25: 1117–1122.
28. Miyaki D, Aikata H, Honda Y, Naeshiro N, Nakahara T, Tanaka M, Nagaoki Y, Kawaoka T, Takaki S, Waki K, Hiramatsu A, Takahashi S, Ishikawa M, Kakizawa H, Awai K and Chayama K: Hepatic arterial infusion chemotherapy for advanced hepatocellular carcinoma according to Child-Pugh classification. J Gastroenterol Hepatol (2012) 27: 1850–1857.
29. Kudo M, Ueshima K, Chiba Y, Ogasawara S, Obi S, Izumi N, Aikata H, Nagano H, Hatano E, Sasaki Y, Hino K, Kumada T, Yamamoto K, Imai Y, Iwadou S, Ogawa C, Okusaka T, Kanai F and Arai Y: Objective Response by mRECIST Is an Independent Prognostic Factor for Overall Survival in Hepatocellular Carcinoma Treated with Sorafenib in the SILIUS Trial. Liver Cancer (2019) 8: 505–519.
30. Kojiro M, Sugihara S, Kakizoe S, Nakashima O and Kiyomatsu K: Hepatocellular carcinoma with sarcomatous change: a special reference to the relationship with anticancer therapy. Cancer Chemother Pharmacol (1989) 23 Suppl: S4–8.