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Original Paper

Hepatic Arterial Infusion Chemotherapy for Advanced Hepatocellular Carcinoma with Portal Vein Thrombosis: Impact of Early Response to 4 Weeks of Treatment

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Key Words
Early response · Hepatic arterial infusion chemotherapy · Hepatocellular carcinoma · Overall survival · Portal vein thrombosis · Progression-free survival

Abstract
Aim: The aim of the study was to investigate the impact of early response (ER) to hepatic arterial infusion chemotherapy (HAIC) on outcomes of patients with advanced hepatocellular carcinoma (HCC) complicated with major portal vein tumor thrombosis (PVTT). ***Methods:*** Thirty-nine patients receiving HAIC with low-dose cisplatin, 5-fluorouracil (5FU), and leucovorin were enrolled. One course of HAIC consisted of 5 days of treatment and 2 days rest per week for 4 consecutive weeks. ER was categorized as complete response, partial response, or minor response and was determined by World Health Organization criteria with dynamic computed tomography findings performed within 1 week after the first course of HAIC. ***Results:*** Thirteen (33%) patients achieved an ER. Twelve (92.3%) of these 13 ER patients achieved a higher overall response than all but one (3.8%) of the 26 non-early responders (NERs) ($p<0.001$). ER was the exclusive independent favorable factor for survival ($p=0.003$). Downstaging of tumors was noted in 76.9% of ERs, and these patients could proceed to loco-regional therapies. ER patients subsequently had a higher 1-year survival (76.9% vs. 3.8%, $p<0.001$) and 6-month progression-free survival (PFS) (84.6% vs. 15.4%, $p<0.001$) than those for NERs. Only 8% of patients experienced grade 3 or higher toxicity during the first 4-week

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course of HAIC. ***Conclusions:*** HAIC can yield a satisfactory ER for advanced HCC with PVTT. Moreover, achievement of ER after HAIC in advanced HCC with PVTT is strongly associated with better overall survival and PFS.

Introduction

Hepatocellular carcinoma (HCC) is a major cause of cancer-related death worldwide [1]. The prognosis for patients with advanced HCC and major portal vein tumor thrombosis (PVTT) is poor: median survival is only about 3–4 months if untreated [2, 3]. Portal vein thrombosis is a strong predictor of mortality for patients with HCC [4–6].

For patients with PVTT, surgical resection might achieve the longest survival [7], but the majority of such patients are unresectable. Transarterial chemoembolization (TACE) is another option but it involves the risk of liver failure [8–10], and no randomized controlled trial has shown a survival benefit [11, 12]. Radioembolization with yttrium-90 microspheres may be effective for some HCC patients with PVTT at portal vein branches, but poor survival rates and severe adverse effects have been reported in patients with cirrhosis and tumor invasion of major portal veins [13, 14]. Sorafenib could prolong survival for advanced HCC patients [15, 16]; however, high costs and low response rates limit its use in most HCC patients [17]. Moreover, sorafenib is not covered by insurance in many countries, including Taiwan.

Hepatic arterial infusion chemotherapy (HAIC) with 5-fluorouracil (5FU) has yielded 17–52% overall response rates [18–23]. Survival benefits have been shown in some non-randomized studies, with a median survival of 6–8 months in patients treated with HAIC compared to 2–4 months in control patients [7, 22, 24]. This benefit is likely because HAIC is able to provide high local concentrations of chemotherapy agents for liver tumors with low systemic toxicity due to a high hepatic extraction rate [25]. HAIC is recommended in Japanese HCC guidelines as a treatment option for patients with portal vein tumor thrombus [26, 27].

Ando et al. reported a response rate of 48% in patients with advanced HCC treated by HAIC with cisplatin and 5FU for 5 days per week [18]. The therapeutic response was the only factor associated with better survival. Because only some patients responded to chemotherapy, early response (ER) to HAIC was suggested as an indicator for "chemo-sensitivity" [24]. However, the definition of ER to HAIC is not clear in these studies.

The aims of the current study were to investigate the impact of ER to 4 weeks of HAIC treatment on overall survival (OS) and progression-free survival (PFS) for patients with advanced HCC and major PVTT. We will not only show the beneficial effect of ER on OS and on PFS compared with those of the non-early responders (NERs) but also show these impacts in subgroups of patients in this study with unfavorable prognostic factors.

Materials and Methods

Patients

This study was a retrospective study from a prospectively collected database. All patients were admitted to our hospital between May 2003 and March 2006. A total of 39 consecutive patients with unresectable advanced HCC and PVTT were enrolled and received HAIC via an implanted injection port. Diagnosis of HCC was established using pathology in 14 patients; cytology in 8 patients; and two typical HCC image findings by computed tomography (CT), magnetic resonance imaging (MRI), or angiography plus serum alpha-fetoprotein (AFP) levels of more than 400 ng/mL in 17 patients. Enrollment criteria

were as follows: (1) age greater than 18 years; (2) PVTT detected by CT scan or MRI; (3) Eastern Cooperative Oncology Group (ECOG) performance status ≤2; (4) adequate liver reserve: Child-Pugh A or B (score ≤8), serum total bilirubin ≤3.0 mg/L, and serum aminotransferase ≤200 IU/L; (5) acceptable bone marrow capacity: white blood cell ≥3000/μL, hemoglobin ≥8 g/dL, and platelet ≥7.5×10^4/μL; (6) serum creatinine ≤2 mg/L; and (7) successful insertion of hepatic arterial infusion catheter and implantation of drug delivery port. Tumor stage was coded using the Okuda stage [5] and Cancer of the Liver Italian Program (CLIP) scores [6]. All patients were categorized as Barcelona Clinic Liver Cancer stage C [3, 28] and American Joint Committee on Cancer stage IIIa (6th edition) [29]. Portal vein thrombosis was evaluated according to Liver Cancer Group of Japan criteria [30]. Vp4 means tumor thrombus in the portal trunk and Vp3 means tumor thrombus in the right or left main portal vein. Vp2 means tumor thrombus only in the second branch of the portal veins. Twenty-eight patients were treatment-naïve. All patients were fully reviewed at the institutional HCC multidisciplinary conference. This study was approved by the institutional review board.

HAIC Protocol

Each cycle of HAIC consisted of infusion with chemotherapy for 5 days per week and rest for the other 2 days. A single course included four consecutive cycles. On the first day of each cycle, the proper position of the catheter tip was confirmed under fluorescence imaging. Cisplatin 7 mg/m^2 in 100 mL of 0.9% normal saline was infused by pump for 1 h. 5FU 170 mg/m^2 mixed with leucovorin 8 mg/m^2 in 250 mL of 5% dextrose water was infused by pump over the following 5 h. Oral metoclopramide or ondansetron were used to prevent vomiting.

Assessment of Therapeutic Response

ER was assessed by dynamic CT scan within 1 week after the first course of HAIC. Follow-up CT scans were done every 3 months thereafter. ER and overall response were assessed according to World Health Organization criteria [31]. Because of the possible small change in tumor size during early assessment, a reduction in tumor size of between 25% and 50% was defined as early minor response (MR). ER was categorized as complete response (CR), partial response (PR), or MR. Patients with early stable disease (SD) and early progressive disease (PD) were referred to as NERs.

Additional Treatments

Additional HAIC, using the same protocol, was given for 1–4 cycles at 1 month after the disappearance of complications arising from previous HAIC. For patients with early SD, additional HAIC was given if acceptable to patients. Surgical resection, TACE, or percutaneous ethanol injection therapy (PEIT) were carried out after downstaging of the tumors. TACE was given if portal flow re-appeared or collateral circulation of the portal vein became prominent. PEIT was administered for nodular tumors less than 5 cm in maximal diameter.

Study Endpoints

The primary endpoint was OS and PFS. The secondary endpoint was ER. OS was calculated from the first day of HAIC to death. PFS referred to the period from the first day of HAIC to PD or death. All patients were followed up at intervals of 1–2 weeks or until death. The date of death was corrected by records at the national cancer registration if the patients did not die in our hospital.

Statistical Analyses

Continuous variables are given as median ± standard deviation. Intergroup differences in categorical variables were analyzed by the chi-square test or Fisher's exact test. The Kaplan-Meier method was used to calculate survival rates, and the log-rank test was used to compare intergroup differences. Cox regression multivariate analysis was used to identify the independent survival prognostic factors. Binary logistic regression was used for multivariate analysis of factors for ER. Correlation between ER and overall response was analyzed by Kappa value from crosstabs. A p-value less than 0.05 was considered to be statistically significant. All statistical analyses were performed using SPSS software (version 15, SPSS, Chicago, IL, USA).

Table 1. Baseline characteristics of patients with advanced HCC and portal vein thrombosis

	No. of patients	Median
Age (years)	39	49 ±10.8 (28–74)
Gender (M/F)	37/2	
Etiology: HBV/HCV/non-B, non-C	32/6/4	
Child-Pugh class A/B	29/10	
ECOG PS (0/1/2)	14/20/5	
Ascites (no/yes)	29/10	
Tumor size (cm)		12.1 ± 4.0 (3.4–19.5)
<12 cm/>12 cm	19/20	
Tumor grade (I/II/III/IV/ND)	2/3/11/6/17*	
Unilateral/bilateral involvement	26/13	
Portal vein thrombosis (Vp2/Vp3/Vp4)	9/9/21	
CLIP scores (1/2/3/4/5)	1/5/16/12/5	
Okuda stage (I/II)	15/24	
Previous treatment (no/yes)	28/11	
Pretreatment laboratory data		
AFP (ng/mL)		1974.0 ± 344290.6 (6.0–1636414.0)
WBC ($\times 10^3/\mu L$)		6.8 ± 2.7 (2.7–13.4)
Platelet ($\times 10^3/\mu L$)		195.0 ± 100.4 (63–561.0)
ALP (U/L)		178.0 ± 99.1 (68–549)
ALT (U/L)		54.0 ± 60.0 (16–274)
AST (U/L)		100.0 ± 120.4 (34–626)
Albumin (g/dL)		3.6 ± 0.6 (2.3–4.9)
Total bilirubin (mg/dL)		1.1 ± 0.5 (0.4–2.7)

ECOG PS=ECOG Performance status; WBC=white blood cell; ALP=alkaline phosphatase; ALT=alanine transaminase; AST=aspartate aminotransferase.

*Diagnosed by two typical imaging studies and serum AFP >400 ng/mL in 17 patients.

Results

Patient Characteristics

The baseline data are shown in table 1. Most patients had hepatitis B virus (HBV) infection. Twenty (51.3%) patients had a tumor larger than 12 cm and 30 (77%) had tumor thrombus in Vp3 or Vp4. Unfavorable prognostic factors were noted in 10 (26%) patients with Child-Pugh B, and three of these had a Child-Pugh score of 8. Poor performance (ECOG PS ≥1) was noted in 25 (64%) patients.

ER, Outcomes, and Prognostic Predictors

Four patients were still alive at the time of analysis. OS and PFS at 6 months, 1, 2, and 3 years were 53.8%, 28.2%, 15.2%, 12.8% (fig. 1a), and 38.5%, 28.2%, 10.3%, 7.7% (fig. 1b), respectively. Median OS was 6.6 months (95% confidence interval (CI) 4.7–8.5) and median

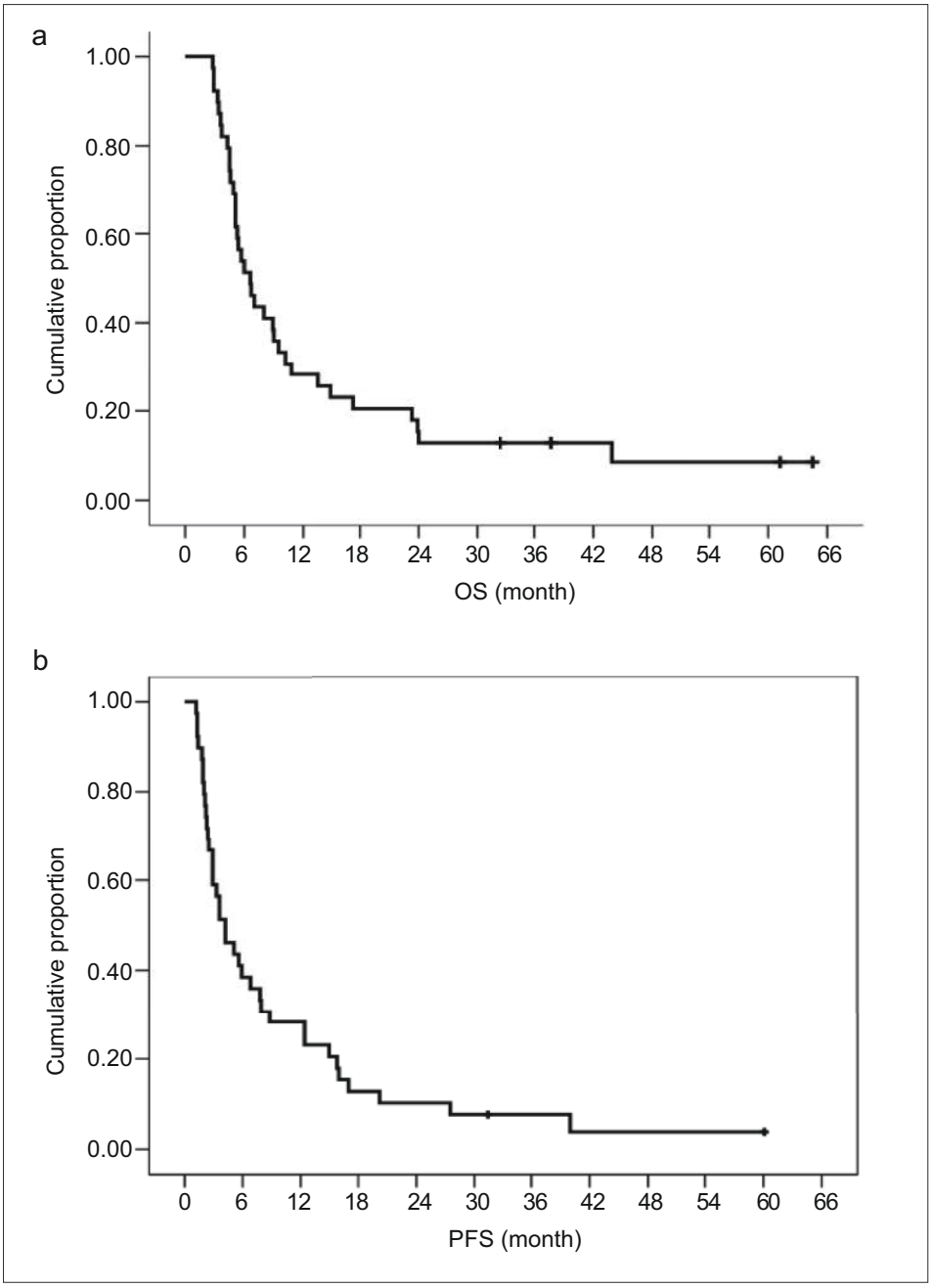

Fig. 1. Kaplan-Meier curves of OS (**a**) and PFS (**b**) for all 39 patients.

PFS was 4.2 months (95% CI 2.0–6.4). The ER rate was 33%, and the breakdown of early CR, PR, MR, SD, and PD is shown in fig. 2. Twenty-one prognostic factors were used for univariate analysis with respect to OS and PFS. The presence of HBsAg, Child-Pugh A, and ascites were significant factors affecting OS. CLIP score <4, Okuda stage I, tumor size <12 cm, and ER were factors significantly affecting both OS and PFS. Major PVTT and poor performance were not adverse prognostic factors for OS or PFS (major PVTT: OS, p=0.607; PFS, p=0.944. Performance status: OS, p=0.198; PFS, p=0.549). By Cox regression analysis, ER was identified as the only independent factor for OS (p=0.003, hazar ratio (HR)=0.06, 95% CI 0.01–0.40) and

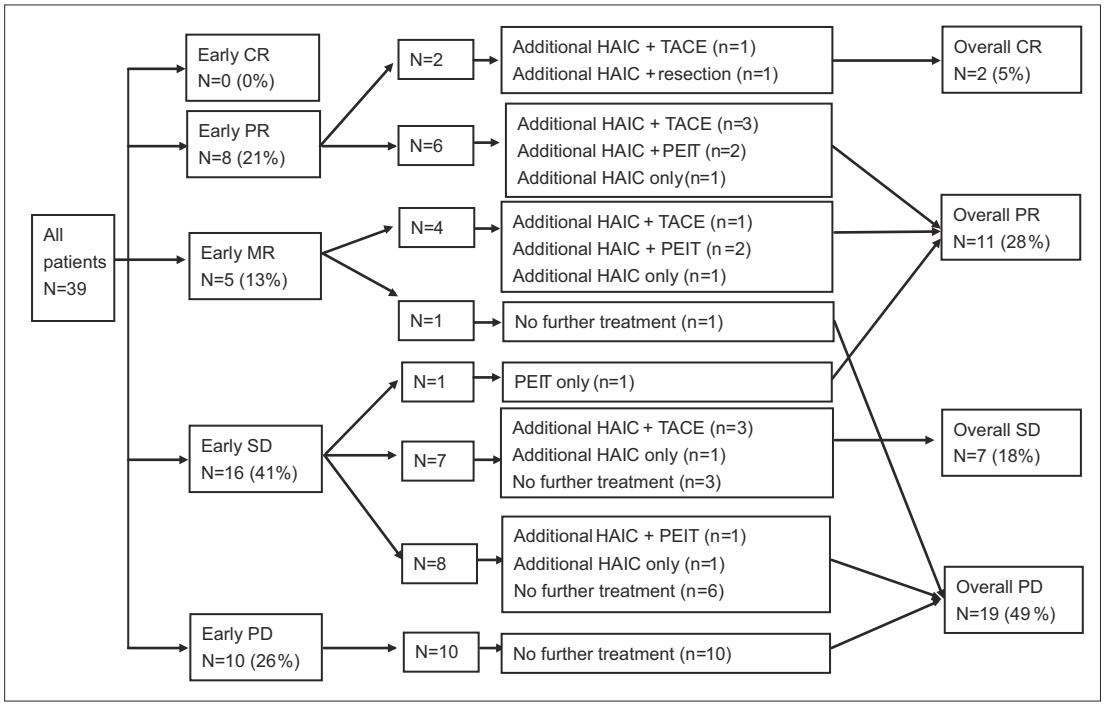

Fig. 2. Breakdown of ER, additional treatments, and overall outcomes. Early responders had a good chance of receiving additional HAIC (12, 92.3%) and further effective treatments (10, 79.6%). One early responder could not receive further additional treatment due to tumor rupture at 1 month after 4-week HAIC. Only one non-early-responder had regression of PVTT and became PR after additional PEIT.

also as one of the three independent factors for PFS (p<0.001, HR=0.09, 95% CI, 0.02–0.33) (table 2).

Additional HAIC, Locoregional Therapies, and Overall Response

Additional HAIC was given to 18 (46%) patients, according to the ER results and patient conditions. A total of 296 cycles of HAIC were performed, and the median number of HAIC cycles was 7.6 ± 4.0 (2–26). Additional HAIC was prescribed for all patients with early PR (8, 100%), 4 (80%) with early MR, 6 (38%) with early SD, and none with early PD (fig. 2). Early responders underwent more cycles of additional HAIC than NERs (10.2 vs. 5.0, p=0.045, table 3). Ten (76.9%) early responders were suitable for surgical resection, TACE, or PEI after downstaging of their tumors (table 3 and fig. 2). Two early PR patients finally achieved overall CR. Both were alive at the last follow-up, with survival times of 64.5 months and 37.7 months. The other six early PR and four early MR patients received additional treatments and achieved overall PR. Only one early MR patient deteriorated to PD. One early SD patient had regression of portal vein thrombus after 4 weeks of HAIC and improved to PR after additional PEI. Six early SD patients received additional HAIC treatments and three of them also received palliative local treatments; none of them ultimately responded. The overall response rates were 2 (5%) for CR, 11 (28%) for PR, 7 (18%) for SD, and 19 (49%) for PD after all treatments (fig. 2). The disease control rate was 46%. Early responders had a higher overall response rate (92.3% vs. 3.8%, p<0.001) and disease control rate (92.3% vs. 23.1%, p<0.001). A strong correlation was found between ER after the first 4 weeks of HAIC treatment and overall response after all treatments (Kappa=0.885, p<0.001).

Table 2. Multivariate analysis of factors for OS and PFS

	OS		PFS	
	p value	HR (95% CI)	p value	HR (95% CI)
ER	0.003	0.06 (0.01–0.40)	<0.001	0.09 (0.02–0.33)
CLIP <4	0.068	0.17 (0.03–1.14)	0.198	0.52 (0.19–1.41)
Tumor size <12 cm	0.407	0.39 (0.04–3.67)	0.015	0.18 (0.04–0.71)
Okuda stage I	0.221	0.21 (0.02–2.56)	0.026	0.16 (0.03–0.81)
Child-Pugh A	0.865	0.87 (0.18–4.22)		
Completeness of 4-week HAIC	0.227	0.33 (0.07–1.98)		
HBV infection	0.682	1.43 (0.26–7.93)		
Ascites	0.771	0.82 (0.22–3.03)		
AFP declined > 50%	0.908	0.93 (0.28–3.10)		

Table 3. Further treatment and outcomes between early responders and NERs

	All patients (39, 100%)		
	Early responders (13, 33%)	NERs (26, 67%)	p value
Receive additional HAIC (n,%)	12 (92.3%)	6 (23.1%)	< 0.001
Additional HAIC cycles (mean ± SD)	10.2 ± 5.6	5.0 ± 1.7	0.045
Further effective treatments (n,%)	10 (76.9%)[a]	4 (15.4%)[b]	< 0.001
Overall response[c] (n,%)	12 (92.3%)	1 (3.8%)	< 0.001
Disease control rate (n,%)	12 (92.3%)	6 (23.1%)	< 0.001
Median survival (month)	23.9 (16.0–31.8)	5.1 (4.6–5.6)	< 0.001
Median PFS (months)	16.0 (8.7–23.2)	2.9 (2.3–3.5)	< 0.001
1-year survival (n,%)	10 (76.9%)	1 (3.8%)	< 0.001
6-month PFS (n,%)	11 (84.6%)	4 (15.4%)	< 0.001

SD=Standard deviation. [a]Effective additional treatments were resection, percutaneous ethanol injection, and TACE in patients after downstaging of tumor by HAIC. [b]Additional treatments were only given for patients with SD. [c]kappa value between ER and overall response was 0.88.

ER Associated with Better Outcomes

OS and PFS were significantly longer in patients with ER than in those without (median OS: 23.9 months vs. 5.1 months, p=0.04, fig. 3; median PFS: 16.0 months vs. 2.9 months, p<0.001, fig. 4). Cumulative survival rates in 13 early responders at 6 months, 1, 2, and 3 years were 92.3%, 76.9%, 46.2%, and 38.5%, respectively (fig. 3). Cumulative PFS rates in early responders at 3 months, 6 months, 1, 2, and 3 years were 92.3%, 84.6%, 69.2%, 30.8%, and 23.1%(fig. 4). Both 1-year OS and 6-month PFS rates were much higher in early responders than in NERs, with odd ratios of 83.3 and 30.2, respectively (table 3). Patients with unfavorable prognostic factors could also obtain outcome benefits if they achieved an ER (table 4). ER rates could be achieved in 15–27% of patients with major PVTT, poor performance status,

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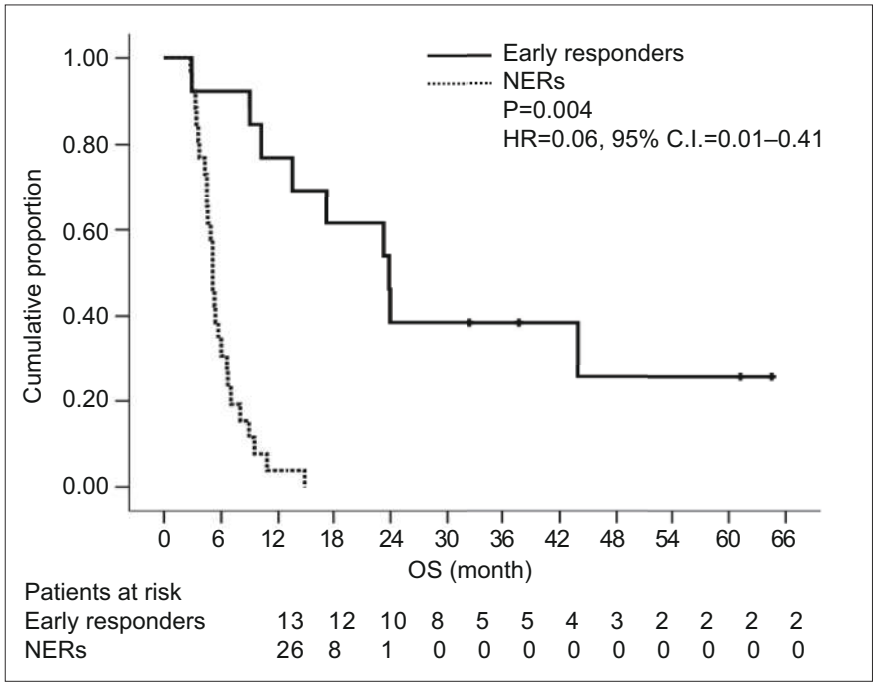

Fig. 3. Median OS was significantly better in early responders than in NERs. Early responders had significantly higher 1-year OS rates than those for NERs (76.9% vs. 3.8%, p<0.001, odds ratio=83.3).

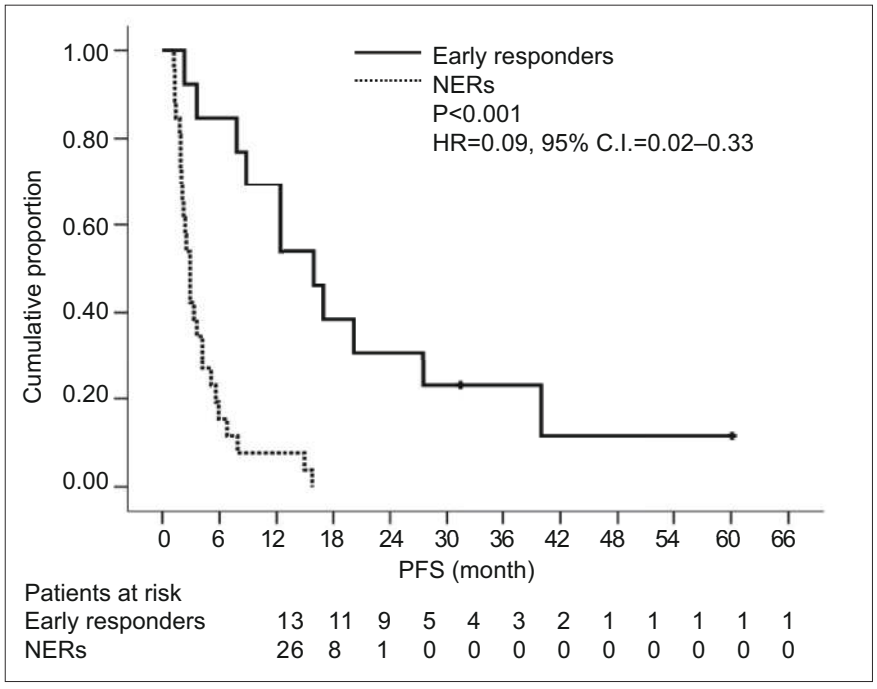

Fig. 4. Median PFS was significantly better in early responders than in NERs. Early responders had significantly higher 6-month PFS rates than those of NERs (84.6% vs. 15.4%, p<0.001, odds ratio=30.2).

Table 4. Survival and PFS between early responders and NERs in patients with unfavorable prognostic factors

Subgroups	n	ER	Survival (months)				PFS (months)			
			ER vs. NER	p value	HR	95% CI	ER vs. NER	p value	HR	95% CI
Major PVTT	30	8 (27%)	23.9 vs 5.1	<0.001	0.086	0.019 –0.387	17.0 vs 2.5	<0.001	0.083	0.018 –0.372
ECOG PS ≥1	25	5 (20%)	46.7 vs 5.5	0.003	0.076	0.010 –0.604	40.0 vs 2.4	0.002	0.073	0.009 –0.576
CLIP score ≥3	33	9 (27%)	43.9 vs 5.1	<0.001	0.072	0.016 –0.325	16.0 vs 5.4	<0.001	0.140	0.046 –0.426
Tumor size >12 cm	20	3 (15%)	13.7 vs 5.1	<0.001	0.019	0.001 –1.731	8.8 vs 2.4	0.022	0.128	0.016 –0.998
Okuda stage II	24	4 (17%)	10.2 vs 5.1	0.020	0.189	0.041 –0.868	8.8 vs 2.4	0.021	0.200	0.045 –0.890
HBV infection	32	7 (22%)	23.9 vs 5.1	<0.001	0.096	0.022 –0.431	17.0 vs 2.9	0.001	0.143	0.041 –0.498

CLIP score ≥3, large tumor size (>12 cm), Okuda stage II, or hepatitis B infection. The median survival time for each subgroup was from 10.2 months to 46.7 months; median PFS was from 8.8 months to 40.0 months. All were significantly better than those for NERs (table 4).

Adverse Effects During First 4 Weeks of HAIC and Thereafter

Most patients tolerated the first 4-week course of HAIC well. Grade I or II nausea or vomiting occurred in 41% of patients, and more than half of these suffered in the first 2 weeks only. There was no deterioration of renal function during the first course of HAIC. Esophageal variceal bleeding occurred in three patients, whereas spontaneous bacterial peritonitis occurred in one patient during HAIC treatment. Three patients had a CLIP score ≥4. Leucopenia of grade 1 or 2 occurred in 10% of patients. Thrombocytopenia occurred in 23% of patients and was up to grade 3 in two of them. Liver function reserves deteriorated from Child-Pugh grade A to B in only two patients during the first course of HAIC. No patients died during the first course of HAIC or within 1 month thereafter.

Discussion

Prognosis for advanced HCC with PVTT is dismal due to poor responses to current treatment modalities. Our study demonstrated a high response rate and benefits for early responders to 4 weeks of HAIC with cisplatin, 5FU, and leucovorin in patients with unresectable advanced HCC and major PVTT. If an ER can be achieved, patients may be able to undergo resection or loco-regional therapies and subsequently benefit from improved OS and PFS.

Treatment of advanced HCC with major PVTT remains a major challenge. HAIC with 5FU-based therapy provides a modest response and low systemic toxicity [18–23]. Compared with supportive treatment, HAIC also improved OS in these patients [7, 22, 24]. Therapeutic response is considered to be an important factor for OS [18–21, 24]. Ando et al. reported a 48% response rate and a 31.6-month median OS for patients with advanced HCC who responded to HAIC, which was significantly better than the 5.4 months for non-responders. Our study

showed similar results: the median survival in early responders was 23.9 months, which was significantly superior to the 5.1 months in NERs.

Evaluation of the response to HAIC was recommended every 3 months after initiation of HAIC in most previous studies [18–23]. Nonetheless, assessing the ER to HAIC has been discussed previously [24]. Better survival was found for patients who responded to 3-month or 8-month courses of HAIC. Chemo-sensitive status has been considered for patients who show responsiveness as early as 3 months after initiation of HAIC. Uka et al. checked the response after every 4-week course of HAIC and reported that CR or PR after two courses of HAIC might indicate a more favorable prognosis [23]. ER, in that study, was evaluated at 3 months after initiation of HAIC. However, unlike that study, we assessed the initial response within 1 week after a 4-week course of HAIC. The response could also be defined as early as 1 month after initiation of HAIC. A number of benefits can be identified if ER is achieved. Most (92%) early responders could achieve a subsequent overall response after additional HAIC. The 6-month PFS and 1-year OS rates of early responders were 85% and 77%, respectively, which were significantly better than those for NERs (table 3).

The current study has shown that OS can be predicted by ER based on dynamic CT studies. Furthermore, patients with unfavorable prognostic factors, such as major PVTT, ECOG PS ≥1, CLIP scores ≥3, tumor size >12 cm, Okuda stage II, or the presence of serum HBsAg, still achieved 15–27% ER rates and significantly better OS and PFS were achieved in early responders than in NERs (table 4). We did not evaluate the impact of ER on patients with Child-Pugh B or the presence of ascites because of the small number of patients. According to our results, better outcomes could be predicted if ER to HAIC was achieved in patients with advanced HCC, including patients with unfavorable prognostic factors.

OS of the 39 patients in this study was shorter than those for previous studies of HAIC with HCC [18, 19]. This could be explained by the more locally advanced tumor stages in our subjects. In the current series, more than half of the patients had a maximum tumor size larger than 12 cm, and three-quarters of patients had thrombus in the major portal veins (Vp3 or Vp4). Despite the more advanced stage of HCC, our overall median survival was similar to the treated arm of patients in one large randomized controlled study from the Asia-Pacific region [15]. Although most NERs did not receive additional HAIC in our study, the overall response rate was comparable to two previous series of HAIC [18, 19].

To our knowledge, there is still no appropriate marker to predict outcomes in HCC patients after molecular targeted therapies [32]. Decline of serum AFP levels during systemic chemotherapy has been reported to correlate with OS [33]. In our study, a decline of serum AFP level was only marginally associated with OS (p=0.075). This may be due to the small sample size. Nevertheless, the current study has shown that OS and PFS can be predicted by ER based on dynamic CT studies.

In this study, all patients were initially unresectable and not suitable for TACE or local ablation therapies. Most (77%) of our early responders could go ahead with surgical resection, TACE, or PEI after downstaging of their tumors. Siegel et al. reported [32] that if a patient is able to downgrade for curative treatments, a rapid response rate might be the key determinant. Similarly, we showed that a 4-week HAIC protocol could achieve ER with low toxicity and downstage tumors for further loco-regional treatments or surgical resection. This could be an option for patients with advanced HCC without extrahepatic metastasis; however, life expectancy may be short in NERs. A shift to other treatments such as sorafenib as soon as possible might prolong their survival [32]. In our series, NERs did not receive sorafenib because the study period came before domestic approval of sorafenib [16].

Toxicity during the first 4 weeks of HAIC was acceptable in our study: only 8% of patients suffered from grade 3 or 4 toxicity during this treatment period. More than two increments in Child-Pugh score occurred in two NERs as a result of tumor progression. No deaths

occurred among the patients during the first 4 weeks of HAIC or within 1 month thereafter. In addition to the acceptable safety, the current regimen of HAIC was less expensive than treatment with molecular targeted agents.

A drawback of 4-week HAIC therapy is prolonged hospitalization. Shorter hospital stays with higher doses of HAIC may be tested in the future. Further studies assessing the safety and response to adjuvant therapy with sorafenib in randomized controlled trials are being conducted in Japan [34]. HAIC using a low dose of 5FU and cisplatin combined with systemic sorafenib might give some hope for these advanced patients.

The limitations of this study were the small number of patients and the retrospective design. Multivariate analysis may not precisely identify factors associated with OS and PFS in such a small study, but we have clearly demonstrated the clinical impact of ER to HAIC on OS and PFS for all patients, and this impact also could be observed in patients with unfavorable factors such as major PVTT, poor performance status, large tumors, or advanced stage. In this retrospective study, the decision to give additional treatment was mostly dependent on the ER. The overall response was the result not only of HAIC but also the result of other additional treatments. Only one non-early responder improved to PR after additional treatment. The use of additional treatments might have led to some bias in the analysis of factors associated with outcomes because some NERs did not receive any further additional treatments. A new study with prospective design to clearly define the criteria of additional treatments after 4 weeks of HAIC is warranted in the future to answer this problem.

Conclusions

An ER to 4-week HAIC therapy was strongly associated with better outcomes in patients with advanced HCC and PVTT. Further courses of HAIC using the same protocol can be administered in early responders because the tumor could potentially be downstaged, leading to subsequent improved PFS and OS.

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Conflict of interest

None

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