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Response to chemotherapy improves hepatic reserve for patients with hepatocellular carcinoma and Child–Pugh B cirrhosis

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Key words

Child–Pugh class B, hepatic arterial infusion chemotherapy, hepatic reserve, hepatocellular carcinoma, response to chemotherapy

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There is no established treatment for patients with advanced hepatocellular carcinoma (HCC) with Child–Pugh class B cirrhosis. The aim of the present study was to assess the efficacy of hepatic arterial infusion chemotherapy (HAIC) according to Child–Pugh score (CPS) and to evaluate the correlation of a patient's response to HAIC with hepatic reserve and outcome. We retrospectively reviewed the medical records of 377 patients treated with HAIC between March 2003 and February 2015. Subjects included 179 with Child–Pugh class B. Median overall survival was 12.1 months for patients with CPS = 7 (n = 75) and 11.9 months for patients with CPS = 8 (n = 58), which were significantly longer compared with those of patients with CPS = 9 (n = 46, 6.3 months). The objective response rates of patients with CPS = 7, 8 and 9 were 26.7%, 27.6% and 6.5%, respectively. The CPS of responders improved significantly after HAIC, whereas those of nonresponders did not. A multivariate analysis demonstrated that improved CPS, responses to HAIC and absence of extrahepatic lesions were independent favorable prognostic factors. Patients with CPS = 7 or 8 tolerated HAIC, but nine (19.6%) of patients with CPS = 9 were unable to complete one course. HAIC is effective and safe for patients with a CPS = 7 or 8 and improved hepatic reserve of responders significantly.

Hepatocellular carcinoma (HCC) remains a health concern worldwide because its incidence continues to increase.[1] Despite recent advances in diagnostic and therapeutic technologies,[2,3] patients with HCC who receive curative treatment frequently experience multicentric recurrence that is difficult to treat. Consequently, patients with advanced HCC have unsatisfactory outcomes.[4]

For patients without cirrhosis or with Child–Pugh class A cirrhosis, the results of a randomized trial establish sorafenib as the standard of care for patients with advanced HCC.[5] In contrast, there is no established treatment for patients with advanced HCC with Child–Pugh class B cirrhosis. Sorafenib may be a treatment option for patients with Child–Pugh class B cirrhosis;[6] however, the outcomes of these patients are worse compared with those with Child–Pugh class A.[7–10] Therefore, the development of alternative treatments is essential.

Hepatic arterial infusion chemotherapy (HAIC) is a promising treatment for a certain number of patients with advanced HCC and is being administered in Asia in particular.[11] However, for example, to our knowledge, there are no reports that evaluate the efficacy and feasibility of HAIC according to Child–Pugh scores (CPS) and change of CPS of patients with advanced HCC and Child–Pugh class B cirrhosis treated with HAIC. The efficacy of HAIC for those patients remains unclear.

The aim of the present study was to determine the efficacy of HAIC for treating patients with advanced HCC with Child–Pugh class B. Moreover, we investigated the effect of patients' responses to treatment on their outcomes and hepatic reserves.

Materials and Methods

Objective patients. We studied consecutive patients with advanced HCC who were treated with HAIC at the Kanazawa University Hospital from March 2003 to February 2015. Because the radiological findings of these patients included vascular invasion and/or intrahepatic multiple lesions, they were judged to be unsuitable for surgical resection, locoregional therapy and transarterial chemoembolization. All patients underwent dynamic computed tomography or dynamic magnetic resonance imaging, and HCC was diagnosed according to the guidelines of the American Association for the Study of Liver Disease.[12] Patients with extrahepatic lesions were eligible for HAIC if their extrahepatic lesions were mild and judged not to be prognostic (i.e. small tumor burden, slowly growing tumor, and no effect of the tumor on patients' symptoms).

Hepatic arterial infusion chemotherapy. The implantation of the reservoir system to deliver agents is performed as previously described.[13] Briefly, catheters were induced through the right femoral artery, and angiography from the celiac artery

was first performed to localize the HCC and evaluate intrahepatic and extrahepatic vascularization. We next inserted a catheter with the side opening into the gastroduodenal artery, positioning the side opening in the common hepatic artery using an image-guided procedure. The gastroduodenal artery, right gastric artery and other arteries that were suspected to nourish the gastroduodenal region were embolized to the extent possible to prevent gastrointestinal mucositis. The other end of the catheter was connected to the injection port that was implanted subcutaneously in the right-lower abdomen. Finally, we confirmed the redistribution of blood flow.

Hepatic arterial infusion chemotherapy was conducted after we confirmed the full recovery of the wound. The treatment protocol was as follows: 5-fluorouracil (330 mg/m^2/day) was administered continuously from days 1 to 5 and days 8 to 12. Some patients received intravenous cisplatin (20 mg/m^2/day) injected into the hepatic artery for 10 min before administration of 5-fluorouracil. Interferon α-2b or pegylated interferon α-2b was used at the physician's discretion. Pegylated interferon α-2b (1.0 μg/kg) was administered subcutaneously on days 1, 8, 15 and 22, and interferonα-2b (3×10^6 U) was administered intramuscularly three times each week. The drugs were administered for a treatment cycle of 28 days followed by a 14-day rest period. The treatment was repeated until tumor progression, unacceptable toxicity, patient refusal of treatment, or death.

Assessment of consequence by treatment. The efficacy of treatment was assessed every 4–6 weeks using dynamic computed tomography or dynamic magnetic resonance imaging during and after treatment. The antitumor effect of treatment was assessed according to the Response Evaluation Criteria in Solid Tumors version 1.1.[14] The Child–Pugh score was assessed every visit using physiological and laboratory findings. Overall survival (OS) was defined as the start of treatment until death. Progression-free survival (PFS) was defined as the start of treatment until the date of radiological progression, death, or the last day of follow-up. An objective response rate was defined as the sum of the complete response rate and the partial response rate.

Data collection. We reviewed patients' medical records and collected demographic, clinical and laboratory data, which included age, sex, Eastern Cooperative Oncology Group performance status, hepatitis virus status, hepatic reserve, imaging data (vascular invasion and extrahepatic lesions) and analyses of tumor markers. The institutional review board of Kanazawa University Hospital approved the study's treatment strategy and study protocol. The study was conducted in accordance with the Declaration of Helsinki.

Statistical analysis. Categorical variables were compared using the χ^2-test when appropriate. The Student *t*-test and the Mann–Whitney test were used for continuous variables. Cumulative survival was calculated using the Kaplan–Meier method to evaluate the association of clinical factors with survival, and differences were evaluated using the log-rank test. Multivariate analysis using Cox's proportional hazards regression model was performed to determine the hazard ratios for risk factors associated with OS. All statistical analyses were performed using the SPSS statistical software program (version 21.0; SPSS, Chicago, OH, USA).

Results

Characteristics of the patients treated with hepatic arterial infusion chemotherapy. Between March 2003 and February 2015, 377 patients were treated with HAIC, and data were collected until 14 March 2015. The median follow-up period was 8.48 (range, 0.23–141.14) months. The Child–Pugh classifications of patients when HAIC commenced were as follows: A, 151 (40.1%); B, 179 (47.5%); and C, 47 (12.5%). Among the patients with Child–Pugh class B, CPS were as follows: CPS = 7, 75 (41.9%), CPS = 8, 58 (32.4%) and CPS = 9, 46 (25.7%). More patients with worse Child–Pugh classification had a statistically significant increase in vascular invasion, extrahepatic spread and α-fetoprotein (AFP) ≥400 ng/mL; and more patients with worse Child–Pugh classification had more advanced stages of HCC according to the criteria of the Liver Cancer Study Group of Japan (Table 1). Patients with CPS = 9 were younger and had worse performance status compared with patients with CPS = 7 or 8 (Table 2). Other patient demographic characteristics are summarized in Tables 1 and 2. At the time of the analysis, 291 patients (77.2%) were deceased. The 377 patients completed a total of 965 courses of treatment, with a median = 2 (range, 0–31). Eighteen patients (10.1%), including three patients (4.0%) with CPS = 7, six patients (10.3%) with CPS = 8, and nine patients (19.6%) with CPS = 9, were unable to complete at least one course of HAIC because of unacceptable toxicities, worse general condition or tumor progression.

Progression-free survival and overall survival of patients treated with hepatic arterial infusion chemotherapy stratified according to Child–Pugh score. The median PFS was 4.8, 4.1 or 1.4 months for patients with Child–Pugh class A, B or C, respectively (Fig. 1a). The median PFS was 4.8, 4.9 and 1.7 months for patients with CPS = 7, 8 and 9, respectively.

Table 1. Demographic characteristic of the patients according to Child–Pugh classification

	Child–Pugh class A (*n* = 151)	Child–Pugh class B (*n* = 179)	Child–Pugh class C (*n* = 47)	*P*-value*
Age, *n* (%)				
≥66	88 (58.3)	93 (52.0)	16 (34.0)	0.015
Sex, *n* (%)				
Male	123 (81.5)	135 (75.4)	37 (78.7)	0.41
ECOG PS, *n* (%)				
0	140 (92.7)	130 (72.6)	29 (61.7)	<0.01
1	11 (7.3)	44 (24.6)	11 (23.4)	
≥2	0	5 (2.8)	7 (14.9)	
HB antigen, *n* (%)				
Positive	40 (26.5)	42 (23.5)	17 (36.2)	0.21
HCV antibody, *n* (%)				
Positive	78 (51.7)	98 (54.7)	22 (46.8)	0.60
Vascular invasion, *n* (%)				
Positive	64 (42.4)	93 (52.0)	31 (66.0)	0.014
Extrahepatic spread, *n* (%)				
Positive	29 (19.2)	48 (26.8)	18 (38.3)	0.025
LCSGJ tumor stage, *n* (%)				
II, III	85 (56.3)	85 (47.5)	16 (34.0)	0.064
IVA	47 (31.1)	56 (31.3)	16 (34.0)	
IVB	19 (12.6)	38 (21.2)	15 (31.9)	
AFP, *n* (%)				
≥400 ng/mL	59 (39.1)	91 (50.8)	32 (68.1)	<0.01

*χ^2-test. AFP, α-fetoprotein; ECOG PS, Eastern Cooperative Oncology Group performance status; HB antigen, hepatitis B virus surface antigen; HCV antibody, hepatitis C virus antibody; LCSGJ, Liver Cancer Study Group of Japan.

Table 2. Demographic characteristic of the patients with Child–Pugh B according to Child–Pugh score

	Child–Pugh score			*P*-value*
	7 (*n* = 75)	8 (*n* = 58)	9 (*n* = 46)	
Age, *n* (%)				
≥66	46 (61.3)	29 (50.0)	18 (39.1)	0.056
Sex, *n* (%)				
Male	57 (76.0)	39 (67.2)	39 (84.8)	0.12
ECOG PS, *n* (%)				
0	55 (73.3)	46 (79.3)	29 (63.0)	0.038
1	20 (26.7)	11 (19.0)	13 (28.3)	
≥2	0	1 (1.7)	4 (8.7)	
HBs antigen, *n* (%)				
Positive	16 (21.3)	16 (27.6)	10 (21.7)	0.67
HCV antibody, *n* (%)				
Positive	39 (52.0)	33 (56.9)	26 (56.5)	0.82
Vascular invasion, *n* (%)				
Positive	36 (48.0)	31 (53.4)	26 (56.5)	0.64
Extrahepatic spread, *n* (%)				
Positive	21 (28.0)	13 (22.4)	14 (30.4)	0.63
LCSGJ tumor stage, *n* (%)				
II, III	40 (53.3)	28 (48.3)	17 (37.0)	0.68
IVA	20 (26.7)	17 (29.3)	19 (41.3)	
IVB	15 (20.0)	13 (22.4)	10 (21.7)	
AFP, *n* (%)				
≥400 ng/mL	43 (57.3)	25 (43.1)	23 (50.0)	0.26

*χ^2-test. AFP, α-fetoprotein; ECOG PS, Eastern Cooperative Oncology Group performance status; HB antigen, hepatitis B virus surface antigen; HCV antibody, hepatitis C virus antibody; LCSGJ, Liver Cancer Study Group of Japan.

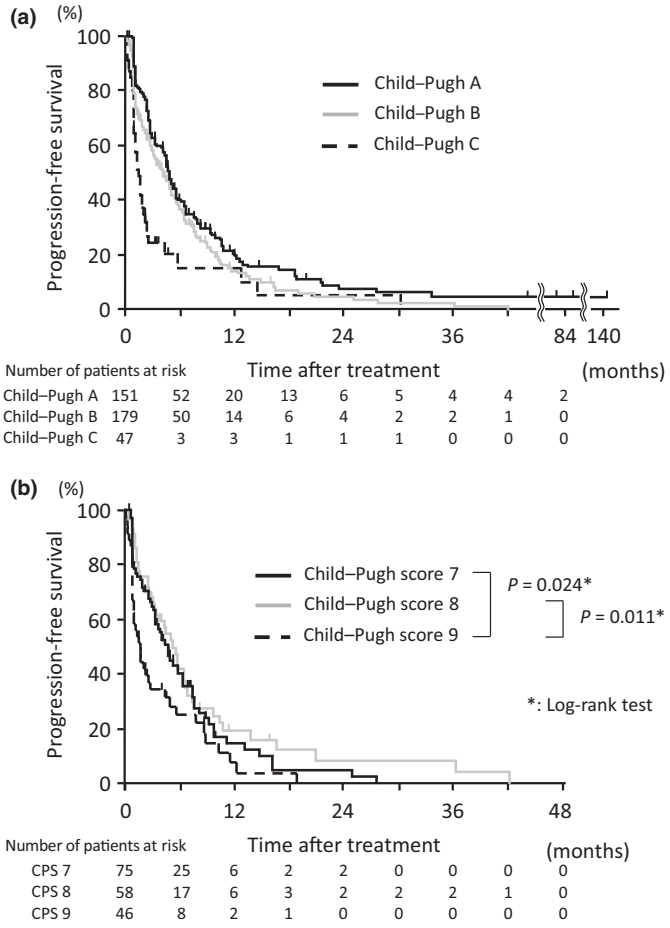

Fig. 1. Kaplan–Meier plot of progression-free survival after hepatic arterial infusion chemotherapy commenced, according to Child–Pugh classification and Child–Pugh score. (a) The median progression-free survival was 4.8, 4.1 or 1.4 months for patients with Child–Pugh class A, B and C, respectively. (b) The median progression-free survival of the patients with Child–Pugh score = 7 was 4.8 months, which was significantly better compared with that of patients with Child–Pugh score = 9, 1.7 months ($P = 0.024$). The median progression-free survival of patients with Child–Pugh score = 8 was 4.9 months, which was significantly better compared with that of patients with Child–Pugh score = 9 ($P = 0.011$).

The PFS of patients with CPS = 7 and 8 was significantly better compared with that of patients with CPS = 9 ($P = 0.024$ and $P = 0.011$ compared with CPS = 7 and 8, respectively) (Fig. 1b).

The median OS was 15.5, 9.9 and 2.9 months for patients with Child–Pugh class A, B and C, respectively (Fig. 2a). The median OS was 12.1, 11.9 and 6.3 months for patients with CPS = 7, 8 and 9, respectively. The OS of patients with CPS = 7 and 8 was significantly better compared with that of patients with CPS = 9 ($P = 0.015$ and $P = 0.043$ compared with CPS = 7 and 8, respectively) (Fig. 2b).

Objective response to with hepatic arterial infusion chemotherapy according to Child–Pugh score. The objective responses to HAIC were 33.8%, 21.8% and 6.4% for patients with Child–Pugh class A, B and C, respectively. For patients with CPS = 7, 8 and 9, their objective responses to HAIC were 26.7%, 27.6% and 6.5%, respectively (Table 3). The objective responses of patients with CPS of 7 and 8 were significantly better compared with those of patients with CPS = 9 ($P < 0.01$ and $P < 0.01$ compared with CPS = 7 and 8, respectively) (Table 4).

Analysis of Child–Pugh score of patients with Child–Pugh class B stratified according to their responses to hepatic arterial infusion chemotherapy. Among patients with Child–Pugh class B, CPS data were available for 173 and 130 patients at 4 and 12 weeks, respectively, after HAIC started (Table S1). Among patients with CPS = 7 when HAIC commenced, the CPS significantly improved for responders to 6.45 after 4 weeks ($P < 0.01$), which was maintained after 12 weeks (the mean CPS 6.30, $P < 0.01$). In contrast, the CPS did not improve for those whose best antitumor effect was stable disease; the mean CPS after 4 and 12 weeks were 7.17 and 7.36, respectively, among patients with CPS = 7 when HAIC commenced ($P = 0.58$ and 0.10, respectively). Moreover, the CPS became worse for those whose best antitumor effect was progressive disease or not evaluable; the mean CPS after 4 and 12 weeks were 7.38 and 7.88, respectively, among the patients with CPS = 7 when HAIC commenced ($P = 0.18$ and 0.038, respectively) (Fig. 3). Among patients with a CPS = 8 or 9 when HAIC commenced, the improvement of CPS for responders was similar to those of patients with CPS = 7 (Table S1).

Effects of hepatic arterial infusion chemotherapy on the Child–Pugh score of patients with main portal vein tumor thrombus. Among patients with Child–Pugh class B, 59 had main portal vein tumor thrombus when HAIC commenced. Nine patients responded to HAIC, and the best antitumor effect was stable disease for 17 patients. The other 33 patients had

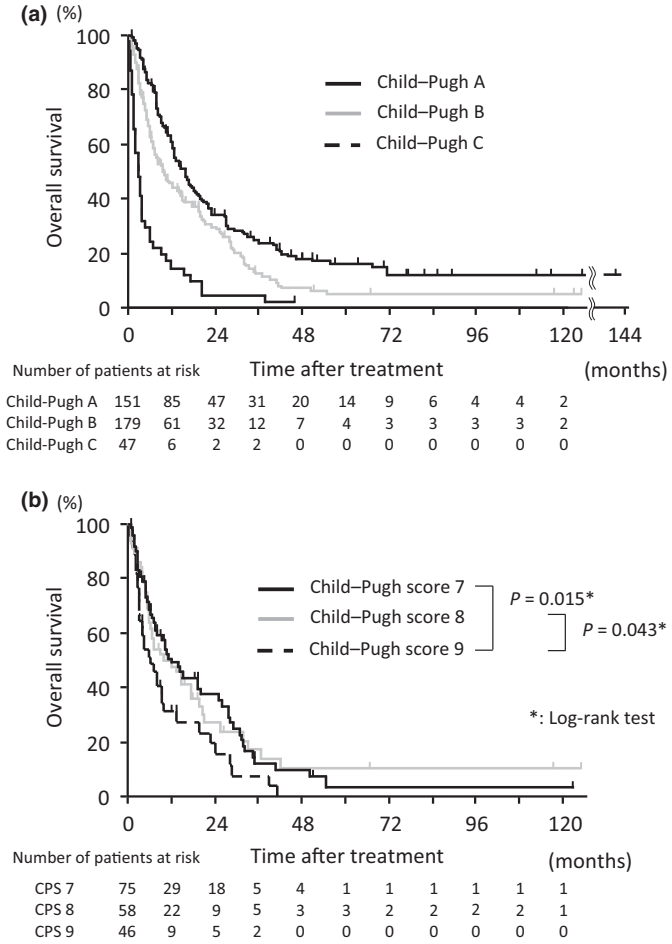

Fig. 2. Kaplan–Meier plot of overall survival after hepatic arterial infusion chemotherapy commenced, according to Child–Pugh class and Child–Pugh score. (a) The median overall survival was 15.5, 9.9 or 2.9 months for patients with Child–Pugh class A, B and C, respectively. (b) The median overall survival of the patients with Child–Pugh score = 7 was 12.1 months, which was significantly better compared with that of patients with Child–Pugh score = 9, 6.3 months ($P = 0.015$). The median overall survival of patients with Child–Pugh score = 8 was 11.9 months, which was significantly better compared with that of patients with Child–Pugh score = 9 ($P = 0.043$).

Table 3. Objective responses to hepatic arterial infusion chemotherapy according to Child–Pugh classification

Response† to hepatic arterial infusion chemotherapy	Child–Pugh class A ($n = 151$)	Child–Pugh class B ($n = 179$)	Child–Pugh class C ($n = 47$)
Complete response	12 (7.9%)	5 (2.8%)	1 (2.1%)
Partial response	39 (25.8%)	34 (19.0%)	2 (4.3%)
Stable disease	54 (35.8%)	62 (34.6%)	13 (27.7%)
Progressive disease	42 (27.8%)	63 (35.2%)	18 (38.3%)
Not evaluated	4 (2.6%)	15 (8.4%)	13 (27.7%)
Objective response rate	33.8%	21.8%	6.4%

Data are presented as *N* (%). †Based on RECIST v1.1.

progressive disease or were not evaluable. When the change in CPS was stratified according to patients' responses to HAIC, CPS was improved for the responders to HAIC of seven

Table 4. Objective responses to hepatic arterial infusion chemotherapy of patients with Child–Pugh B according to Child–Pugh score

Response to hepatic arterial infusion chemotherapy†	Child–Pugh score 7 ($n = 75$)	8 ($n = 58$)	9 ($n = 46$)
Complete response	2 (2.7%)	2 (3.4%)	1 (2.2%)
Partial response	18 (24.0%)	14 (24.1%)	2 (4.3%)
Stable disease	23 (30.7%)	18 (31.0%)	16 (34.8%)
Progressive disease	28 (37.3%)	19 (32.8%)	21 (45.7%)
Not evaluated	4 (5.3%)	5 (8.6%)	6 (13.0%)
Objective response rate	26.7%***	27.6%***	6.5%

Data are presented as *N* (%). †Based on RECIST v1.1. ***$P < 0.01$ (χ^2-test) compared with the objective response rate for patients with CPS = 9.

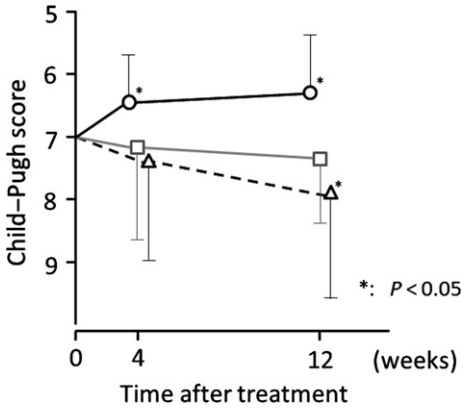

Fig. 3. Changes of Child–Pugh score (± SD) of patients with Child–Pugh score = 7. The mean Child–Pugh scores of responders (circles and black line) at 4 and 12 weeks after hepatic arterial infusion chemotherapy commenced was significantly improved. For patients whose best antitumor effects were stable (squares and gray line), the mean Child–Pugh score did not improve. For patients whose best antitumor effect was progressive disease or not evaluable (triangles and dashed line), the mean Child–Pugh score became worse.

(77.8%) at 4 and 12 weeks (Table S2). In contrast, at these same times, CPS was improved for six (35.3%) and five patients (29.4%) whose best antitumor effect was stable disease and eleven (33.3%) and two (6.1%) whose best antitumor effect was progressive disease or who were not evaluable (Table S2).

Analysis of each factor for Child–Pugh score of patients stratified according to their responses to with hepatic arterial infusion chemotherapy. When the change in each factor for CPS was evaluated individually, all factors tended to exhibit an improvement for responder to HAIC, although it was difficult to evaluate encephalopathy, because of the small number of patients with this condition (Fig. 4). For example, the mean albumin level (± SD) of responders was 3.04 (± 0.44) when HAIC commenced and improved to 3.22 (± 0.46) after 12 weeks. In contrast, all factors associated with CPS did not improve for those whose best antitumor effect was stable disease or for those with progressive disease or those who were not evaluable (Fig. 4). For example, the mean albumin levels of patients with stable disease were 2.95 (± 0.46) when HAIC commenced and 3.00 (± 0.46) 12 weeks after HAIC

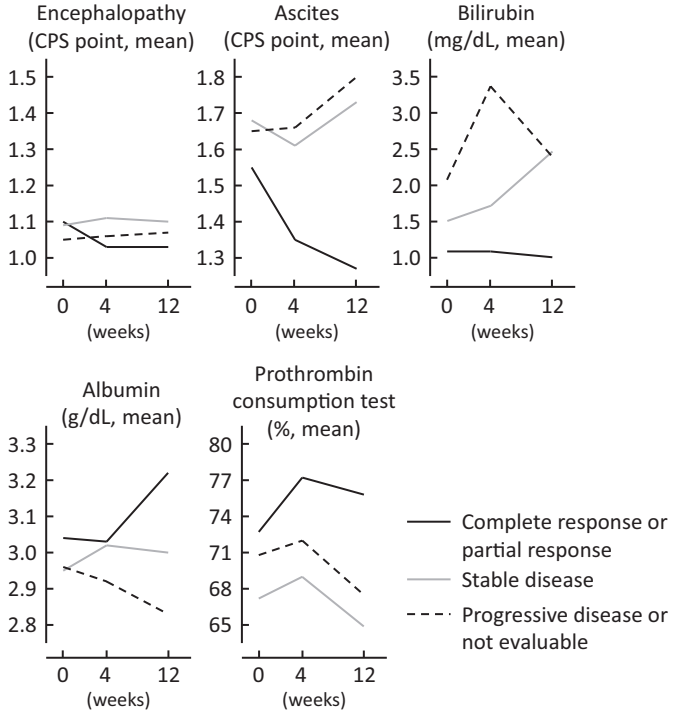

Fig. 4. Analysis of factors that influence the Child–Pugh score of patients at 0 (baseline), 4 and 12 weeks after hepatic arterial infusion chemotherapy commenced. All factors improved for responders (black line), except for encephalopathy. In contrast, all factors did not improve for those whose best antitumor effect was stable disease (gray line), progressive disease, or for those who were not evaluable (dashed line).

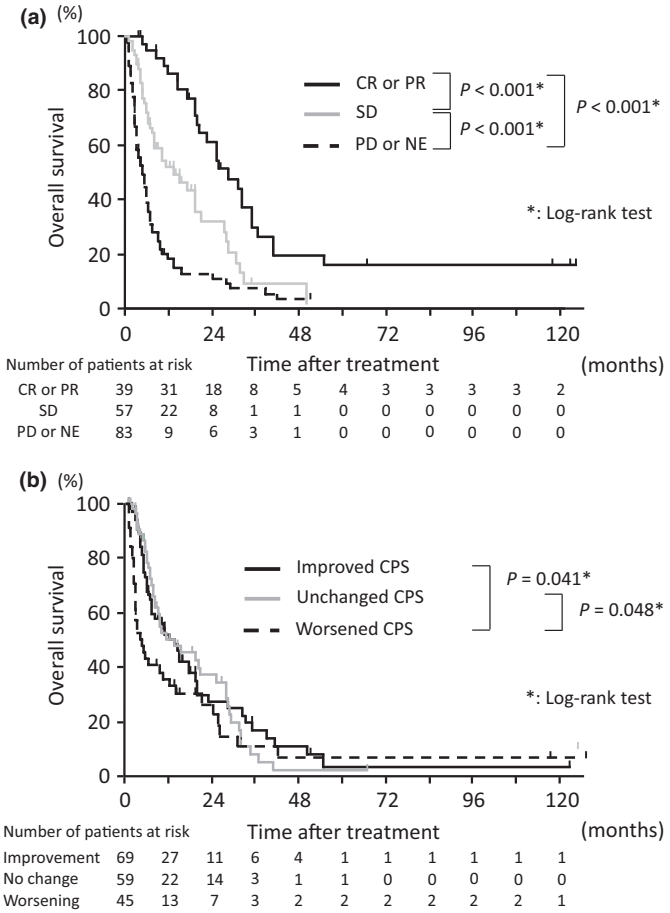

Fig. 5. Kaplan–Meier plot of overall survival after hepatic arterial infusion chemotherapy commenced according to response and changes in Child–Pugh score. (a) The median overall survival of a patient whose best antitumor effect was a complete or partial response, stable disease, or progressive disease or not evaluable was 28.7, 13.6 or 5.0 months, respectively. (b) The median overall survival times of patients whose Child–Pugh scores were improved, unchanged or worsened were 13.6, 13.2 or 4.3 months, respectively.

commenced, and the mean albumin levels of patients with progressive disease or those who were not evaluable were 2.96 (± 0.44) when HAIC commenced, and 2.83 (± 0.58) 12 weeks after HAIC commenced.

Effects of with hepatic arterial infusion chemotherapy on overall survival and Child–Pugh score. When OS was stratified according to patients' responses to HAIC, those of responders were significantly better compared with those of patients with stable or progressive disease according to RECIST v1.1 ($P < 0.001$ and $P < 0.001$, respectively) (Fig. 5a). The median OS of responders was 28.7 months, whereas that of the patients with stable and progressive disease was 13.6 and 5.0 months, respectively. Similarly, the OS of the patients with improved or unchanged CPS was significantly better compared with patients with worsened CPS ($P = 0.041$ and $P = 0.048$) (Fig. 5b). The median OS values of patients with improved, unchanged and worsened CPS were 13.6, 13.2 and 4.3 months, respectively. Improved CPS (hazard ratio compared with worsened CPS, 0.609; $P = 0.030$), response to HAIC (hazard ratio compared with progressive disease, 0.223; $P < 0.001$), stable disease (hazard ratio, 0.537; $P = 0.0031$), and absence of extrahepatic lesions (hazard ratio 0.543; $P = 0.005$) were identified as independent factors for favorable prognosis using a multivariate Cox regression model (Table 5).

Discussion

Chronic liver disease is the underlying pathological condition of most patients with HCC, and impaired hepatic reserve caused by chronic liver disease often adversely affects a patient's outcome and quality of life.[15] Moreover, unlike other types of cancer, a patient's outcome strongly depends on hepatic reserve as well as tumor factors which can be reflected by tumor markers such as serum AFP levels.[16]

Novel targeted agents have been developed for patients with advanced HCC, including drugs which are being investigated in the late-phase clinical trials. However, the study populations are restricted to patients with sufficient hepatic reserve, namely Child–Pugh class A, or those without detectable liver cirrhosis.[17–19] These selective criteria were imposed because of the difficulty in analyzing patients with impaired hepatic reserve.[20] Furthermore, our present findings indicate that the development of HCC, which was characterized according to progressive intrahepatic lesions and portal vein tumor thrombus, affected patients' hepatic reserve and that patients with more advanced stages of HCC had increased impairment of hepatic reserve (Table 1). At least 50% of the patients who underwent HAIC were diagnosed with Child–Pugh class B. Therefore, more effective treatment strategies are urgently required to improve the outcomes of patients with advanced HCC and Child–Pugh class B cirrhosis.

Table 5. Contributing factors to patients' outcome

	N	Median overall survival (months)	Hazard ratio (95% CI)†	Multivariate *P*-value†
CPS 4weeks after HAIC				
Worsened or not evaluable	45	4.3		
Unchanged	59	13.2	0.728 (0.460–1.152)	0.18
Improved	69	13.6	0.609 (0.388–0.953)	0.030
Vascular invasion				
Presence	93	7.0		0.20
Absence	86	15.4	0.775 (0.523–1.149)	
Extrahepatic lesion				
Presence	48	5.8		0.0046
Absence	131	13.6	0.543 (0.356–0.829)	
AFP, ng/mL				
≥400	91	7.3		0.054
<400	88	13.7	0.675 (0.452–1.007)	
Best response to HAIC				
Progressive disease or not evaluable	83	5.0		
Stable disease	57	13.6	0.537 (0.356–0.811)	0.0031
Complete response or partial response	39	28.7	0.223 (0.136–0.366)	<0.001

AFP, α-fetoprotein; CI, confidence interval; CPS, Child–Pugh score; HAIC, hepatic arterial infusion chemotherapy. †Cox's proportional hazards regression model.

In an attempt to overcome this difficult challenge, the first aim of the present study was to investigate the feasibility and efficacy of HAIC according to detailed CPS in patients with Child–Pugh class B. Published studies of small numbers of patients with advanced HCC and Child–Pugh class B who underwent HAIC did not analyze the relationship of efficacy or tolerability to every aspect of the CPS.[21–23] They concluded that the effectiveness of HAIC, according to response or time to progression of patients with Child–Pugh class B, was comparable with that of patients with Child–Pugh class A. In contrast, the OS of the patients with Child–Pugh class B was worse compared with those with Child–Pugh class A. Our present findings are consistent with those of the reports for patients with a CPS = 7 or 8;[21,22] however, the responses to HAIC and the outcomes of patients with CPS = 9 were significantly worse compared with those with Child–Pugh class A or CPS = 7 or 8 and were equal to those with Child–Pugh class C. Moreover, the high rate of discontinuation (approximately 20%) during the first course of HAIC demands careful attention for patients with CPS = 9 and suggests that appropriate candidates for HAIC were patients with a CPS 8 or better. In contrast, for patients with a CPS 9 or worse, the efficacy of HAIC was very limited, and patients' outcomes were very poor.

The most important insight provided by our current study is that a response to HAIC improved hepatic reserve, which contributed to prolonging survival. In previous reports, the clinical benefit of a response to treatment has been only assessed in the context of survival prolongation.[24] To our knowledge, the present study is the first to demonstrate a significant merit to hepatic reserve by HAIC treatment to HCC and the influence of the improvement of hepatic reserve. Progressive intrahepatic lesions and portal vein tumor thrombus can often lead to impairment of hepatic reserve in part, as described above. For example, a main portal vein tumor thrombus may disturb portal blood flow and adversely affect liver function, which is consistent with our findings, because shrinkage of the lesions contributes to the improving hepatic reserve by mitigating the effects of tumor localization on hepatic reserve. Moreover, improvement of hepatic reserve may increase treatment options, such as administering sorafenib to patients with Child–Pugh class A. Thus, such therapies can contribute to controlling tumor progression, although sufficient hepatic reserve is a favorable prognostic factor itself. The treatment for patients with advanced HCC should aim at relief from discomfort due to the impaired hepatic function as well as outcomes of survival. Hepatic reserve closely correlates with quality of life of patients with chronic liver disease.[25] Therefore, HAIC may improve the quality of life and prolong the survival of patients with HCC, although no definite data other than for hepatic reserve was assessable here.

In conclusion, HAIC is effective for treating patients with advanced HCC with a CPS = 7 or 8. The CPS of responders also improved their outcomes, compared to nonresponders. Although the present study is limited due to the retrospective design and subjects, who were treated in a single center, our findings are informative for determining treatment strategies or designing future clinical trials of agents to treat patients with advanced HCC.

Disclosure Statement

The authors have no conflict of interest to declare.

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

Table S1. Changes of Child–Pugh score according to response to hepatic arterial infusion chemotherapy

Table S2. Changes of Child–Pugh score according to response to hepatic arterial infusion chemotherapy among the patients with main portal vein tumor thrombus