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Pretreatment predictor of response, time to progression, and survival to intraarterial 5-fluorouracil/interferon combination therapy in patients with advanced hepatocellular carcinoma

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Background. Several studies have reported survival benefits of combination therapy with intraarterial 5-fluorouracil (5-FU) and subcutaneous interferon (IFN) α for advanced hepatocellular carcinoma (HCC) with portal vein tumor thrombosis (PVTT). We investigated the pretreatment predictive factors of early response, time to progression (TTP), and survival in response to intraarterial 5-FU/IFN combination therapy. ***Methods.*** Patients with nonresectable HCC and variable PVTT grades (without PVTT to PVTT in the trunk) received intraarterial 5-FU/IFN combination therapy (n = 55). ***Results.*** After two courses of the combination therapy, 1 (2%), 15 (27%), 16 (29%), 12 (22%), and 11 (20%) of 55 patients showed complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), or had dropped out (DO), respectively, when their early response to treatment was assessed. Univariate analysis identified only hepatitis C virus (HCV) antibody positivity as having significantly influenced the early response (P = 0.028) and TTP (P = 0.021). Multivariate analysis identified performance status (P = 0.003) and HCV antibody positivity (P = 0.007) as significant and independent determinants of survival. PVTT grade did not influence early response, TTP, or survival. The survival rate was significantly higher in patients who achieved CR or PR than in those that assessed as SD or PD, or DO (P < 0.0001, each). ***Conclusions.*** HCV antibody positivity may be a significant pretreatment predictor of early response, TTP, and survival of patients with advanced HCC treated with 5-FU/IFN. CR or PR as the early response to the combination therapy might indicate a more favorable prognosis in patients with advanced HCC. PVTT grade did not seem to influence the efficacy of combination therapy.

Key words: advanced hepatocellular carcinoma, 5-fluorouracil and interferon, early response, survival, HCV

Introduction

Hepatocellular carcinoma (HCC) is a life-threatening neoplasm and one of the most common neoplasms in Africa and Asia, including Japan. Deaths due to HCC are increasing worldwide.[1–3] Advances in biotechnology have resulted in new diagnostic techniques, such as ultrasonography, computed tomography (CT), magnetic resonance imaging, and angiography. Similarly, new treatment options have become available, such as surgical resection, radiofrequency ablation (RFA), percutaneous ethanol injection (PEI), and transcatheter arterial chemoembolization (TACE). As a result, the prognosis of HCC patients has gradually improved. Nevertheless, the survival rates of patients with advanced HCC and complications such as portal vein tumor thrombosis (PVTT) or distant metastasis remains extremely poor.[4–8]

Advances in implantable drug delivery systems have allowed repeated arterial infusions of anticancer agents. First, monotherapy with intraarterial 5-fluorouracil (5-FU) for unresectable HCC was reported.[9,10] However, such treatment resulted in a low response rate (13.0% and 22.0%). Next, several authors reported favorable results with low-dose cisplatin and 5-FU for advanced HCC with PVTT, with a response rate ranging from 33.0% to 48.0%.[11–13] Recently, several studies have reported survival benefits of combination therapy with intraarterial 5-FU and subcutaneous interferon (IFN) α for advanced HCC with PVTT, with a response rate ranging from 43.6% to 72.7%.[14–17] In these studies, only HCC patients with PVTT (in the main trunk or first branch) without distant metastases were treated. The

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pretreatment predictive factors of response, time to progression (TTP), and survival of HCC patients treated with the combination therapy remain unclear. At present, some patients with nonresectable HCC are treated with TACE. However, some patients are not suitable candidates for TACE because of PVTT or poor response to TACE. Because of the poor prognosis of patients with nonresectable HCC who are not treatable by TACE, effective treatment is needed. There is little information about assessment of patients with advanced HCC (e.g., nonresectable HCC with PVTT in the second branch or nonresectable HCC without PVTT but with poor response to TACE) treated with combination therapy of intraarterial 5-FU and IFN. In the present retrospective cohort study, we assessed the efficacy of intraarterial 5-FU with IFN for various types of nonresectable advanced HCC and investigated the pretreatment predictive factors of early response, TTP, and survival in response to the combination therapy.

Materials and methods

Patients

From June 2003 to December 2006, 265 consecutive patients with unresectable HCC were admitted to our hospital. Of the 265 patients with advanced HCC, 94 were treated with TACE, 34 patients received systemic chemotherapy, and 13 patients received best supportive care. The remaining 124 patients were selected as suitable candidates for intraarterial 5-FU and IFN combination therapy. Forty-one patients refused the therapy. Thus, 83 patients with advanced HCC were treated with intraarterial 5-FU and IFN. Of these 83 patients, 24 with distant metastases and four with hepatic venous invasion were excluded from this study, so we assessed 55 patients without distant metastases or hepatic venous invasion in this retrospective cohort study. Of the 55 patients, 30 had been treated with TACE before enrollment. Table 1 lists the baseline characteristics of the 55 patients. PVTT grade, based on the location of the tumor thrombus, was determined according to the criteria of the Liver Cancer Study Group of Japan (LCSGJ).[18] PVTT grading was as follows: Vp 0, no PVTT; Vp 1, tumor thrombus in a third or more of the peripheral branches of the portal vein; Vp 2, tumor thrombus in a second branch of the portal vein; Vp 3, tumor thrombus in the first branch of the portal vein; and Vp 4, tumor thrombus in the trunk of the portal vein. Tumor staging was defined based on the TNM staging system of the LCSGJ:[18] stage I (fulfilling three intrahepatic conditions: solitary, <2 cm, no vessel invasion), stage II (fulfilling two of the three intrahepatic conditions), stage III (fulfilling one of the three intrahepatic conditions), stage IVA (fulfilling none of the three intrahepatic conditions with no distant metastases or any intrahepatic conditions with lymph node metastases), and stage IVB (any intrahepatic conditions with distant metastases).

Eligibility

This was a retrospective cohort study to investigate pretreatment predictive factors of TTP, survival, and

Table 1. Clinical profile of the 55 HCC patients

Age (years)[a]	67 (38–79)
Sex (M/F)	44/11
Etiology: HBV/HCV/other	15/36/4
Total bilirubin (mg/dl)	1.1 (0.4–6.4)
Platelet count ($\times 10^4$ mg/dl)	13.0 (5.1–54.5)
Albumin (mg/dl)	3.5 (2.4–4.8)
Child Pugh stage (A/B/C)	43/10/2
PS (0/1)	45/10
Intrahepatic tumor volume (≤50%/>50%)	38/17
Tumor stage (III/IVA)	20/35
Vp[a] (0/2/3/4)	20/6/15/14
AFP (ng/ml)	934 (14.3–525 900)
AFP-L3 (%)	47.3 (<0.5–87.6)
DCP (mAU/ml)	3729 (10–722 140)
Previous treatment (performed/not performed)	30/25

Data are expressed as median with range values in parentheses, or number of patients HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HBV, hepatitis B virus; PS, Eastern Cooperative Oncology Group performance status; AFP, α-fetoprotein; AFP-L3, lens culinaris agglutinin-reactive fraction of α-fetoprotein; DCP, des-γ-carboxy prothrombin; PVTT, portal vein tumor thrombosis

[a] PVTT grade: Vp 0, no PVTT; Vp 1, tumor thrombus in a third or more of the peripheral branches of the portal vein; Vp 2, tumor thrombus in a second branch of the portal vein; Vp 3, tumor thrombus in the first branch of the portal vein; Vp 4, tumor thrombus in the trunk of the portal vein

response to intraarterial 5-FU/IFN combination therapy. Eligibility criteria were as follows: age, 18–80 years; leukocyte count, >2000/μl; neutrophil count, >1200/μl; hemoglobin, >8 g/dl; platelet count, >50 000/μl; unresectable or not suitable for local ablation therapy, including RFA or PEI; with PVTT or TACE was ineffective; without hepatic venous invasion; without distant metastases; and Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–1.[19] There was no eligibility criterion regarding hepatic reserve function, including serum total bilirubin levels. All patients gave written informed consent to this study, which was approved by the Institutional Review Board of Hiroshima University.

Treatment protocol

Patients received repeated arterial infusions of anticancer agents via the injection port. One course of chemotherapy lasted 4 weeks. 5-FU (500 mg body weight/day, Kyowa Hakko, Tokyo, Japan) was administered over 5 h with a mechanical infusion pump on days 1 to 5 of the first and second weeks (5 g in one course). Recombinant IFN α-2b (Intron A, Schering-Plough Pharmaceuticals, Osaka, Japan); 3×10^6 U (3 MU), or natural IFN α (OIF, Otsuka Pharmaceuticals, Tokyo, Japan); 5×10^6 U (5 MU) was administered intramuscularly on days 1, 3, and 5 of each week (total dose, 36 and 60 MU, respectively). In principle, treatment was repeated several times unless PS changed to 3 or 4 during the treatment. A 2- to 4-week rest period of no treatment was allowed after each treatment course. As for the two types of IFN, we previously reported similar effects of recombinant IFN α-2b and natural IFN α when combined with intraarterial 5-FU for the treatment of advanced HCC.[20]

Implantation of the arterial catheter

A catheter was inserted through the right femoral artery by the Seldinger method. After localization of the HCC, a 3-French heparin-coated catheter was inserted and its tip advanced to the common hepatic artery or proper hepatic artery. The other end of the catheter was connected to the injection port, which was implanted in a subcutaneous pocket created in the right lower abdominal quadrant. The gastroduodenal artery and right gastric artery were occluded with steel coils to prevent gastroduodenal injury by the chemotherapeutic agents.

Evaluation

The early response to the combination therapy was assessed with contrast-enhanced CT after two courses of the combination therapy. The response was defined according to the criteria of the Response Evaluation Criteria in Solid Tumors (RECIST).[21] A complete response (CR) was defined as the complete disappearance of all target lesions. A partial response (PR) was defined as a decrease of at least 30% in the sum of the longest diameter of the target lesions with the baseline sum of the longest diameter of the target lesions as the reference. Progressive disease (PD) was defined as an increase of at least 20% in the sum of the longest diameter of target lesions. Stable disease (SD) was defined as meeting neither the PR nor the PD criteria. The duration of the response was measured from the date of the start of treatment to the date of documented progression. Adverse reactions were assessed with the National Cancer Institute Common Toxicity Criteria (NCI-CTC; version 3.0)[22] every week during the treatment.

Additional therapy

After two courses of the combination therapy, we assessed the response to therapy in all patients. According to the response, we provided various additional therapies such as RFA, TACE, or radiotherapy (RT) to patients treated with the combination therapy. These additional therapies were considered for patients with PS of 0–1 and a Child-Pugh stage of A or B. Patients assessed with PR continued to receive the combination therapy repeatedly. Then, when downstaging of advanced HCC was achieved (single tumor ≤50 mm in diameter or 1–3 tumors ≤30 mm in diameter) by the repeated combination therapy, RFA was considered. For patients assessed with SD or PD, in addition to the combination therapy, TACE with cisplatin–lipiodol suspension was performed. The catheter tip was advanced superselectively into the feeding artery so that sufficient anticancer agent was delivered. Among the patients assessed with SD or PD, RT was performed for PVTT if present. For patients assessed with CR, the clinical course was observed without adjuvant chemotherapy or additional therapy.

Statistical analysis

Statistical analysis was performed on 1 April 2007. Differences between groups were examined for statistical significance using the Mann-Whitney *U* test, logistic regression test, or χ-squared test as appropriate. Cumulative survival rate and TTP were calculated from the initial date of the combination therapy and assessed by the Kaplan-Meier life-table method, and differences were evaluated by the log rank test. Univariate and multivariate analyses of predictors for early response to the combination therapy were assessed by logistic

regression test. Univariate analysis of predictors of TTP and survival of patients with HCC who received the combination therapy was assessed by the Kaplan-Meier life-table method, and differences were evaluated by the log rank test. Multivariate analysis of predictors of TTP and survival was assessed by Cox proportional hazard model. Statistical significance was defined as a *P* value of less than 0.05. All analyses described above were performed with SPSS software (version 11, SPSS, Chicago, IL, USA). In this study, we investigated pretreatment predictive factors of early response, TTP, and survival in response to the combination therapy.

Results

Response to the combination therapy

The early response of the 55 patients was assessed after two courses of 5-FU/IFN combination therapy. As a result, 1 (2%), 15 (27%), 16 (29%), 12 (22%), and 11 (20%) patients showed CR, PR, SD, PD, or dropped out (DO), respectively. The reasons for DO were confusion (one patient), refusal after initiation of therapy (one patient), exanthema (one patient), infection around the catheter (four patients), and stenosis of the hepatic artery (four patients). We investigated the pretreatment determinants of the early response to the combination therapy. Univariate analysis identified positivity to HCV antibody as the only factor with significant influence on the early response (P = 0.028, Table 2, Fig. 1). Of the HCV antibody-positive patients, 38.9% (14/36) showed an early response of CR or PR, but only 10.5% (2/19) of other patients. When we compared the early response between patients with Vp 0–2 and those with Vp 3/4, 30.8% (8/26) of patients with Vp 0–2 and 27.6% (8/29) of those with Vp 3/4 achieved CR or PR, but the difference was not significant.

Time to progression

The median TTP in all 55 patients was 7.5 months [95% confidence interval (CI), 5.1–9.9 months], and the cumulative TTP rates at 6, 12, 18, and 24 months were 60%, 41%, 30%, and 24%, respectively. We investigated the pretreatment determinants of TTP after initiation of the combination therapy. Univariate analysis identified positivity for HCV antibody as the only factor with significant influence on TTP (P = 0.021, Table 3, Fig. 2). The median TTP in patients with Vp 0–2 and those with Vp 3/4 was 5.2 and 7.5 months, respectively. There was no significant difference in TTP between these two groups.

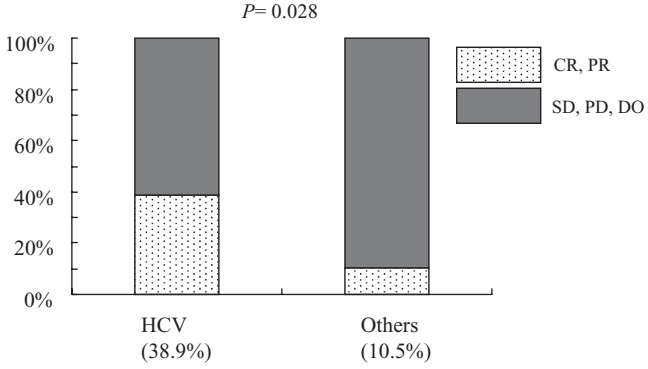

Fig. 1. Comparison of the early response rate between the hepatitis C virus (HCV)-positive group and others. The rate was significantly higher in the HCV-positive group (logistic regression test: P = 0.028). *CR*, complete response; *PR*, partial response; *SD*, stable disease; *PD*, progressive disease; *DO*, dropped out

Table 2. Univariate analysis of predictors for early response to 5-FU/IFN combination therapy

Variable	Odds Ratio	95% CI	*P* value
Age (≤65 vs. >65 years)	0.463	0.136–1.572	0.217
Sex (M vs. F)	2.327	0.445–12.168	0.317
HCV antibody (positive vs. negative)	6.071	1.216–30.314	0.028
Total bilirubin (≤1.5 vs. >1.5 mg/dl)	0.931	0.240–3.614	0.918
Platelet count (≤150000 vs. >150000 mg/dl)	0.978	0.278–3.437	0.972
Albumin (≤3.5 vs. >3.5 mg/dl)	1.390	0.441–4.376	0.574
Child Pugh stage (A vs. B, C)	2.172	0.413–11.420	0.360
PS (0 vs. 1)	4.965	0.576–42.810	0.145
Intrahepatic tumor volume (≤50% vs. >50%)	1.690	0.458–6.237	0.431
Tumor stage (III vs. IVA)	1.709	0.533–5.478	0.367
Vp (0–2 vs. 3, 4)	0.988	0.314–3.106	0.983
AFP (≤10000 vs. >10000 ng/ml)	0.978	0.278–3.437	0.972
AFP-L3 (≤50 vs. >50%)	0.776	0.229–2.625	0.683
DCP (≤10000 vs. >10000 mAU/ml)	0.606	0.186–1.974	0.406
Treatment (performed vs. not performed)	1.833	0.563–5.970	0.314

5-FU, 5-fluorouracil; IFN, interferon; CI, confidence interval

Table 3. Univariate analysis of predictors of time to progression

Variable	Hazard Ratio	95% CI	*P* value
Age (>65 vs. ≤65 years)	1.348	0.177–10.263	0.773
Sex (M vs. F)	1.788	0.403–7.935	0.445
HCV antibody (positive vs. negative)	2.775	1.169–6.590	0.021
Total bilirubin (≤1.5 vs. >1.5 mg/dl)	0.618	0.216–1.768	0.370
Platelet count (≤150000 vs. >150000 mg/dl)	0.739	0.307–1.777	0.500
Albumin (≤3.5 vs. >3.5 mg/dl)	0.705	0.300–1.655	0.421
Child Pugh stage (A vs. B, C)	2.381	0.314–18.045	0.401
PS (0 vs. 1)	1.348	0.177–10.263	0.773
Intrahepatic tumor volume (≤50% vs. >50%)	0.710	0.298–1.691	0.440
Tumor stage (III vs. IVA)	1.107	0.469–2.616	0.816
Vp (0–2 vs. 3, 4)	1.195	0.512–2.790	0.680
AFP (≤10000 vs. >10000 ng/ml)	1.325	0.484–3.626	0.584
AFP-L3 (≤50% vs. >50%)	2.371	0.696–8.076	0.167
DCP (≤10000 vs. >10000 mAU/ml)	1.145	0.486–2.701	0.756
Treatment (performed vs. not performed)	0.671	0.282–1.595	0.367

Table 4. Univariate analysis of predictors of survival of patients with HCC who received 5-FU/IFN combination therapy

Variable	Hazard Ratio	95% CI	*P* value
Age (≤65 vs. >65 years)	0.763	0.402–1.449	0.408
Sex (M vs. F)	1.208	0.527–2.769	0.655
HCV antibody (positive vs. negative)	2.283	1.165–4.474	0.016
Total bilirubin (≤1.5 vs. >1.5 mg/dl)	0.628	0.308–1.278	0.199
Platelet count (≤150000 vs. >150000 mg/dl)	0.690	0.355–1.340	0.273
Albumin (≤3.5 vs. >3.5 mg/dl)	0.760	0.398–1.451	0.406
Child Pugh stage (A vs. B, C)	0.527	0.228–1.216	0.133
PS (0 vs. 1)	3.413	1.391–8.375	0.007
Intrahepatic tumor volume (≤50% vs. >50%)	0.753	0.383–1.481	0.411
Tumor stage (III vs. IVA)	0.670	0.342–1.313	0.243
Vp (0–2 vs. 3, 4)	0.745	0.389–1.427	0.374
AFP (≤10000 vs. >10000 ng/ml)	0.947	0.445–2.017	0.888
AFP-L3 (≤50% vs. >50%)	0.898	0.430–1.871	0.773
DCP (≤10000 vs. >10000 mAU/ml)	0.753	0.394–1.438	0.390
Treatment (performed vs. not performed)	0.627	0.319–1.230	0.175
Additional therapy (performed vs. not performed)	1.129	0.583–2.188	0.719

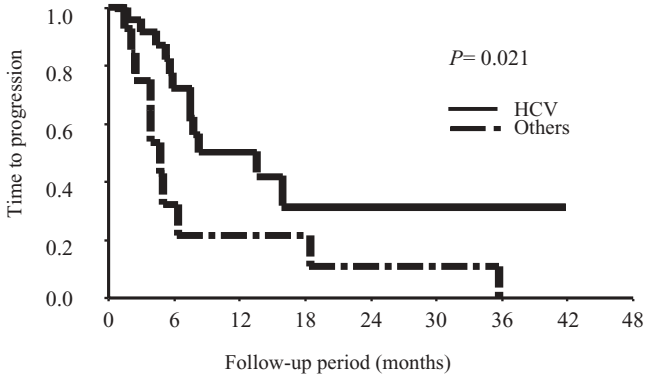

Fig. 2. Comparison of the time to progression between the HCV antibody-positive group and others. The rate was significantly higher in the HCV-positive group (log-rank test: $P = 0.021$)

Survival

The median survival in the whole group was 9.0 months (95% CI, 7.0–11.0 months), and the cumulative survival rates at 6, 12, 18, and 24 months were 67%, 39%, 22%, and 17%, respectively. We investigated the pretreatment determinants of survival after initiation of the 5-FU/IFN combination therapy. Univariate analysis identified PS = 0 ($P = 0.007$) and positivity for HCV antibody ($P = 0.016$) (Table 4, Fig. 3) as factors that significantly influenced survival. Since it was possible that the variables were mutually correlated, we performed a multivariate analysis and identified PS = 0 ($P = 0.003$) and positivity for HCV antibody ($P = 0.007$) as significant and independent determinants of survival (Table 5). The median survival time of patients with Vp 0–2 and of those with Vp 3/4 was 13.0 and 8.0 months, respectively. There was no significant difference in survival between these two groups.

Table 5. Multivariate analysis of predictors of survival of patients with HCC who received 5-FU/IFN combination therapy

Variable	Hazard Ratio	95% CI	*P* value
PS (0 vs. 1)	4.056	1.601–10.276	0.003
HCV antibody (positive vs. negative)	2.555	1.286–5.079	0.007

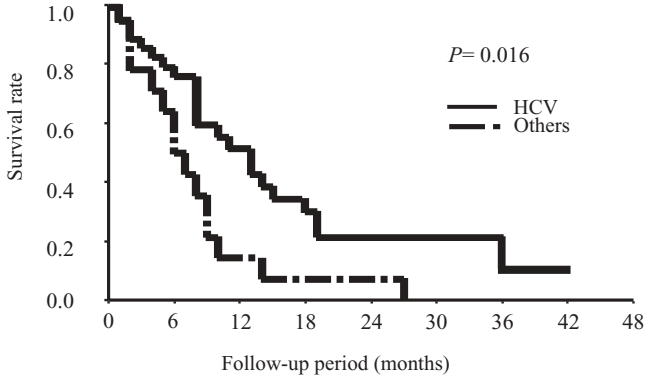

Fig. 3. Comparison of the cumulative survival rates between the HCV antibody-positive group and others. The rate was significantly higher in the HCV-positive group (log-rank test: $P = 0.016$)

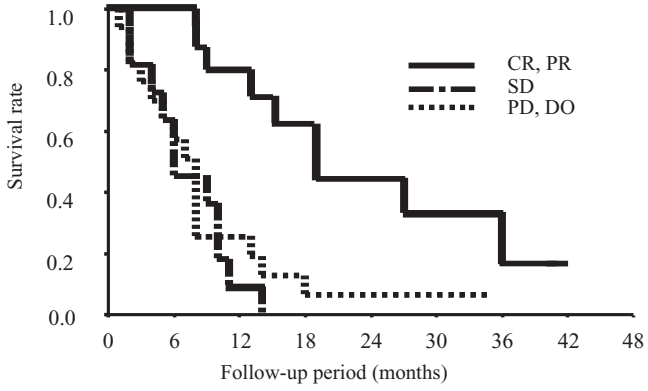

Fig. 4. Comparison of the cumulative survival rates among patients with CR/PR, SD, or PD/DO. The rate was significantly higher in patients who achieved CR/PR than those who showed SD (log-rank test: $P < 0.0001$) or PD/DO (log-rank test: $P < 0.0001$)

The cumulative survival rates of patients who achieved CR/PR at 6 and 12 months were 100% and 80%, respectively. On the other hand, the cumulative survival rates of patients who showed SD or PD/DO at 6 and 12 months were 64% and 9%, and 57% and 25%, respectively. The survival rate was significantly higher in patients who achieved CR/PR than in the other patients ($P < 0.0001$, Fig. 4).

Adverse reactions and complications

The most common adverse reactions were fever, nausea, and loss of appetite, but these were mostly NCI-CTC grade 1 or 2. Among patients with various NCI-CTC grade 3 adverse reactions, leukopenia was observed in seven (12.7%) patients, and thrombocytopenia in five (9.1%). None required administration of granulocyte colony-stimulating factor or blood transfusion. Five (9.1%) patients showed infection associated with the indwelling catheter. In this study, the number of patients with serum total bilirubin levels >3 mg/dl was three (3.7 mg/dl, 4.7 mg/dl, and 6.4 mg/dl). Other hepatic reserve functions and PS of the three patients was good (albumin, 4.1, 3.3, and 3.9 g/dl; prothrombin time, 60, 91, and 83%; PS, 0 in all cases). These three patients did not show any severe adverse reaction.

Additional therapy

Among the 55 patients, one (2%), ten (20%), and four (8%) patients were treated with RFA, TACE, and RT, respectively, as additional therapies for PVTT. The median survival time in patients receiving and in those not receiving additional therapies was the same at 9.0 months. There was no significant difference in survival between the two groups (Table 4).

Causes of death

Seventeen patients were still alive at the end of the observation period, and 38 patients had died. All 38 patients died of intrahepatic HCC-related disease.

Discussion

The median survival time of HCC patients with PVTT in the portal trunk is reported to be about 90 days with supportive care.[23] Recent studies have reported the efficacy and survival benefits of combination therapy with intraarterial 5-FU and IFN in a large number of patients with advanced HCC.[16,17] In particular, Ota et al.[16] assessed 55 patients with advanced HCC, multiple lesions, and Vp 3 or 4, and Obi et al.[17] assessed 116 patients with advanced HCC with Vp 3 or 4. These two studies assessed only patients with advanced HCC/

Vp 3 or 4. Thus, the favorable survival results they reported suggest that combination therapy with intraarterial 5-FU and IFN is potentially useful also for HCC with Vp 0–2. Although TACE is the standard treatment option for nonresectable HCC, many patients with nonresectable HCC either show a poor response to TACE or are not suitable candidates for TACE. The prognosis of patients with nonresectable HCC who are not treated with TACE is poor, so an effective treatment for such patients is needed. In this study, we treated a heterogeneous group of patients with advanced HCC (i.e., patients with nonresectable HCC and Vp 3 or 4, those with nonresectable HCC and Vp 2 who were not suitable candidates for TACE, and those with nonresectable HCC without PVTT who showed a poor response to TACE). There was no significant difference in early response, TTP, or survival between HCC patients with Vp 0–2 and those with Vp 3/4. Hence, with regard to the response to 5-FU/IFN combination therapy, PVTT grade does not seem to be an important factor.

The objective response rates (CR and PR patients/all patients) reported in the above two studies[16,17] were 43.6% (24/55 patients) and 52.6% (61/116 patients). In our study, the objective response rate, based on the early response, was 29% (16/55 patients). One reason for the discrepancy may be that the response was evaluated differently in the three studies. Ota et al.[16] and Obi et al.[17] used ECOG criteria, but we used RECIST criteria. Second, the inclusion criteria were different. Ota et al.[16] included patients with aspartate aminotransferase (AST) or alanine aminotransferase (ALT) of less than 100 IU/l and patients with total bilirubin of less than 1.4 mg/dl, whereas Obi et al.[17] mentioned no inclusion criteria related to AST or ALT, though they used a total bilirubin level of 3.0 mg/dl as a cutoff. In our study, we used no inclusion criteria related to AST or ALT. Third, the assessment day in our protocol may be earlier than that in the other two studies. In our study, the early response cumulative survival rate was significantly higher in patients who achieved CR/PR than in those with SD or PD/DO ($P < 0.0001$, each). The early response is an important posttreatment predictor of survival of patients with advanced HCC on 5-FU/IFN combination therapy. An early response of CR or PR promises a good prognosis.

The cumulative survival rates reported by Ota et al.[16] and Obi et al.[17] at 12 and 24 months were 48.9% and 28.8%, and 34% and 18%, respectively. In our study, the cumulative survival rates at 12 and 24 months were 39% and 17%, respectively. We obtained survival rates almost identical to those reported by Obi et al.,[17] but Ota et al.[16] obtained better survival rates. This discrepancy may be due to the differences in the inclusion criteria, as described above.

Our results indicated that HCV antibody positivity was a significant pretreatment predictor of early response, TTP, and survival of patients with advanced HCC treated with 5-FU/IFN. On the other hand, PVTT grade and total bilirubin levels were not significant predictors. Though we established no eligibility criterion regarding serum total bilirubin levels, the median total bilirubin level was 1.1 mg/dl (range, 0.4–6.4). Therefore, total bilirubin levels may not be statistically significant predictors in this study. In this study, three patients had serum total bilirubin levels >3 mg/dl. These patient achieved PR, SD, and PD. Though the three patients with high bilirubinemia (≥3 mg/dl) were safely treated in this study, we think that 5-FU/IFN combination therapy should be used with caution in patients with advanced HCC with high bilirubinemia. In general, the prognosis of HCC patients with Vp 3 or 4 is poorer than those with Vp 0–2. In this study, we treated a heterogeneous group of patients with advanced HCC as described above. Therefore, HCC with Vp 0–2 cases were advanced HCC cases in this study. All 55 patients were thought to have a poor prognosis at the time of enrollment in this study. Achievement of a good early response is important for good survival. A study with larger sample size may show the importance of PVTT grade and total bilirubin level.

Obi et al.[17] also reported that positivity to HCV antibody might be a predictor of CR in patients with advanced HCC treated with 5-FU/IFN. Why is HCV antibody positivity a predictor of the efficacy of combination therapy? One reason may be the underlying mechanisms associated with hepatocarcinogenesis. In our study, 36 patients were infected with HCV, 15 with hepatitis B virus (HBV), and four with non-B non-C hepatitis. Although the probability of hepatocarcinogenesis is high for both HBV and HCV infections, some differences have been noted with regard to their relationship with HCC.[24,25] HCV is an RNA virus, and viral genes are not integrated into the host genome. On the other hand, HBV is a DNA virus with reverse-transcriptase activity. HBV-mediated hepatocarcinogenesis is reported to be associated with the integration of viral DNA into the host genome.[26–28] The integration of the HBV genome into the host genome may diminish the effect of intraarterial 5-FU/IFN combination therapy. A second reason may be the differentiation of the cytokine pattern in HBV and HCV hepatitis.[29] Falasca et al.[29] reported the presence of high levels of Th1 cytokines, particularly during the course of chronic hepatitis B. They also reported that interleukin (IL)-18 and IL-6 levels might play important roles in both inflammation and hepatic injury, particularly during the course of hepatitis C infection. IFN may play a different role in patients with advanced HCC associated with HBV or HCV. In this study, the efficacy of the

combination therapy for advanced HCC patients with non-B non-C hepatitis was not clear because of the small number ($n = 4$) of those patients.

The DO proportion was high in this study (20%). Two major reasons for DO were infection around the catheter and stenosis of the hepatic artery. In this study, we established no eligibility criterion regarding the hepatic reserve function, including serum total bilirubin. Poor hepatic reserve function and high bilirubinemia might affect infection around the catheter. On the other hand, previous treatment with TACE might injury the hepatic artery and affect hepatic artery stenosis.

In conclusion, HCV antibody positivity might be a pretreatment predictive factor for early response, TTP, and survival of patients with advanced HCC treated with intraarterial 5-FU/IFN combination therapy. Early response to the combination therapy might be a significant posttreatment predictor of survival. Thus, patients who do not achieve CR or PR during the early phase of combination therapy should be switched to another treatment modality. Our results also showed that PVTT grade does not seem to be an important factor in the prognosis of patients with advanced HCC treated with 5-FU/IFN combination therapy. Further studies with long-term follow-up and a larger sample size are needed.

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