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Assessment of Outcome of Hepatic Arterial Infusion Chemotherapy in Patients with Advanced Hepatocellular Carcinoma by the Combination of RECIST and Tumor Markers

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ABSTRACT

To assess the outcome of stable disease (SD) patients with advanced hepatocellular carcinoma (HCC) by tumor markers after the first course of hepatic arterial infusion chemotherapy (HAIC). The study subjects were 156 HCC patients treated with HAIC and classified as Child Pugh A, with no extrahepatic metastasis, and no history of sorafenib treatment. In the study and validation cohorts, the AFP and DCP ratios of patients who were considered SD to the first course of HAIC were analyzed by AUROC for a prediction of response to the second course of HAIC. The imaging response to the first course of HAIC was classified as partial response (PR), SD and progressive disease (PD) in 29 (18.8%), 80 (51.9%), and 44 (28.6%) patients respectively. For SD patients, the α-fetoprotein (AFP) and des-γ-carboxy prothrombin (DCP) ratios of patients who were considered SD to the first course of HAIC were analyzed by the receiver operating characteristic curve for prediction of response to the second course of HAIC in the study cohorts. The area under the curve of AFP ratio was 0.743. The area under the curve of DCP ratio was 0.695. The cut-off values of AFP and DCP ratios were 1.3 and 1.0, respectively. In the validation cohort, the accuracy of the prediction of response in this validation cohort (71.4%) showed no significant difference compared to that in the study cohort (72.4%) ($p = 1.0$). The results suggested that patients with a high tumor marker ratio could be switched to alternative therapeutic regimens despite the SD response to HAIC.

Key words: *Hepatocellular carcinoma, Hepatic arterial infusion chemotherapy, RECIST, Tumor marker*

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the second leading cause of cancer-related mortality worldwide[6,9)]. Advances in biotechnology have made it possible to develop new diagnostic techniques, such as ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), and angiography. Similarly, new treatment modalities have been invented, such as surgical resection, radiofrequency ablation (RFA), percutaneous ethanol injection (PEI), transcatheter arterial chemoembolization (TACE), and hepatic arterial infusion chemotherapy (HAIC), which have improved the prognosis of HCC patients[1,3,4,7,8,14,15,23,25)]. However, the survival rates of patients with advanced HCC and associated complications such as portal vein tumor thrombosis (PVTT), venous tumor thrombosis (VTT), and refractoriness to TACE, have not improved enough.

Two phase III clinical trials of sorafenib for advanced HCC showed significant efficacy in terms of overall survival time (OST) compared with a placebo [2,6)]. Based on these studies, sorafenib has become the standard therapy for advanced HCC. Sorafenib contributed to prolonging OST by 2.3-2.8 months and the response rate (RR) by 2.0-3.3%. However, the survival advantage of sorafenib is described as insufficient.

HAIC is widely undergone in Asia, especially Japan. Several studies have shown the survival benefits of HAIC for advanced HCC free of extrahepatic metastasis, with a response rate ranging from 20.8 to 52%, and have reported that median survival time (MST) in responders is 17.6-40.7 months[1,11,19,23,27,28)].

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However, large randomized trials are not demonstrated efficiently. In most of the retrospective studies, survival time was much longer in responders than in non-responders. We have reported that survival after switching HAIC treatment to sorafenib was better than that of continuous HAIC[20]. At present, however, there is no biomarker that can be used to predict the response to HAIC treatment. Such a marker could help in decision making on whether to continue HAIC treatment or not.

The treatment response to HCC is assessed by imaging studies. One of the most common methods for response evaluation is the Response Evaluation Criteria in Solid Tumors (RECIST) [5]. However, it is inefficient to evaluate response to the first course of treatment by imaging studies alone. On the other hand, some studies have shown the usefulness of a-fetoprotein (AFP) and des-γ-carboxy prothrombin (DCP) not only as tumor markers, but also as prognostic factors for HCC[13,17,22,26]. We reported that patients with AFP and DCP ratios of >1 had significantly poorer survival than others (MST 7.4 vs 12.6 months, p=0.014), among patients with stable disease (SD) based on imaging response to first course of chemotherapy[21]. To our knowledge, there are no clear cut-off values for AFP ratio and DCP ratio.

The present retrospective study was designed to analyze the cut-off values of the AFP and DCP ratios for outcome to the first course of chemotherapy in HCC patients with SD.

MATERIALS AND METHODS

Patients. Between June 2000 and March 2015, 364 patients with unresectable HCC were treated with HAIC at our hospital. HAIC was selected as the therapeutic option for patients with advanced HCC who presented also with PVTT and VTT, and refractoriness to TACE. We excluded the following patients from HAIC: *1)* The performance status of the Eastern Cooperative Oncology Group (ECOG) was ≥3 (n=1). *2)* Child–Pugh score of ≥7 (n=109), *3)* extrahepatic metastasis (n=80), *4)* treatment with sorafenib before and after HAIC (n=18). After the exclusion of the above 208 patients, the remaining 156 patients were enrolled in this retrospective cohort study (Fig. 1). The study protocol was approved by the Human Ethics Review Committee of Hiroshima University and a signed consent form was obtained from each subject.

Hepatic arterial infusion chemotherapy (HAIC). Patients were given arterial infusions of anticancer agents via the injection port. Two drug regimens are used in HAIC. We used intra-arterial low-dose cisplatin (CDDP, Nihonkayaku, Tokyo, Japan) with 5- fluorouracil (5FU, Kyowa Hakko, Tokyo) (FP), or intra-arterial 5FU with subcutaneous interferon (5FU+IFN). One course of chemotherapy was undergone for 2 weeks. 5FU (300 mg body weight/day) was administered over 24 hr by using a mechanical infusion pump from days 1 to 5 of the first and second weeks in both regimens. CDDP was injected intra-arterially via a pump at 6 mg/body weight/day on days 1-5 and 8-12. The IFN in the 5FU+IFN regimen was recombinant IFNα-2b [Intron A, Schering-Plough Pharmaceuticals, Osaka, Japan, 3×10^6 U (3 MU)], or natural IFN-α [OIF, Otsuka Pharmaceuticals, Tokyo, 5×10^6 U (5 MU)] administered intramuscularly on days 1, 3, and 5 of each week (total dose, 36 and 60 MU, respectively). We reported previously that recombinant IFNα-2b had an equal effect to natural IFN-α when the combination of 5FU+IFN was used for the treatment of advanced HCC[28].

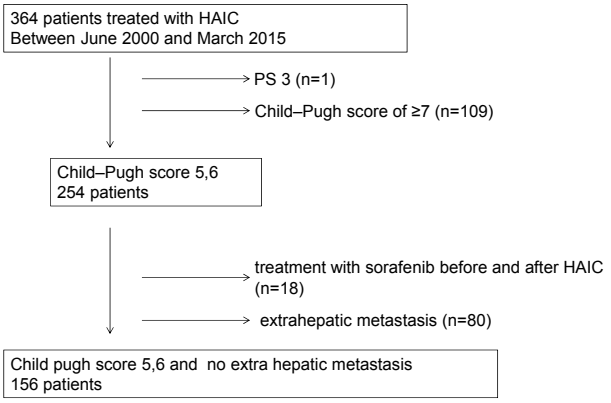

Fig. 1. Patient recruitment process

Assessment of response to HAIC. Each patient underwent dynamic CT before HAIC and also after each course of HAIC. In this study, we defined the terms imaging response and AFP/DCP tumor marker response. The imaging response to HAIC was evaluated by RECIST (version 1.1) on dynamic CT after the first course of HAIC (4 weeks later). A complete response (CR) was defined as the disappearance of all target lesions after one course of HAIC. A partial response (PR) was defined as the sum of the longest diameter reducing by more than at least 30% compared to before HAIC. Progressive disease (PD) was defined as the sum of the longest diameter of the target lesion increasing more than at least 20%. Stable disease (SD) was defined as corresponding neither to the criteria of PR nor PD. HAIC was continued repeatedly as long as the treatment response was better than SD. To evaluate the AFP/DCP tumor marker response, we measured these markers from the serum concentrations after each course of HAIC (each 4 weeks). In our hospital, the normal range of AFP is within 10 ng/ml, while that of DCP is within 30 mAU/ml. The AFP ratio represented the AFP value after one course of HAIC divided by the AFP value before treatment. The DCP ratio was measured similarly. When both tumor mark-

ers were within the normal range before and after treatment, the tumor marker ratio was ≤ 1.

Adverse drug reactions were defined according to the Common Terminology Criteria for Adverse Events version 4.0.

Follow-up and other therapies. Treatment with sorafenib was not administered throughout the clinical course. Instead, other therapies such as RFA, TACE and radiotherapy were used for partial and non-responders. PR patients continued to receive HAIC regularly in combination with other therapies. Patients whose advanced HCC was down-staged to a single tumor ≤ 50 mm in diameter or 1-3 tumors each ≤ 30 mm in diameter following the combination therapy, were considered to receive RFA or hepatectomy. In addition to HAIC, PD patients received TACE. TACE was used after HAIC in the following situations: 1) additional TACE aimed at downstaging HCC when patients showed an effective response to HAIC, and 2) palliative TACE aimed to prevent HCC rupture or rapid growth when patients showed non-response to HAIC. PD patients were also considered for radiotherapy when complicated with portal venous tumor thrombosis (PVTT). For CR patients, the clinical course was observed without adjuvant chemotherapy or additional therapy.

Statistical analysis. Statistical analysis was performed in August 2015. Differences between groups were examined for statistical significance using the Mann-Whitney U test, logistic regression test, or squared test, as appropriate. The cumulative survival rate was calculated from the date of initiation of HAIC, assessed by the Kaplan-Meier life-table method, and differences between groups were evaluated by the log rank test. Univariate analysis of the factors that correlated with survival of patients with HCC treated with HAIC was assessed by the Kaplan-Meier life-table method, and differences were evaluated by the log rank test. Multivariate analysis of the factors that influenced survival was assessed by the Cox proportional hazard model. Statistical significance was defined as p value of less than 0.05.

Cut-off points for continuous variables were determined by analysis of the receiver operating characteristic (ROC) curve based on the minimum balanced error rate (BER)[18]. BER is the average of the proportion of incorrect classifications in each class.

The cut-off value associated with maximum accuracy, sensitivity, and negative and positive predictive values of the PD to the second course of treatment was computed. The chi-squared test was used to compare the accuracy of the prediction score in the study cohort with that of the validation cohort.

All analyses described above were performed with The Statistical Package for Social Sciences software (version 11, SPSS, Chicago, IL).

RESULTS

Baseline characteristics. Patient characteristics are listed in Table 1. The study subjects were 140 men and 16 women, and the median age was 68

Table 1. Clinical characteristics of HCC patients treated with HAIC (n=156)

Age (years) *	68.0 (32-85)
Gender (M/F)	140/16
ECOG performance status (0/1/2)	133/21/2
Child-Pugh score (5/6)	84/72
Etiology (HBV/HCV/others)	42/85/29
Number of HCC tumors (solitary/multiple)	22/134
Size of liver tumor (mm) *	60 (10-180)
HCC stage (II/III/IVa) †	4/49/103
Vp (0/1/2/3/4) §	49/6/24/44/33
Vv (0/1/2/3) ‡	132/1/10/13
Relative tumor size in the liver (<50%/≥50%)	117/39
Platelet count (/mm^3) *	12 (4.6-88.8)
AFP (ng/ml) *	464 (2.9-1895000)
DCP (mAU/ml) *	1733 (7-666480)
HAIC regimen (FP/5FU+IFN)	86/70

*Data are median and (range) values, or number of patients.

†According to the Liver Cancer Group of Japan.

§Portal invasion. ‡Venous invasion.

CP: Child Pugh, ECOG: Eastern Cooperative Oncology Group, HCV: hepatitis C virus, HBV: hepatitis B virus, HCC: hepatocellular carcinoma, Vp2: tumor thrombus in the second branch of the portal vein, Vp3: tumor thrombus in the first branch of the portal vein, Vp4: tumor thrombus in the trunk of the portal vein, Vv2: tumor thrombus in the right, middle or left hepatic vein trunk, posterior inferior hepatic vein trunk or short hepatic vein, Vv3: tumor thrombus in inferior vena cava, AFP: α-fetoprotein, DCP: des-γ-carboxy prothrombin, FP: intra-arterial low-dose cisplatin and 5FU therapy, 5FU+IFN: intra-arterial 5-FU with IFN combination therapy.

years. The Child-Pugh score was 5 points in 84 patients and 6 points in 72 patients. The background liver disease was hepatitis C viral (HCV) infection in 85 patients, hepatitis B viral (HBV) infection in 42, and non-HCV-non-HBV in 29. Solitary HCC was detected in 22 patients and multiple HCCs in 134. HCC was classified as stage II, III and IVa in 4, 49 and 103 patients, respectively. Portal venous invasion was identified in 107 patients and venous invasion in 24 patients. The median value of AFP was 464 ng/ml and that of DCP was 1733 mAU/ml.

Imaging response after first course of HAIC and overall survival. Imaging response by RECIST to the first course of treatment was CR in one (0.6%) patient, PR in 29 (18.8%), SD in 80 (51.9%) and PD in 44 (28.6%) patients. MST varied significantly among the Imaging response groups ($p < 0.0001$) and was 26.6, 12.2 and 5.5 months in the PR, SD and PD groups, respectively (Fig. 2). The percentage of SD patients was more than 50%, and accordingly we examined the factors that could stratify the survival of SD patients to the first course of HAIC. In the median survival time of HAIC, there is no significant difference between FP (MST 11 months) and 5FU+IFN (MST 10 months) (p=0.8).

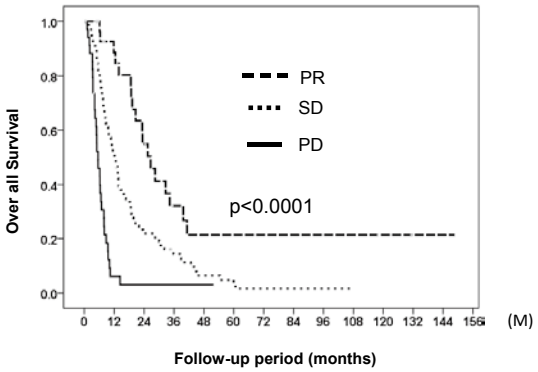

Fig. 2. Cumulative survival rates according to imaging response to the first course of HAIC

Background of SD patients by imaging response to first course. Table 2 lists the background of SD patients according to imaging response to the first course of HAIC. Among the 156 patients, 80 patients were classified as SD by the imaging response.

With regard to AFP and DCP, 23 patients who were treated with warfarin or vitamin K were excluded from analysis. Of the remaining 57 patients, 54 were men and 3 were women, with a median age of 68 years. The background liver disease was HCV infection in 36 and other diseases in 21. The Child-Pugh score was 5 in 28 patients and 6 in 29 patients. HCC was classified as stage II, III, and IVa in 1, 17, and 39 patients, respectively. In this group, the median value of AFP ratio was 1.27 while that of DCP ratio was 0.99. For the study cohort, data from 28 consecutive patients who were treated between 2000 and 2007 with HAIC were collected. Data from 29 patients treated between 2007 and 2015 were also collected as an independent validation cohort (Table 3). There was no significant difference between study cohort and validation cohort in their background.

Imaging response to second course of HAIC and overall survival among SD patients to first course of HAIC. Patients who were considered SD to the first course of HAIC were assessed again by CT after the second course of HAIC. One (1.65%) patient was classified as CR, 11 (17.7%) as PR, 27 (43.5%) as SD and 23 (37.1%) patients as

Table 2. Background of SD patients (n=57) according to the imaging response to the first course of chemotherapy

Age (years) *	68 (34-85)
Gender (M/F)	54/3
ECOG performance status (0/1)	50/7
Child-Pugh score (5/6)	28/29
Etiology (HBV/HCV/others)	13/36/8
Number of HCC tumors	4 (1-100)
Size of liver tumor (mm) *	69 (10-180)
HCC stage (II/III/IVa) †	1/17/39
Vp (0-2/3-4) §	31/26
Vv (0-1/2-3) ‡	50/7
Relative tumor size in the liver (<50%/≥50%)	42/15
Platelet count (/mm^3) *	12.2 (5.1-49.8)
AFP (ng/ml) *	387.3 (2.9-869800)
DCP (mAU/ml) *	1512 (10-120070)
AFP ratio *	1.27 (0.02-29.3)
DCP ratio *	0.99 (0.008-12.4)
Regimen (IFN+5FU/CDDP+5FU)	22/35

For abbreviations see Table 1.

Table 3. Background of SD patients (n=57) according to the imaging response to the first course of chemotherapy in the study cohort and the validation cohort

	Study cohort (n=28)	validation cohort (n=29)	p value
Characteristics			
Age (years) *	67.0 (45-85)	75 (34-84)	0.506
Gender (M/F)	26/2	28/1	0.532
ECOG performance status (0/1)	25/3	25/4	0.723
Child-Pugh score (5/6)	11/17	17/12	0.144
Etiology (HBV/HCV/others)	4/21/3	9/15/5	0.182
Number of liver tumors *	6 (1-40)	5 (1-20)	0.435
Size of liver tumors (mm) *	50 (18-105)	80 (21-180)	0.089
HCC stage (II/III/IVa) †	1/7/20	0/10/19	0.487
Vp (0-2/3-4) §	15/13	16/13	0.903
Vv (0-1/2-3) ‡	25/3	25/4	0.723
Relative tumor size in the liver (<50%/≥50%)	20/8	22/7	0.704
Platelet count (/mm^3) *	10.3 (5.1-49.8)	14.8 (6.1-39.5)	0.143
AFP (ng/ml) *	905 (10-394000)	332 (2.9-869800)	0.893
DCP (mAU/ml) *	1702 (10-120070)	2868 (41-102590)	0.893
HAIC regimen (FP/5FU+IFN)	11/17	11/18	0.916
Response to the first course (CR/PR/SD/PD)	1/8/8/11	0/2/17/10	0.021

For abbreviations see Table 1.

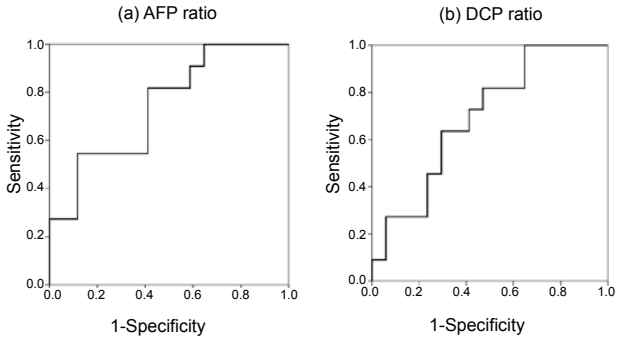

Fig. 3. Area under the receiver operating characteristics curve for (a) AFP ratio and (b) DCP ratio among SD patients to the first course of HAIC in study cohort.
The cut-off value associated with maximum accuracy, sensitivity, and negative and positive predictive values of the PD to the second course of treatment was computed.

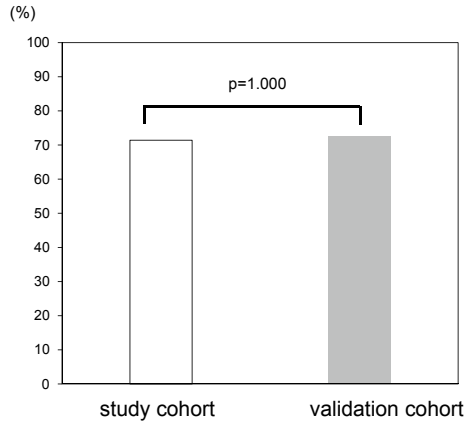

Fig. 4. The accuracy of the prediction of response to the second course of HAIC in study and validation cohort

PD. Among the SD patients to the first course HAIC and MST varied significantly ($p < 0.0001$) and were 32.1, 13.3 and 6.9 months in the PR, SD and PD groups, respectively.

Prediction of response to the second course of HAIC in the study and validation cohorts. First, the AFP and DCP ratios of patients who were considered SD to the first course of HAIC were analyzed by ROC for prediction of response to the second course of HAIC in the study cohort (Fig. 3). The sensitivities and specificities of the AFP and DCP ratios among these patients are shown in Figs. 3a and b. The area under the curve of AFP ratio was 0.743, with a sensitivity of 81.8% and specificity of 58.8%. The area under the curve of the DCP ratio was 0.695, with a sensitivity of 63.6% and specificity of 58.8%. The cut-off values of the AFP and DCP ratios were 1.3 and 1.0, respectively. That is, AFP ratio >1.3 and DCP ratio >1.0 were defined as a prediction of PD to the second course. We next evaluated the accuracy of the prediction score using an independent validation cohort consisting of 29 patients. The positive predictive value (PPV) and negative predictive value (NPV) for PD were 66.7% and 73.6% in the study cohort. On the other hand, the PPV and NPV for PD were 75.0% and 72.0% in the study cohort.

The accuracy of the prediction of response in this validation cohort (71.4%) showed no significant difference compared to that in the study cohort (72.4%) (p=1.0, Fig. 4).

Table 4. Results of multivariate analysis of determinants of survival in SD patients to the first course of HAIC

Parameters	Univariate analysis		Multivariate analysis	
	p value	Hazard ratio	95% CI	p value
All patients				
Age (<65/≥65 years)	0.894			
Gender (M/F)	0.454			
Etiology (HCV/others)	0.05			
AFP ratio >1.3 and DCP ratio >1.0/others	0.0025	2.012	1.36-3.907	0.035
Relative size of liver tumor (50%/≥50%)	0.005			
Vascular invasion (positive/negative)	0.903			
Number of liver tumors (single/multiple)	0.649			
Size of liver tumor (<50 mm/≥50 mm)	0.24			
TACE refractoriness (presence/absence)	0.228			
Regimen (IFN+5FU/CDDP+5FU)	0.176			

For abbreviations see Table 1.

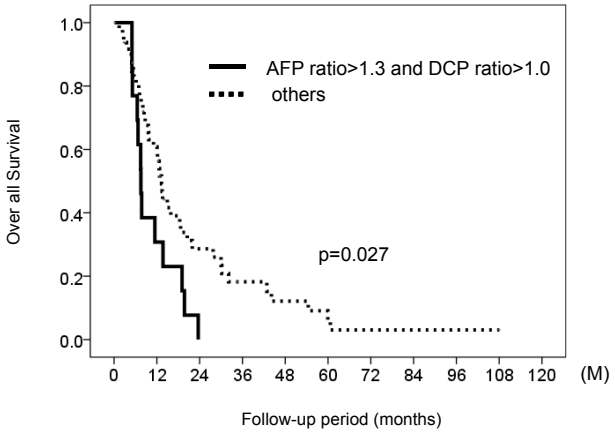

Fig. 5. Overall survival among SD patients to the first course of HAIC, according to tumor markers.
Solid line: patients with AFP ratio > 1.3 and DCP ratio > 1.
Dotted line: others.

Multivariate analysis of factors contributing to overall survival in SD patients by imaging response to first course. Univariate analysis was used to investigate the relationship between overall survival of patients who were considered SD to the first course of HAIC. Overall survival correlated significantly with etiology (p=0.05), AFP ratio > 1.3 and DCP ratio > 1.0 (p=0.0025), and tumor size relative to liver size (p=0.005). Inclusion of the above factors in multivariate analysis showed that an AFP ratio > 1.3 and DCP ratio > 1.0 was the only determinant of overall survival in patients considered SD to the first course of HAIC (p=0.035: hazard ratio 2.012, 95%CI 1.36-3.907) (Table 4).

Overall survival according to AFP and DCP ratios among SD patients to first course of HAIC. The MST of SD patients with AFP ratio of ≤ 1.3 and DCP ratio of ≤ 1, > 1.3 and ≤ 1, ≤ 1.3 and > 1, and > 1.3 and > 1 were 13.3, 12.1, 13.6 and 7.5 months, respectively (p=0.067). We also divided the patients into two groups: AFP ratio of > 1.3 and DCP ratio of > 1, and others. SD patients with AFP ratio of > 1.3 and DCP ratio of > 1 had a significantly poorer survival than others (MST 7.5 vs 13.3 months, p=0.027, Fig. 5). These results indicated that the cut-off values of AFP and DCP ratios could be used to predict the overall survival after the second course of HAIC in SD patients to the first course.

DISCUSSION

The response to HCC treatment is assessed according to RECIST or mRECIST with imaging modalities. In clinical practice, there is no biomarker that can be used to predict the response to HAIC and, accordingly, there are no criteria that can be used for continuation or discontinuation of HAIC. Patients who show a CR or PR response should continue HAIC while those who show PD should be switched to other treatments including sorafenib. However, in our hospital, the number of patients who showed a SD response was more than half of all patients. For this reason, we analyzed their data to identify HCC tumor markers that could predict overall survival. The results showed that patients with the combination of an AFP ratio of > 1.3 and a DCP ratio of > 1 had significantly poorer survival than others among SD patients to the first course of HAIC.

Previous studies analyzed the prognosis of HCC patients treated with HAIC using RECIST or mRECIST with imaging modalities, which is regarded as the gold standard for evaluation of therapeutic response. Sorafenib was introduced recently as a molecular targeting therapy for advanced HCC, though there are no guidelines for assessment of the response to such treatment. In the present study, we analyzed first the treatment response to the first course of HAIC by the combination of RECIST and tumor marker ratios. We also analyzed the data for whether the response to the first course of HAIC can be used to predict the prognosis of patients. The results showed that the

AFP and DCP ratio can be used to determine treatment selection; i.e., continuation or change from HAIC. We reported previously that the survival of patients with AFP and DCP ratios of > 1 was significantly poorer and that the response did not change to CR or PR during the course of treatment in SD patients[21]. However, the cut-off values of AFP and DCP were decided without statistics. That is, we decided the cut-off values of AFP and DCP by only the elevation after treatment. As a result, we decided the cut-off values of AFP and DCP by ROC analysis in the present study. Furthermore, in order to confirm that the cut-off values were appropriate, we studied the cut-off values of AFP and DCP by study cohort and validation cohort in the present study. Therefore, the present study determined the cut-off values of AFP and DCP ratios by statistics. Based on the imaging responses to the second course of HAIC, the median survival time was 6.9 months in the PD groups. Therefore, we used ROC analysis to determine the cut-off values that were associated with the highest accuracy, sensitivity, and negative and positive predictive values of PD to the second course of HAIC. The results showed that the best cut-off values were 1.3 for the AFP ratio and 1.0 for the DCP ratio in the study cohort. We next evaluated the accuracy of the prediction response using an independent validation cohort consisting of 29 patients. The accuracy of the prediction of response in this validation cohort (71.4%) was not significantly different compared to that in the study cohort (72.4%) (p=1.0).

Further analysis showed that patients with an AFP ratio of > 1.3 and DCP ratio of > 1 had significantly poorer survival than others (MST 7.5 vs 13.3 months, p=0.027), indicating that the tumor marker response can accurately predict refractoriness to HAIC.

Saeki et al [24] categorized their patients according to Child-Pugh, AFP and DCP responses after a half course of HAIC (2 weeks) and showed significantly different prognoses. However, they defined AFP- or DCP-positive-response as a reduction in serum AFP or DCP of more than 20% from baseline after half a course of HAIC. However, no reason was given for the selection of 20% reduction. It is possible that some patients showed a good overall survival despite a less than 20% reduction in serum AFP or DCP after a half course of HAIC. In our study, none of the patients who showed PR or CR in the second course had a AFP ratio of > 1.3 and DCP ratio of > 1 because the cut-off was determined by ROC analysis. Furthermore, the study of Saeki et al [24] included patients with extrahepatic metastasis and classified it as Child-Pugh B. It is reported that patients with extrahepatic metastases treated with HAIC show poor overall survival[10]. Furthermore, overall survival is also poor in Child-Pugh B patients treated with sorafenib[12]. Thus, the above study included many biases with the exception of tumor markers. In comparison, our study was limited to tumor markers, excluded patients treated with sorafenib before and after HAIC, extrahepatic metastasis and Child-Pugh B, and thus allowed us to study the prognosis of patients treated by HAIC.

Sorafenib is currently the standard treatment for advanced HCC patients. In two randomized studies, placebo-controlled clinical trials, sorafenib extended overall survival by 2.3-2.8 months and the response rate by 2.0-3.3%[2,16]. Although the effectiveness of HAIC for advanced HCC has been reported in some reports, large randomized trials are lacking. To our knowledge, there is no defined strategy for the standard of treatment with sorafenib and HAIC for advanced HCC patients. We think that it is important to pick up responders to HAIC as early as possible. In other words, HAIC must be switched to sorafenib as early as possible for PD patients of HAIC. Therefore, in this study, the patients were limited to Child-Pugh A patients who could be treated with sorafenib. The efficacy of sorafenib and HAIC on advanced HCC are currently being assessed in a few clinical trials in Japan. We are currently conducting an ongoing HICS study (pilot study of HAIC followed by sorafenib for advanced HCC, UMIN#000009094). Another Japanese clinical study based on the same purpose (HAIC followed by sorafenib) is ongoing: the SCOOP-II trial (Sequential hepatic arterial infusion chemotherapy with cisplatin followed by sorafenib versus sorafenib alone in advanced hepatocellular carcinoma, UMIN#000006147). These studies are designed to pick up refractoriness to HAIC using the combination of imaging response and tumor marker response after every course of therapy.

The present study has certain limitations. First, it was a retrospective cohort study that examined a small population. A prospective study of a larger patient population is needed to confirm the findings. Second, various chemotherapeutic regimens were used in the study population. However, previous studies showed no significant differences in response or survival among these regimens[21]. A validation study of HCC patients treated with a single regimen is required.

In conclusion, we used RECIST to evaluate the response of SD patients to the first course of HAIC and demonstrated that the combination of AFP ratio of > 1.3 and DCP ratio of > 1 could be used to predict the prognosis of patients with advanced HCC. The results emphasize the need to switch to alternative therapies in patients with a high tumor marker ratio despite SD response to HAIC.

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