

Therapeutic Efficacy of Combination Therapy With Intra-Arterial 5-Fluorouracil and Systemic Pegylated Interferon α -2b for Advanced Hepatocellular Carcinoma With Portal Venous Invasion

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BACKGROUND: The prognosis of advanced hepatocellular carcinoma (HCC) remains poor, particularly among patients with portal vein tumor thrombosis (PVTT). This study evaluated the efficacy of combined 5-fluorouracil and pegylated interferon (PEG-IFN) α -2b in patients with advanced HCC. **METHODS:** Subjects comprised 59 HCC patients with PVTT treated using subcutaneous administration of PEG-IFN α -2b (50-100 μ g on day 1 of each week for 4 weeks) and intra-arterial infusion of 5-fluorouracil (250 mg/d for 5 hours on days 1-5 of each week for 4 weeks). One treatment cycle lasted 4 weeks. The current therapy was discontinued in patients with progressive disease (PD). For responses other than PD, treatment was repeated for ≥ 1 cycle. The primary efficacy endpoint was the objective early response rate. Secondary efficacy endpoints were progression-free survival (PFS) and overall survival. **RESULTS:** Objective early response rate was 73.0%. Cumulative PFS rates were 67.4% at 6 months, 30.2% at 12 months, 25.9% at 18 months, and 20.7% at 24 months. Median PFS was 9.7 months. Cumulative survival rates were 82.4% at 6 months, 73.6% at 12 months, 52.8% at 24 months, and 44.0% at 36 months. Median survival time was 29.9 months. All adverse reactions were controllable by temporary suspension of treatment. Serious complications and treatment-related deaths were not observed. **CONCLUSIONS:** Although a prospective randomized controlled trial using a larger population of patients with advanced HCC is needed to evaluate combination therapy with 5-fluorouracil and PEG-IFN α -2b, this new combination therapy may be useful for patients with advanced HCC. *Cancer* 2012;118:3302-10. © 2011 American Cancer Society.

KEYWORDS: 5-fluorouracil, hepatic arterial infusion chemotherapy, hepatocellular carcinoma, pegylated interferon α -2b, portal venous invasion.

INTRODUCTION

The prognosis of advanced hepatocellular carcinoma (HCC) remains poor, particularly among patients with portal vein tumor thrombosis (PVTT). The majority of patients with PVTT survive no longer than 6 months after initial diagnosis.¹⁻³ PVTT causes widespread intrahepatic and extrahepatic dissemination by spreading out of tumor cells through the portal tract. Furthermore, PVTT, particularly in the first branch (Vp3) or main trunk (Vp4), can cause portal hypertension resulting in variceal rupture, uncontrollable ascites, ischemic liver failure, and worsening of performance status (PS).⁴ These pathological states lead to simultaneous decreases in quality of life; hence, any treatment for HCC is contraindicated under such conditions, especially for those patients with HCC and PVTT in Vp3 or Vp4.

Two recent phase 3 clinical trials have shown that sorafenib, an orally available multikinase inhibitor, improves median overall survival in patients with advanced HCC.^{5,6} However, patients with HCC and PVTT usually have very short survival and grave prognosis even when treated with sorafenib.⁷

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Conversely, recent advances in implantable drug delivery systems have enabled repeated arterial infusion of chemotherapeutic agents.^{8,9} Compared with systemic chemotherapy, hepatic arterial infusion chemotherapy (HAIC) has the benefits of increasing the local concentration of drugs and reducing systemic side effects. This approach has thus been used in palliative treatment for patients with HCC complicated by PVTT in Japan. Several authors in this field have reported the efficacy of HAIC, with favorable results achieved using a regimen consisting of 5-fluorouracil and interferon (IFN) α .^{10,11}

Pegylation of therapeutic proteins is a well-established method for delaying clearance and reducing protein immunogenicity, and pegylated proteins are safe and effective in humans.^{12,13} Since 2005, pegylated (PEG) IFN α 2b has been available as a therapy for hepatitis C virus (HCV)-related chronic hepatitis (CH). In contrast to IFN α , PEG-IFN α -2b is administered once weekly, allowing the maintenance of higher plasma concentrations.¹⁴ The therapeutic effects of 5-fluorouracil combined with PEG-IFN α -2b may thus exceed those of 5-fluorouracil combined with IFN α . We have already administered 5-fluorouracil and PEG-IFN α -2b to patients displaying advanced HCC with PVTT and reported favorable preliminary results.^{15,16} The aim of this study was to elucidate the efficacy of this therapy by analyzing the clinical results in 59 HCC patients with PVTT treated in this manner.

MATERIALS AND METHODS

Eligibility Criteria

Eligibility criteria for treatment were as follows: 1) PVTT grade Vp2-Vp4; 2) no indications for radiotherapy, surgical resection, or nonsurgical interventions such as radiofrequency ablation (RFA), microwave coagulation therapy (MCT), percutaneous ethanol injection (PEI), or transhepatic arterial chemoembolization; 3) age >20 years; 4) Eastern Cooperative Oncology Group PS⁴ level 0-2; 5) no uncontrollable ascites or pleural effusion; 6) platelet count $>0.5 \times 10^5/\mu\text{L}$, leukocyte count $>2000/\mu\text{L}$, total bilirubin $<3 \text{ mg/dL}$, and serum creatinine $<1.5 \text{ mg/dL}$; and 7) CH or compensated cirrhosis with a Child-Pugh class of A or B.

The presence of PVTT was confirmed in all cases using the following criteria: 1) a low-attenuation intraluminal mass that expanded the portal vein or portal branch on ultrasonography (US) or enhanced computed tomography (CT) scan; 2) the thread-and-streaks signs, which

reflect intraportal tumor growth or arteriportal shunts on hepatic angiography; or 3) filling defects in the portal vein or in the portal branch on an indirect portogram obtained from a venous phase angiogram of the superior mesenteric artery. Portal venous thrombosis was excluded from the criteria of PVTT. PVTT grade was determined according to the criteria of the Liver Cancer Study Group of Japan.¹⁷ PVTT grading was as follows: Vp0, no PVTT; Vp1, tumor thrombus in a third or more of peripheral branches of the portal vein; Vp2, tumor thrombus in a second branch of the portal vein; Vp3, tumor thrombus in the first branch of the portal vein; and Vp4, tumor thrombus in the trunk of the portal vein.

Underlying liver conditions such as CH or cirrhosis were confirmed by laboratory, pathological, and radiological examinations. Liver function in CH was classified as Child-Pugh class A, because chronic hepatitis is a known precirrhotic condition.

Patients

Between September 2006 and November 2010, a total of 143 consecutive HCC patients with PVTT were admitted to the Hospital of Iwate Medical University. Diagnosis of HCC was assessed by CT, magnetic resonance imaging (MRI), and abdominal US. Furthermore, CT was obtained during arterial portography and computed tomographic hepatic arteriography. Further assessment of HCC was conducted by measuring levels of α -fetoprotein (AFP) and des- γ -carboxy prothrombin (DCP). On the basis of these examinations, all patients were diagnosed with advanced HCC and were thus considered unsuitable for surgical resection or nonsurgical interventions such as RFA, MCT, PEI, or transhepatic arterial chemoembolization. Among these 143 patients, 89 met the eligibility criteria described above. Of those 89 HCC patients with PVTT, 59 patients agreed to be treated with HAIC using 5-fluorouracil and PEG-IFN α -2b.

Informed consent was obtained from all patients. All study protocols were approved by the ethics committee of Iwate Medical University in accordance with the 1975 Declaration of Helsinki.

Technique of Catheter Placement

The catheter was inserted through the femoral artery using the Seldinger method. After detection of HCC, an indwelling 4- or 5-Fr catheter (Anthon P-U Catheter; Toray Medical, Tokyo, Japan) was placed. The tip of the catheter was placed in the common or proper hepatic artery. The other end of the catheter was connected to the

injection port, and the device was implanted in a subcutaneous pocket. The gastroduodenal and right gastric arteries were occluded using steel coils (interlocking detachable coil, Diamond coil; Boston Scientific, Natick, Mass) to prevent gastroduodenal injury from anticancer agents. To prevent occlusion of the catheter, 5 mL (5000 U) of heparin solution was infused biweekly via the injection port.

Treatment Regimen

After insertion of the drug delivery system, patients received arterial infusion of chemotherapeutic agents via the injection port. Patients were treated with subcutaneous administration of PEG-IFN α -2b (PegIntron; Schering-Plough, Osaka, Japan) and intra-arterial infusion of 5-fluorouracil (Kyowa Hakko, Tokyo, Japan). One treatment cycle lasted 4 weeks. PEG-IFN α -2b dose was weight-adjusted (50 μ g for body weight $\leq$ 50 kg, 100 μ g for body weight $>$ 50 kg) and administered subcutaneously on day 1 of every week. Administration of 5-fluorouracil (250 mg/d) into the hepatic artery for 5 hours via mechanical infusion pump was performed on days 1 to 5 of each week.

Evaluation of Therapeutic Effects

The primary efficacy endpoint of the current study was the objective response rate. Secondary efficacy endpoints were progression-free survival (PFS) and overall survival (OS). In addition, univariate and multivariate analyses were performed to determine predictors of survival.

CT or MRI was performed before and after treatment. CT or MRI images were reviewed by 2 radiologist who did not participate in the procedures. In addition to serum biochemical markers, tumor markers such as AFP or DCP were also measured before and after treatment. The primary efficacy endpoint was evaluated by assessments performed $\geq$ 4 weeks after initiating treatment. Therapeutic effects were also evaluated by CT or MRI inspection every 2 months to 3 months. Tumors were bidimensionally measured by dynamic CT or dynamic MRI. Response to treatment was evaluated according to the Response Evaluation Criteria in Solid Tumors.¹⁸ Complete response (CR) was defined as complete disappearance of all target lesions. Partial response (PR) was defined as a $\geq$ 30% decrease in the sum of maximum diameters of target lesions compared with the baseline sum of maximum diameters. Progressive disease (PD) was defined as a $\geq$ 20% increase in the sum of maximum diameters of target lesions. Stable disease (SD) was defined as disease meeting neither PR nor PD criteria.

PFS was calculated from the time of initiating treatment to disease progression, death, or last follow-up visit. OS was calculated from the time of initiating treatment to death or last follow-up visit.

The current therapy was discontinued in patients with PD. For responses other than PD, treatment was repeated for $\geq$ 1 cycle. A 1- to 2-month rest period of no treatment was allowed after each treatment course. Toxicity was evaluated according to the National Cancer Institute Common Toxicity Criteria, version 3.0 (NCI-CTC).¹⁹ When side effects of grade 3 or more according to NCI-CTC with the exception of platelet and leukocyte counts of $<$ 30,000/ μ L and 2000/ μ L, respectively, were identified, treatment was immediately terminated.

Additional Therapy

In principle, the treatment course was repeated several times unless the tumor progressed during the therapy. Then, when down-staging of advanced HCC was achieved (single tumor $\leq$ 50 mm in diameter or 1-3 tumors $\leq$ 30 mm in diameter) by the repeated therapy, surgical resection or RFA was considered. For patients assessed with PD, additional therapies such as systemic chemotherapy, intra-arterial infusion chemotherapy with Lipiodol-cisplatin suspension, or best supportive care (BSC) were considered.

Statistical Analysis

Baseline data are expressed as mean $\pm$ standard deviation or as median and range. Statistical analysis was performed on December 1, 2010. Cumulative survival rate and PFS were calculated from the date of therapy initiation and assessed by the Kaplan-Meier life-table method, and differences were evaluated using the log-rank test. Univariate analysis of predictors for survival of patients was assessed by the Kaplan-Meier life-table method, and differences were evaluated using the log-rank test. Multivariate analysis of predictors for survival was assessed by the Cox proportional hazard model. Statistical significance was defined for values of $P < .05$. All analyses described above were performed using SPSS version 11 software (SPSS, Chicago, Ill).

RESULTS

Patient Profiles

Baseline characteristics of all 59 patients (44 men, 15 women) are summarized in Table 1. Median age was 66 years (range, 38-81 years). CH was present in 17 patients

Table 1. Baseline Characteristics of the 59 Patients

Characteristics	Value
Enrolled patients, No.	59
Age, y, median (range)	66 (38-81)
Sex, male/female	44/15
Etiology, HBV/HCV/NBNC	12/30/17
Underlying liver disease, CH/LC	17/42
Child Pugh classification, A/B	31/28
Extrahepatic metastases, yes/no	4/55
Maximum tumor size, mm, mean $\pm$ SD	96.7 $\pm$ 36.4
PVTT grade, Vp2 ^a /Vp3 ^b /Vp4 ^c	9/34/16
Total bilirubin, mg/dL, mean $\pm$ SD	1.1 $\pm$ 0.9
Albumin, g/dL, mean $\pm$ SD	3.5 $\pm$ 0.6
Prothrombin time, %, mean $\pm$ SD	78.8 $\pm$ 15.3
Platelet count, $\times 10^4$ /L, mean $\pm$ SD	15.2 $\pm$ 8.6
AFP, ng/mL, median (range)	194 (2.0-132,200)
AFP-L3, ng/mL, median (range)	25.0 (<0.5-83.5)
DCP, mAU/mL, median (range)	800 (3-205,360)
Previous treatment, yes/no	23/36

Abbreviations: AFP, α -fetoprotein; AFP-L3, lens culinaris agglutinin-reactive fraction of α -fetoprotein; CH, chronic hepatitis; DCP, des- γ -carboxy prothrombin; HBV, hepatitis B virus; HCV, hepatitis C virus; LC, cirrhosis; NBNC, negative for hepatitis B surface antigen and HCV antibody; PVTT, portal vein tumor thrombosis; SD, standard deviation.

Data are expressed as median values with ranges, means with standard deviations, or number of patients.

^aVp2: tumor thrombus in a second branch of the portal vein.

^bVp3: tumor thrombus in first branch of the portal vein.

^cVp4: tumor thrombus in trunk of the portal vein.

and compensated cirrhosis in 42 patients (Child-Pugh class A, $n = 31$; class B, $n = 28$). With respect to virus markers, 12 patients were positive for hepatitis B surface antigen, 30 patients were positive for HCV antibody, and 17 patients were negative for both markers. All patients were classified as Barcelona Clinic Liver Cancer stage C.²⁰ PVTT was noted in the main portal vein (Vp4) in 16 patients, in the first branch (Vp3) in 34 patients, and in the second branch (Vp2) in 9 patients. Mean diameter of the main tumor was 96.7 mm (range, 35-235 mm). Serum AFP levels were >10 ng/mL in 45 patients, and 49 patients were DCP positive (>40 mAU/mL).

Early Response to Therapy

A total of 104 cycles of HAIC were administered, with a median of 1 cycle given per patient (range, 1-6 cycles). Early response status in the 59 patients was assessed after the first course of therapy. As a result, 2 patients (3.5%) had a CR, 41 patients (69.5%) had a PR, 11 patients (18.6%) had SD, and 5 patients (8.4%) had PD (response rate [CR + PR/all cases] = 73.0%; Table 2). With regard to AFP levels, of the 45 patients who showed elevated baseline levels, 31 patients had decreased AFP levels, and 24 patients had a $>50\%$ decrease in AFP levels. With regard to DCP levels, of the 49 patients who had elevated

Table 2. Numbers of Early Responses to Therapy

Response	No. (%)
CR	2 (3.5)
PR	41 (69.5)
SD	11 (18.6)
PD	5 (8.4)
Objective early tumor response ^a	43 (73.0)

Abbreviations: CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

Data are expressed as number of patients.

^aObjective response was defined as the sum of CR and PR.

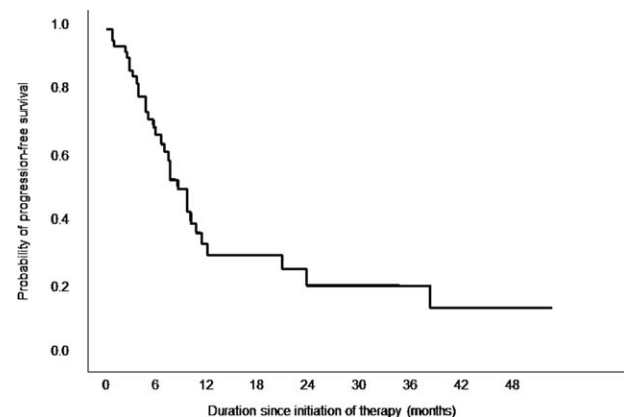


Figure 1. Cumulative progression-free survival (PFS) rates in 59 patients treated with 5-fluorouracil and pegylated interferon α -2b are shown. Cumulative PFS rates were 67.4% at 6 months, 30.2% at 12 months, 25.9% at 18 months, and 20.7% at 24 months.

baseline levels, 27 patients had decreased DCP levels, and 19 patients had a $>50\%$ decrease in DCP levels.

Survival

Cumulative PFS rates were 67.4% at 6 months, 30.2% at 12 months, 25.9% at 18 months, and 20.7% at 24 months, (Fig. 1). Median PFS was 9.7 months (95% confidence interval [CI], 6.4-11.3 months). Figure 2 shows cumulative survival rates. Cumulative survival rates were 82.4% at 6 months, 73.6% at 12 months, 52.8% at 24 months, and 44.0% at 36 months (Fig. 2). Median survival time was 29.9 months (95% CI, 13.2 months to not available).

Cumulative survival rates of patients who achieved CR/PR were 89.2% at 6 months, 84.7% at 12 months, 64.2% at 24 months, and 53.5% at 36 months. Conversely, cumulative survival rates of patients who showed SD/PD were 61.2% at 6 months, 30.6% at 12 months, 0% at 24 months, and 0% at 36 months. Survival rate was

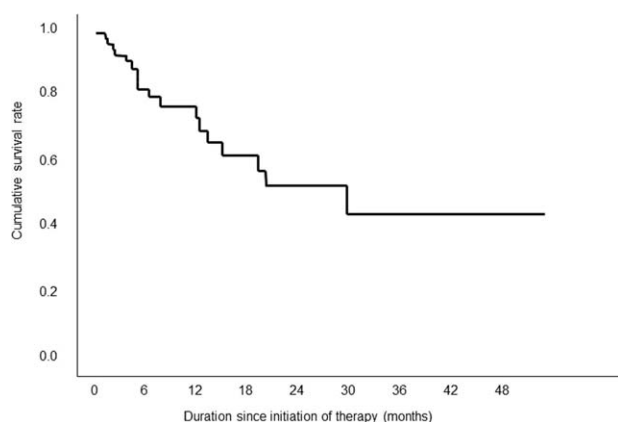


Figure 2. Cumulative survival rates in 59 patients treated with 5-fluorouracil and pegylated interferon α -2b are shown. Cumulative survival rates were 82.4% at 6 months, 73.6% at 12 months, 52.8% at 24 months, and 44.0% at 36 months.

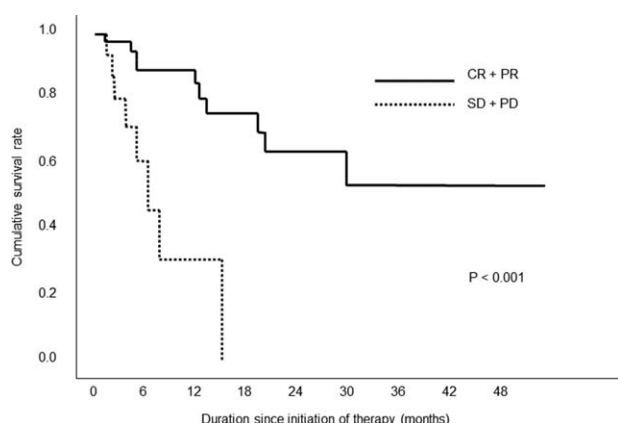


Figure 3. Cumulative survival rates between patients who achieved complete response (CR)/partial response (PR) and patients showing stable disease (SD)/progressive disease (PD) are compared. Cumulative survival rates of patients who achieved CR/PR were 89.2% at 6 months, 84.7% at 12 months, 64.2% at 24 months, and 53.5% at 36 months. Conversely, cumulative survival rates of patients who showed SD/PD were 61.2% at 6 months, 30.6% at 12 months, 0% at 24 months, and 0% at 36 months. Survival rates were significantly higher in patients who achieved CR/PR than in patients showing SD/PD ($P < .001$).

significantly higher in patients who achieved CR/PR than in patients who achieved SD/PD ($P < .001$; Fig. 3).

Prognostic factors affecting patient survival were analyzed by examining 21 potential parameters (Table 3). Univariate analysis revealed 2 significant prognostic factors related to survival: PVT grade ($P = .038$) and therapeutic effect ($P < .001$).

Multivariate analysis performed using factors identified as $P < .2$ in univariate analysis revealed therapeutic

Table 3. Univariate Analysis of Predictors of Survival in Patients Receiving 5-Fluorouracil and PEG-IFN α -2b Therapy

Variable	Hazard Ratio	95% Confidence Interval	P
Age, ≤ 65 vs > 65 years	0.681	0.263-1.767	.423
Sex, M vs F	0.519	0.149-1.816	.305
Previous treatment, no vs yes	1.021	0.394-2.644	.965
HCV antibody, positive vs negative	1.178	0.688-2.017	.549
Underlying liver disease, CH vs LC	1.201	0.425-3.395	.729
JIS score, 3 vs 4 or 5	1.140	0.433-3.005	.791
Child Pugh classification, A vs B or C	1.326	0.512-3.432	.561
Total bilirubin, ≤ 1.0 vs > 1.0 mg/dL	1.878	0.701-5.032	.210
Albumin, ≤ 3.5 vs > 3.5 mg/dL	0.612	0.234-1.600	.317
Prothrombin time, ≤ 96 vs $> 96\%$	0.502	0.194-1.302	.157
AST, ≤ 55 vs > 55 IU/L	1.528	0.588-3.970	.384
ALT, ≤ 43 vs > 43 IU/L	1.263	0.462-3.450	.649
Platelet count, $\leq 13 \times 10^4$ vs $> 13 \times 10^4$ /L	0.610	0.238-1.562	.303
Extrahepatic metastases, no vs yes	4.752	0.493-45.797	.178
PVT grade, Vp2 or Vp3 vs Vp4	2.852	1.062-7.660	.038
Maximum tumor size, > 100 vs ≤ 100 mm	0.561	0.215-1.460	.236
AFP, > 1000 vs ≤ 1000 ng/mL	1.296	0.484-3.468	.606
AFP-L3, ≤ 25 vs $> 25\%$	1.009	0.394-2.583	.985
DCP, > 1000 vs ≤ 1000 mAU/mL	1.879	0.722-4.887	.197
Therapeutic effect, CR + PR vs SD + PD	0.136	0.046-0.398	$< .001$
Adverse effects, ^a grade 0 or 1 vs 2 or 3	2.398	0.937-6.136	.068

Abbreviations: AFP, α -fetoprotein; AFP-L3, lens culinaris agglutinin-reactive fraction of α -fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CH, chronic hepatitis; CR, complete response; DCP, des- γ -carboxy prothrombin; F, female; HCV, hepatitis C virus; JIS, Japan integrated staging (the JIS score is obtained by adding the scores for the TNM stage and the Child-Turcotte-Pugh stage); LC, cirrhosis; M, male; PD, progressive disease; PR, partial response; PVT, portal vein tumor thrombosis; SD, stable disease.

^aAdverse effect was evaluated according to the National Cancer Institute Common Toxicity Criteria, version 3.0.

effect ($P < .001$) as the only independent factor affecting survival.

Adverse Effects

All patients were evaluated for adverse effects and implantable port system-related complications. Port systems were successfully implanted in all patients.

Table 4 summarizes the adverse effects. No treatment-related deaths or discontinuations were encountered. No grade 4 treatment-related adverse effects were noted in this study. Although 3 of 5 patients who displayed grade 3 thrombocytopenia required a dose reduction, no other patients displaying adverse effects required a dose reduction. All adverse reactions were controllable by medical treatment and/or temporary suspension of HAIC. The most frequent side effect was pyrexia, but this symptom was mild and transient. Severe hepatic or renal insufficiency was not observed.

Table 4. Adverse Effects Among the 59 Patients

Adverse Effect	Grade 1, No. (%)	Grade 2, No. (%)	Grade 3, No. (%)	Grade 4, No. (%)
Fever	42 (71.1)	9 (15.2)	— (—)	— (—)
General fatigue	7 (11.8)	3 (5.1)	— (—)	— (—)
Anorexia	4 (6.7)	4 (6.7)	— (—)	— (—)
Nausea/vomiting	4 (6.7)	— (—)	— (—)	— (—)
Leucopenia	15 (25.4)	17 (28.8)	6 (10.1)	— (—)
Thrombocytopenia	16 (27.1)	16 (27.1)	5 (8.4)	— (—)
Anemia	18 (30.5)	13 (22.0)	— (—)	— (—)
AST/ALT	3 (5.1)	4 (6.7)	— (—)	— (—)
Hepatic/renal failure	— (—)	— (—)	— (—)	— (—)
Gastric ulcer	— (—)	1 (1.7)	— (—)	— (—)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Data are expressed as number of patients with percentages in parentheses.

Additional Therapy

Among the 43 patients who achieved CR/PR, 5 patients (11.6%) and 1 patient (2.3%) were treated with surgical resection and RFA, respectively, as additional therapies. Conversely, among the 16 patients who showed SD/PD, 4 patients (25.0%), 1 patient (6.2%), and 5 patients (31.2%) were treated with systemic chemotherapy, intra-arterial infusion chemotherapy with Lipiodol-cisplatin suspension, and BSC, respectively, as additional therapies. The remaining 6 patients (37.6%) who were maintaining SD were treated with 5-fluorouracil and PEG-IFN α -2b repeatedly. After the additional therapies, 8 (13.5%) of 59 patients (2 CR patients, and 6 PR patients who had effective additional therapies) exhibited disappearance of viable HCC. The median PFS and OS in patients not receiving additional therapies such as surgical resection or RFA were 7.6 months and 29.2 months, respectively.

DISCUSSION

Advanced HCC is often accompanied by PVTT, but no standard therapeutic modality has been established for HCC with PVTT, particularly for Vp3 and Vp4. Prognosis is very poor, and several investigators have reported that the survival period for HCC patients with PVTT is typically around 2 months to 3 months.²¹⁻²³ Moreover, the degree of PVTT is a significant clinicopathological variable known to influence survival in patients with advanced HCC.²⁴ However, this vascular involvement is generally refractory to treatment. Although surgery is considered the most effective treatment for HCC patients with PVTT, surgery is suitable in only a limited number of cases because of the dissemination of the tumor throughout the liver or concomitant cirrhosis. Although transhepatic arterial chemoembolization has also been

widely applied to unresectable HCC, reported outcomes have been poor, particularly for HCC with Vp3 and Vp4.^{25,26} Two recent phase 3 clinical trials have shown that sorafenib, an orally available multikinase inhibitor, improves median overall survival in patients with advanced HCC.^{5,6} Llovet et al²⁰ have proposed the use of sorafenib as a first-line treatment for patients with HCC categorized as Barcelona Clinic Liver Cancer stage C. However, patients with HCC and PVTT usually have very short survival and grave prognosis even when treated with sorafenib.⁷

Recent progress in implantable drug delivery systems has enabled repeated arterial infusion of chemotherapeutic agents for patients with advanced HCC. Regional HAIC is a reasonable drug delivery system for patients with advanced HCC, because the tumors derive most of their blood supply from the hepatic artery, whereas the portal vein supplies the normal liver parenchyma.²⁷ HAIC thus seems to selectively deliver high concentrations of chemotherapeutic agents to HCC tissues, with low toxicity to noncancerous liver tissues and the whole body. Several groups have reported the combination therapy of intra-arterial 5-fluorouracil and cisplatin for HCC with Vp3 and Vp4.^{28,29} Furthermore, recent reports have described the efficacy and survival benefits of combination therapy using intra-arterial 5-fluorouracil and systemic IFN α for advanced HCC.^{10,11}

Concerning the antitumor effects of combination therapy with 5-fluorouracil and IFN α for advanced HCC, IFN α increases intracellular concentrations of 5-fluoro-2-deoxyuridine 5-monophosphate, the metabolite of 5-fluorouracil in the body,³⁰ thus enhancing cytotoxicity against malignant tumor cells^{31,32} and elevating inhibition of thymidylate synthetase.³² In addition, IFN α suppresses cancer cells directly and/or indirectly via several

pathways, such as inhibition of the cell cycle, boosting p53 activation, and activation of immunocytes.³³⁻³⁷ Moreover, Kondo et al³⁸ reported that the combination of 5-fluorouracil and IFN α strongly induces cell growth inhibition of human HCC cells and indicated that the effects of combination therapy may be attributable to alterations in the induction of apoptosis through IFN α / β receptor in human HCC cells.

PEG-IFN α -2b has been widely used since 2005 as a drug to treat CH patients with HCV infection. This agent is a derivative of recombinant IFN α -2b containing a single straight-chain molecule of polyethylene glycol, which has an average molecular weight of 12,000 Da, attached by covalent linkage primarily to histidine-34 on IFN α -2b.³⁹ Pegylation of IFN α -2b does not compromise the tertiary structure or spectrum of activity, but significantly decreases clearance, achieving a 10-fold increase in plasma half-life.¹⁴ As a result, PEG-IFN α -2b can be administered once weekly, and the increased area under the curve compared with standard 3 $\times$ weekly dosing with IFN α -2b results in increased drug exposure without a proportional increase in toxicity.¹⁴ The therapeutic effects of 5-fluorouracil combined with PEG-IFN α -2b may thus exceed those of 5-fluorouracil combined with IFN α . Yano et al⁴⁰ compared in vivo antitumor effects of PEG-IFN α -2b and IFN α in nude mice injected with cultured HCC cells (HAK-1B), and revealed that PEG-IFN α -2b induced apoptosis more strongly than IFN α . Furthermore, they reported that the antitumor effect of PEG-IFN α -2b was expressed at approximately 1/3 of the clinical dose. On the basis of these results, in this study we used 5-fluorouracil and PEG-IFN α -2b, not IFN α . This fact might have contributed to the better results in our study compared with the previous 5-fluorouracil and IFN α studies.^{10,11}

Compared with previous reports describing 5-fluorouracil and IFN α combination therapy,^{10,11} the present regimen used a different method of 5-fluorouracil administration. In previous reports, 5-fluorouracil was administered at 450 to 500 mg/d into the hepatic artery with continuous infusion over 5 hours or 24 hours on days 1 to 5 of weeks 1 and 2. Conversely, 5-fluorouracil in the present study was administered at 250 mg/d into the hepatic artery for 5 hours on days 1 to 5 each week. This period of administration was used because 5-fluorouracil is classified as a time-dependent drug exhibiting cytotoxic activities.⁴¹ In addition, 5-fluorouracil induces apoptosis in a dose-dependent manner.⁴² Ueshima et al⁴³ investigated combination therapy with 5-fluorouracil and cisplatin for advanced HCC by comparing 5- and 24-hour administra-

tion of 5-fluorouracil (250 mg/d), and reported a higher objective response rate for the 5-hour administration. We selected the administration time and period for 5-fluorouracil based on the effects of dose-dependent and long-term administration of 5-fluorouracil. These facts also might have contributed to the good results achieved in this study.

The overall median survival rate in the present study was 29.9 months. The outcome in the present study was far superior to that of a sorafenib study.⁶ In the SHARP trial,⁶ among the 299 patients who were treated with sorafenib, 2 patients (2%) and 211 patient (71%) had PR and SD, respectively. Conversely, the response rate in the present study was 73.0%, and 8 (13.5%) of 59 patients exhibited disappearance of viable HCC after the additional therapies. Although sorafenib is likely to delay disease progression, it is probably not suitable to make patients tumor free. Moreover, the SHARP trial⁶ showed that the rate of sorafenib discontinuation because of adverse events was 38%, and dose reductions because of adverse events occurred in 26% of patients who were treated using sorafenib. In contrast, there was no discontinuation of treatment because of adverse events in this study, and dose reductions because of adverse events occurred in only 5% of patients treated using 5-fluorouracil and PEG-IFN α -2b. This relatively mild level of side effects enabled continuation of the basic regimen and may lead to marked clinical effects, because tumor regrowth is often observed at times when treatment is interrupted because of adverse effects.

In our study, the early response cumulative survival rate was significantly higher in patients who achieved CR/PR than in those with SD/PD ($P < .001$). Early response is an important post-treatment predictor of survival among patients with advanced HCC with 5-fluorouracil and PEG-IFN α -2b combination therapy. Early response of CR or PR is a sign of good prognosis.

Nagamatsu et al⁴⁴ recently reported the efficacy of HAIC using intra-arterial 5-fluorouracil and Lipiodol-cisplatin for HCC patients with grade Vp2, Vp3, and Vp4 PVTT. In their report, the response rate was 86.3%, and overall survival rates at 12, 24, and 36 months were 72.9%, 58.1%, and 34.9%, respectively, with an overall median survival of 33 months. Although our regimen differed from theirs, the efficacies of treatment were similar. A recent study demonstrated that sorafenib prolongs the survival of patients with advanced HCC.⁶ However, many unresolved issues remain regarding the optimal usage of sorafenib. In particular, most patients enrolled in

this trial showed Child-Pugh class A cirrhosis with favorable clinical parameters. The benefits and safety profile of sorafenib in unselected advanced HCC patients, particularly those with Child-Pugh B/C or other poor prognostic factors, remain unclear. In the present study and the previous investigation by Nagamatsu et al, almost half of the patients had Child-Pugh class B cirrhosis. Nevertheless, good results were observed in patients who received HAIC therapy.

In conclusion, the present study demonstrated the efficacy of HAIC with PEG-IFN α -2b and 5-fluorouracil for advanced HCC patients. Furthermore, most adverse effects were transient and well tolerated. On the basis of our findings, this newly developed combination therapy is likely to be useful for patients with advanced HCC, although a large-scale randomized controlled study in comparison with sorafenib or HAIC using intra-arterial 5-fluorouracil and Lipiodol-cisplatin is needed to properly evaluate the efficacy of this therapy.

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