Repetitive Short-Course Hepatic Arterial Infusion Chemotherapy With High-Dose 5-Fluorouracil and Cisplatin in Patients With Advanced Hepatocellular Carcinoma

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BACKGROUND. Hepatic arterial infusion chemotherapy (HAIC) has often been selected as a therapeutic option for patients with advanced hepatocellular carcinoma (HCC). The objective of the current study was to evaluate the efficacy and safety of repetitive HAIC with high-dose 5-fluorouracil (5-FU) and cisplatin given for 3 days in patients with advanced HCC.

METHODS. Between January 2001 and December 2004, a total of 41 patients with unresectable advanced HCC were enrolled. The patients underwent HAIC via the implantable port system with 5-FU (at a dose of 500 mg/m^2 on Days 1–3) and cisplatin (at a dose of 60 mg/m^2 on Day 2) every 4 weeks. Tumor response was assessed at the end of every 3 cycles.

RESULTS. The median age of the patients was 53 years and 34 patients (82.9%) had evidence of portal vein thrombosis. In total, 230 cycles of HAIC were administered to the 41 patients, with a median of 6 cycles given (range, 1–14 cycles). Nine patients (22.0%) achieved a partial response and 14 patients (34.1%) had stable disease. The median time to disease progression and overall survival were 7.0 months and 12.0 months, respectively. The overall survival was found to be significantly longer in the successful disease control group (patients with a complete response, partial response, and stable disease) than in the disease progression group (median of 14.0 months vs 6.0 months; $P < .001$). Adverse reactions were tolerable and successfully managed with conservative treatment.

CONCLUSIONS. HAIC with high-dose 5-FU and cisplatin given for 3 days achieved effective and safe results in patients with advanced HCC. Therefore, repetitive short-course HAIC with high-dose 5-FU and cisplatin may be useful as an alternative therapeutic option for patients with advanced HCC. ***Cancer* 2007;110:129–37.** © *2007 American Cancer Society.*

KEYWORDS: hepatocellular carcinoma, hepatic arterial infusion chemotherapy, high-dose, short course, 5-fluorouracil, cisplatin.

Worldwide, hepatocellular carcinoma (HCC) is the sixth most common cancer (with 626,000 new cases reported in 2002) and the third most common cause of death from cancer.[1] Patients with early-stage HCC may benefit from potentially curative treatments, such as surgical resection or percutaneous local therapy. Unfortunately, the majority of patients with HCC are not candidates for any curative treatments because of advanced disease at time of presentation and/or underlying cirrhosis. The majority of patients with advanced HCC reportedly survive ≤6 months from the time of initial diagnosis.[2,3] Although variable therapeutic approaches for

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these patients may be attempted, to our knowledge, the treatment strategies for patients with advanced HCC have not yet been established.[4–6]

Repetitive hepatic arterial infusion chemotherapy (HAIC) with various chemotherapeutic regimens via the implantable port system has been reported to be a useful therapeutic modality for patients with advanced HCC.[7–15] The advantage of intra-arterial chemotherapy compared with systemic therapy is pharmacologically explained by the concepts of "first-pass effect" and "increased local concentration."[16] Chemotherapeutic agents are delivered in the liver via the implanted port system and catheter with a high concentration and lower toxicity compared with systemic chemotherapy. Several chemotherapeutic agents (such as cisplatin, 5-fluorouracil (5-FU), epirubicin, doxorubicin, and mitomycin-C) are administered individually or in combination for advanced HCC. However, to our knowledge, there has been no consensus to date regarding the most useful agents to administer by HAIC or their optimal schedule, dosage, and treatment duration.

Several studies have reported that repetitive HAIC, comprised of low doses of cisplatin and 5-FU, in patients with advanced HCC has achieved favorable results.[11–15] However, the treatment schemes of these reports were comprised mainly of protracted infusions of low-dose cisplatin and 5-FU. This may require relatively long-term treatment and hospitalization. It is desirable to tailor the treatment scheme to a shorter duration without compromising tumor response as well as the incidence of adverse events. In the current study, we evaluated the clinical utility of repetitive HAIC with high doses of 5-FU and cisplatin for 3 days, using an implantable port system in patients with unresectable, advanced HCC, a disease entity that is especially not suitable for other treatment modalities.

MATERIALS AND METHODS

Patients

The study recruited patients between January 1, 2001 and December 31, 2004. The diagnosis of HCC was made either by histopathologic confirmation or typical radiologic evidence of HCC with elevated serum levels of α-fetoprotein (AFP) (>400 ng/mL) in the setting of cirrhosis. Patients with advanced HCC who were not suitable for surgical resection, liver transplantation, or nonsurgical interventions (such as percutaneous ethanol injection, radiofrequency ablation, or transcatheter arterial chemoembolization) because of multiple tumor involving both lobes of the liver or portal vein thrombosis were enrolled. Other eligibility criteria included the following: ages 18 to 75 years, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1, Child-Pugh class of A or B, preserved organ function (serum creatinine level $\leq$1.5 mg/dL and aminotransferase $\leq$5 times the institutional upper limit of normal), acceptable blood cell counts (absolute neutrophil count of $\geq$1500 cells/mm^3, a platelet count $\geq$75,000 cells/mm^3, and hemoglobin $\geq$10 g/dL), and at least 1 unidimensionally measurable lesion. Previous antitumor therapy was allowed if it was performed >8 weeks before enrollment in this study. Patients were ineligible if they had another concurrent type of malignancy or extrahepatic metastases, had experienced recent upper gastrointestinal bleeding, or had any other underlying serious medical condition that would interfere with participation in the study. Patient disease was staged using the TNM staging system, the Okuda staging system, Cancer of the Liver Italian Program (CLIP), and Japan Integrated Staging (JIS). The Okuda stage was determined by the summation of the points for 4 variables including tumor size, ascites, albumin, and bilirubin (stage I indicates a score of 0, stage II indicates a score of 1 or 2, and stage III indicates a score of 3 or 4). The CLIP score was calculated by the summation of the points for 4 variables: Child-Pugh class, tumor morphology, AFP levels, and portal venous invasion. The JIS score was obtained by the summation of the tumor stage score (stage I indicates a score of 0, stage II indicates a score of 1, stage III indicates a score of 2, and stage IV indicates a score of 3) and the Child-Pugh class (Child-Pugh class A indicates a score of 0, Child-Pugh class B indicates a score of 1, and Child-Pugh class C indicates a score of 2).

Written informed consent was obtained from each participant or responsible family members after the possible complications of port system implantation and HAIC had been explained fully. The Institutional Review Board of the Severance Hospital approved this study.

Implantation of the Port System

After injection of local anesthetic, the Seldinger technique was used to gain access to the femoral artery. Arteriography of the celiac trunk and superior mesenteric artery was performed to visualize the arterial vascularization of the liver and to evaluate portal vein patency, respectively. After detection of the HCC and its feeding artery, the tip of the catheter (Port-A-Cath®; Deltac, St Paul, Minn) was placed at the common hepatic artery or proper hepatic artery under fluoroscopic guidance. The proximal end of the catheter was connected to the injection port and

the device was implanted in a subcutaneous pocket in the right iliac fossa. To prevent occlusion of the catheter, 10 mL (10,000 units) of a heparin solution was infused via the injection port after each cycle of chemotherapy. The hepatic angiography via the port system was performed every 2 to 3 cycles of treatment.

Study Treatment and Dose Modification

Chemotherapeutic agents were administered via the implantable port system. Patients received 5-FU (Choong-wae, Seoul, South Korea; 500 mg/m^2 for 5 hours on Days 1–3) and cisplatin (Il-dong, Seoul, South Korea; 60 mg/m^2 for 2 hours on Day 2) into the hepatic artery. Intravenous hydration was performed before cisplatin infusion to prevent nephrotoxicity and all patients were given prophylactic antiemetic treatment comprised of 5-HT$_3$ antagonists and dexamethasone. Treatment cycles were repeated every 4 weeks until evidence of disease progression, unacceptable toxicity, or patient refusal to continue. Dose adjustments were made depending on the toxicity observed with each treatment cycle. The following cycle of treatment was reduced by 30% in the case of repeated grade 2 or any grade 3 or 4 toxicity during the preceding cycle. Treatment was delayed until resolution from any grade 3 or grade 4 toxicity. If a patient required a delay of >4 weeks for recovery, the patient was taken off the study.

Study Assessments

The primary efficacy endpoint of the current study was an objective response rate (complete response [CR] plus partial response [PR]) and the secondary efficacy endpoints were time to disease progression (TTP) and overall survival (OS). Pretreatment evaluation included medical history and physical examination, whereas laboratory tests included serum AFP, chest X-ray, and computed tomography (CT) scan, which was performed within 2 weeks before the initiation of treatment. During treatment, a physical examination (including toxicity assessment, laboratory tests, and chest X-rays) was performed every 4 weeks before each cycle. CT scans were performed every 3 cycles to evaluate treatment response or, if needed, for the documentation of disease progression. The tumor responses were classified according to the World Health Organization tumor response criteria with the European Association for the Study of the Liver modifications.[6] Patients who achieved CR, PR, and stable disease (SD) were considered to have achieved successful disease control. SD was required to last at least 24 weeks. Anticancer effects were evaluated by examining changes in tumor size and serum AFP level.

TTP was calculated from the time of study entry to disease progression. OS was calculated from the time of study entry to death or last follow-up visit. All patients who received at least 1 cycle of HAIC were considered for toxicity evaluation. The observed toxicities were evaluated according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC; version 3.0).

Statistical Analysis

The Kaplan-Meier method was used in the analysis of time-to-event variables and the 95% confidence interval (95% CI) for the median time to event was computed. The univariate analysis to identify parameters predictive of survival was performed by computing survival curves according to the Kaplan-Meier method. For the evaluation of continuous variables, the cutoff level chosen was their median value. In this analysis, composed variables such as Child-Pugh class as well as the TNM, JIS, and Okuda stages were replaced by their constitutive variables. Significant parameters of univariate analysis were entered into a multivariate Cox regression model to identify independent predictors of survival. The chi-square test and Student *t* test were used for the analysis of clinical characteristics and prognostic factors between the successful disease control group (CR + PR + SD) and the disease progression group (progressive disease [PD]).

The intensity of the actually delivered dose was calculated as the ratio of the total dose (expressed in mg) per meter squared actually received by the patient divided by the actual total treatment duration expressed as weeks. The relative dose intensity was calculated as the ratio of the intensity of the actually delivered dose to the dose intensity planned by the protocol.

A P value $<.05$ was considered to indicate statistical significance. All statistical analysis was performed using commercially available software (SPSS software [version 13.0]; SPSS Inc., Chicago, Ill).

RESULTS

Patient Characteristics

A total of 41 patients were enrolled into the study between January 2001 and December 2004. The baseline characteristics of the patients are summarized in Table 1. The patients were 29 males and 12 females, with a median age of 53 years (range, 38–73 years). The etiology of the background liver disease was hepatitis B virus in 36 patients, hepatitis C virus

TABLE 1
Baseline Patient and Disease Characteristics

Characteristic		No. of patients
Enrolled patients		41
Evaluable for response		34
Age, y	Median (range)	53 (38–73)
Male:female ratio		29:12
ECOG performance status	0/1	35/6
Etiology	HBV/HCV/alcoholism	36/4/1
Child-Pugh class	A/B	36/5
Staging		
Tumor stage*	III/IV-A	8/33
Okuda stage	I/II	13/28
CLIP score	0/1–3/4–6	0/30/11
JIS score	2/3/4	5/33/3
Tumor type	Nodular/massive/diffuse	13/10/18
Tumor size (cross-sectional area on imaging)	<50%/≥50%	19/22
Lobar involvement	Unilobar/bilobar	20/21
Portal vein thrombosis	Yes/no	34/7
Ascites	Yes/no	6/35
Previous treatment	TACE/surgery/RFA/none	9/5/3/32
Pretreatment laboratory data, median (range)		
Bilirubin (mg/dL)		1.0 (0.2–2.4)
Albumin (g/dL)		3.6 (2.6–4.6)
Platelet count ($\times 10^3$/mL)		150.0 (84.7–451.0)
ALT (IU/L)		48.0 (13.0–160.0)
Prothrombin activity ratio (%)		90 (58–100)
α-fetoprotein (ng/mL)		189.40 (1.79–83,000)

ECOG indicates Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus; CLIP, Cancer of the Liver Italian Program; JIS, Japan Integrated Staging; TACE, transcatheter arterial chemoembolization; RFA, radiofrequency ablation; ALT, alanine aminotransferase.
* Based on the modified criteria of the International Union Against Cancer.

in 4 patients, and alcoholism in 1 patient. Thirty-four patients (82.9%) had evidence of portal vein thrombosis at baseline. The degree of vascular invasion to the portal vein was Vp3 or 4 (the first branch or main portal trunk) in 30 patients and Vp2 (the second branch) in 4 patients. Thirty-three patients (80.5%) had stage IV-A disease. Twenty-two patients had ≥50% of their liver replaced by the tumor. Okuda staging of the 41 patients demonstrated that 13 patients had stage I disease and 28 patients had stage II disease. The median serum AFP was 189.40 ng/mL (range, 1.79–83,000 ng/mL), being normal (<20 ng/mL) in 22.0% of patients and >400 ng/mL in 41.5% of patients.

Clinical Efficacy

A total of 230 cycles of HAIC were administered with a median of 6 cycles given per patient (range, 1–14 cycles). The delivered relative dose intensities were 0.92 for 5-FU and 0.90 for cisplatin. Thirteen patients required dose reductions or treatment delays at some point in their therapy.

The primary efficacy endpoint for this study was the objective response rate and 34 of 41 patients (82.9%) were assessable for tumor response. Seven patients (17.1%) were not assessable for response due to early withdrawal from the study, but were included in the intent-to-treat analysis (2 patients with lung metastases, 2 patients with progressive liver disease, 1 patient who withdrew from the study voluntarily, and 2 patients with implantable port system infections). On intent-to-treat analysis, 9 of 41 patients (22.0%) experienced a PR and 14 patients (34.1%) experienced SD, whereas 11 patients (26.8%) developed PD. Therefore, the objective response rate was 22.0% and 23 patients (56.1%) achieved successful disease control with this treatment approach. The response characteristics are shown in Table 2.

The Kaplan-Meier method was used to calculate the median TTP at 7.0 months (95% CI, 6.3–7.7 months) and the median OS at 12.0 months (95% CI, 9.7–14.3 months). The 6-month and 1-year cumulative survival rates were 76.5% and 47.1%, respectively (Fig. 1). The patients who achieved a PR had a median survival of 16.0 months (95% CI, 7.2–24.8 months), whereas the patients with SD had a median survival of 14.0 months (95% CI, 11.6–16.4 months). The OS rate was found to be significantly longer

TABLE 2
Treatment Response

	ITT no. (%)	PP no. (%)
Total no. of patients	41	34
Complete response	0	0
Partial response	9 (22.0)	9 (26.5)
Stable disease	14 (34.1)	14 (41.2)
Progressive disease	11 (26.8)	11 (32.3)

ITT indicates intent-to-treat; PP, per protocol.

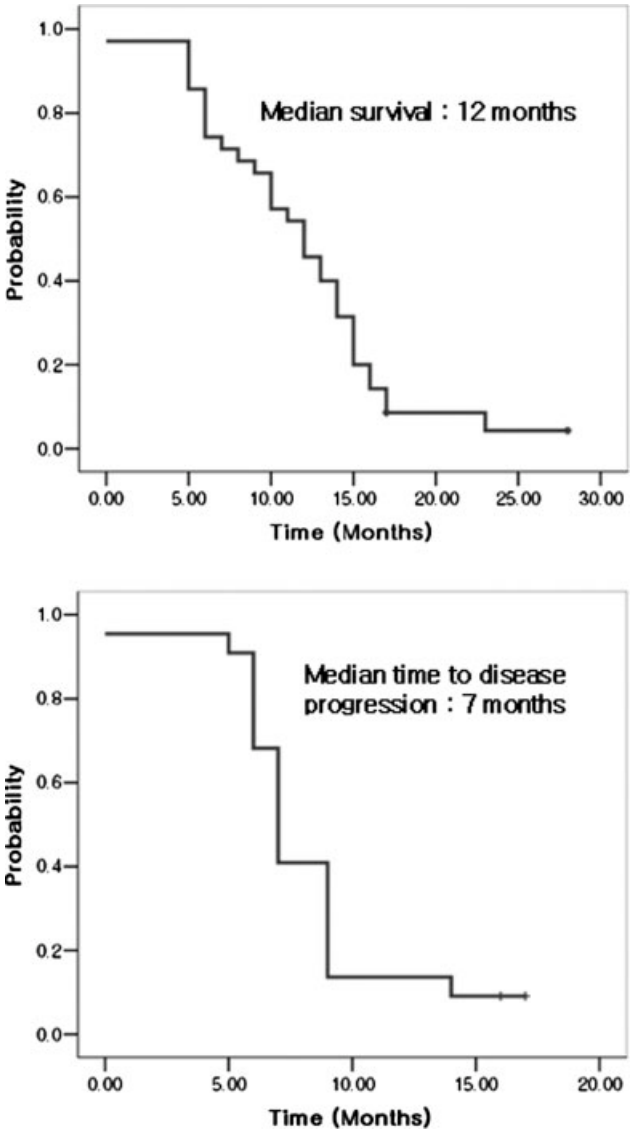

FIGURE 1. Overall survival and time to disease progression.

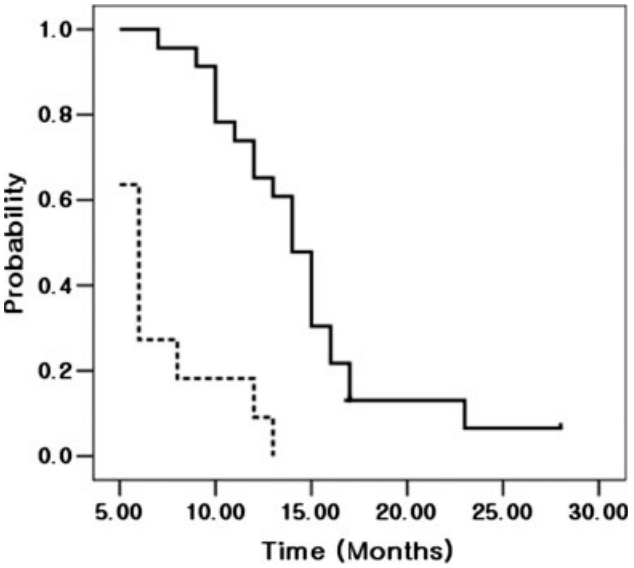

FIGURE 2. Cumulative survival of patients. The overall survival was significantly longer in the successful disease control group (those with a complete response, partial response, and stable disease) compared with the disease progression group (PD) (median of 14.0 months vs 6.0 months; $P < .001$). The solid line indicates the successful disease control group, dashed line, the disease progression group.

in the successful disease control group (CR+PR+SD) compared with the group with PD (median of 14.0 months vs 6.0 months; $P < .001$) (Fig. 2). The 1-year survival rate of the successful disease control group was 65.2%. The duration of survival demonstrated a close correlation with disease control after chemotherapy.

Prognostic Factors

The prognostic factors affecting patient survival were analyzed by examining 22 potential parameters (Table 3). Univariate analysis revealed 6 significant prognostic factors related to survival: ECOG performance status ($P = .001$), Child-Pugh class ($P = .004$), the presence of ascites ($P = .003$), the serum albumin level ($P = .044$), the serum AFP level ($P = .038$), and successful disease control ($P < .001$). Multivariate analysis revealed successful disease control (95% CI, 1.626–16.215; $P = .005$) to be the only independent predictor of survival.

The comparisons of baseline characteristics between the successful disease control group and PD group are provided in Table 4. Sex, tumor stage, Okuda stage, CLIP score, JIS score, tumor type, tumor extension, portal vein thrombosis, previous treatment, and the baseline laboratory data (with the exception of serum AFP level) were not found to differ significantly between the 2 groups. Significantly,

TABLE 3
The Parameters Influencing The Cumulative Survival of Patients Analyzed Using Univariate Analysis

Parameters	*P*
Age, y (≤53/>53)	.061
Sex (male/female)	.649
ECOG performance status (0/1)	**.001**
Etiology (HBV/HCV/alcoholism)	.374
Child-Pugh class (A/B)	**.004**
Staging	
Tumor stage* (III/IV-A)	.340
Okuda stage (I/II)	.111
CLIP score (1–3/4–6)	.337
JIS score (2/3/4)	.133
Tumor type (nodular/massive/diffuse)	.583
Tumor size (<50%/≥50%)	.638
Lobar involvement (unilobar/bilobar)	.722
Portal vein thrombosis (yes/no)	.340
Ascites (yes/no)	**.003**
Previous treatment (yes/no)	.794
Pretreatment laboratory data	
Bilirubin (≤1.0 mg/dL / >1.0 mg/dL)	.902
Albumin (≤3.6 g/dL / > 3.6 g/dL)	**.044**
Platelet count (≤150.0 × 10^3/mL / >150.0 × 10^3/mL)	.479
ALT (≤48.0 IU/L / >48.0 IU/L)	.450
Prothrombin activity ratio (≤90% / > 90%)	.419
α-fetoprotein (≤189.40 ng/mL / >189.40 ng/mL)	**.038**
Successful disease control group (PR+SD/PD)	<**.001**

ECOG indicates Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus; CLIP, Cancer of the Liver Italian Program; JIS, Japan Integrated Staging; ALT, alanine aminotransferase; PR, partial response; SD, stable disease; PD, progressive disease.
The cutoff for continuous variables is the median value.
* Based on the modified criteria of the International Union Against Cancer.

patients in the successful disease control group were younger than those in the PD group ($P = .010$). A statistically significant correlation was observed between the presence of ascites or a poor ECOG performance status and tumor progression ($P = .028$). The pretreatment serum AFP level was found to be higher in the PD group compared with the successful disease control group ($P = .015$).

Treatment-Related Toxicity

All patients were evaluated for toxicities and implantable port system-related complications. The port systems were successfully implanted in all patients. The worst toxicities associated with treatment are reported in Table 5. Overall, toxicities were transient and tolerable, and they were successfully managed by conservative treatment. The hematologic toxicities, including leukopenia, anemia, and thrombocytopenia, were mild. Two patients experienced grade 3 to 4 thrombocytopenia, but there were no episodes of thrombocytopenia-related bleeding reported. The major clinical problems were hepatic toxicities such as elevation of the aminotransferase or bilirubin levels. Elevated liver enzymes in documented cases of HCC progression were not considered to be treatment-related toxicities. Grade ≥3 elevations in the aminotransferase and alkaline phosphatase levels occurred in 4 patients (9.8%) and 1 patient (2.4%), respectively. Of the patients with elevated aminotransferase due to treatment, 2 patients returned to normal levels, usually within 1 month of discontinuing treatment. Five patients (12.2%) demonstrated a ≥ grade 3 elevation in their bilirubin level. Three patients who later developed persistent hyperbilirubinemia after receiving treatment were withdrawn from this study. Two of these patients experienced hepatitis and hyperbilirubinemia due to hepatitis B virus reactivation, and were received lamivudine treatment immediately. These toxicities returned to baseline levels within 2 months. These patients resumed further HAIC after resolution of toxicity, but went off the study. One patient experienced cholangitis that was considered to be a 5-FU-related toxicity. This patient had been treated successfully with percutaneous transhepatic biliary drainage and antibiotic treatment, and therefore demonstrated improvement of the biliary stricture that did not require further therapy after 1 month.

Occlusion of the implantable port system occurred in 1 patient. The occluded port system was removed and the patient resumed HAIC after the implantation of new port system. Infection of the port system occurred in 2 patients. After administering antibiotics and conservative care, port system infection was controlled, but these patients discontinued HAIC with the implantable port system.

DISCUSSION

HCC is among the most frequent causes of death from malignancy and the overall prognosis is very poor in patients with advanced HCC.[1–3] To our knowledge, a standard therapeutic method for patients with unresectable advanced HCC has not been established to date.[4–6] Recently, HAIC has been reported to be a useful palliative therapeutic option for patients with advanced HCC.[7–15] HAIC is delivered directly by means of selective catheterization into the hepatic arterial branches feeding the tumors. The rationale for HAIC is the possibility to achieve increased local drug concentrations at the tumor to levels not achievable by intravenous systemic treatment, while reducing systemic exposure and therefore side effects. Although several chemotherapeutic agents (including cisplatin, 5-FU, epirubicin, doxoru-

TABLE 4
Differences in Baseline Characteristics between The Successful Disease Control Group (CR + PR + SD) and The Disease Progression Group (PD)

Parameters	Disease control group (N = 23)	Disease progression group (N = 11)	*P*
Age, y	51.3 ± 8.8	60.0 ± 8.4	.010
Sex (male:female)	17:6	6:5	NS
ECOG performance status (0/1)	23/0	8/3	.028
Etiology (HBV/HCV/alcoholism)	21/1/1	8/3/0	NS
Child-Pugh Score (A/B)	23/0	9/2	NS
Tumor stage* (III/IV-A)	5/18	1/10	NS
Okuda stage (I/II)	11/12	2/9	NS
CLIP score (1–3/4–6)	20/3	7/4	NS
JIS score (2/3/4)	4/19/0	0/10/1	NS
Tumor type (nodular/massive/diffuse)	10/5/8	3/2/6	NS
Tumor size (<50%/≥50%)	12/11	4/7	NS
Lobar involvement (unilobar/bilobar)	13/10	5/6	NS
Portal vein thrombosis (yes/no)	18/5	10/1	NS
Ascites (yes/no)	0/23	3/8	.028
Previous treatment (yes/no)	5/18	2/9	NS
Pretreatment laboratory data			
Bilirubin (mg/dL)	0.9 ± 0.4	1.0 ± 0.4	NS
Albumin (g/dL)	3.7 ± 0.5	3.4 ± 0.6	NS
Platelet count ($\times 10^3$/mL)	170.7 ± 100.6	133.3 ± 61.1	NS
ALT (IU/L)	51.6 ± 32.3	42.3 ± 24.0	NS
Prothrombin activity ratio (%)	88.9 ± 12.6	87.6 ± 12.7	NS
α-fetoprotein (ng/mL)	2187.59 ± 8847.60	17329.94 ± 25525.36	.015

PR indicates partial response; SD, stable disease; PD, progressive disease; NS, not significant; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus; CLIP, Cancer of the Liver Italian Program; JIS, Japan Integrated Staging; ALT, alanine aminotransferase.
Values are shown as the mean ± the standard deviation.
* Based on the modified criteria of the International Union Against Cancer.

TABLE 5
Treatment-related Toxicity

	Maximum toxicity grade per patient according to the NCI-CTC (version 3.0) (n = 41)			
Toxicity	**Grade 1 no. (%)**	**Grade 2 no. (%)**	**Grade 3 no. (%)**	**Grade 4 no. (%)**
Hepatologic toxicity				
Leukopenia	3 (7.3)	8 (19.5)	1 (2.4)	–
Neutropenia	4 (9.8)	7 (17.1)	–	–
Anemia	5 (12.2)	3 (7.3)	–	–
Thrombocytopenia	2 (4.9)	9 (22.0)	1 (2.4)	1 (2.4)
Nonhematologic toxicity				
AST	8 (19.5)	11 (26.8)	2 (4.9)	–
ALT	10 (24.4)	9 (22.0)	3 (7.3)	–
ALP	10 (24.4)	4 (9.8)	1 (2.4)	–
Bilirubin	6 (14.6)	6 (14.6)	4 (9.8)	1 (2.4)
Nausea/vomiting	13 (31.7)	9 (22.0)	3 (7.3)	–
Diarrhea	7 (17.1)	–	–	–
Renal impairment	1 (2.4)	–	–	–
Fever	3 (7.3)	2 (4.9)	–	–
Neuropathy	5 (12.2)	1 (2.4)		
Implantable port system-related complication				
Infection			2 (4.9)	
Occlusion			1 (2.4)	

NCI-CTC indicates the National Cancer Institute Common Toxicity Criteria; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase.

bicin, and mitomycin-C) have been used for HAIC, 5-FU and cisplatin are the most commonly used agents in HAIC for HCC.[11–15] Ando et al.[12,13] reported the usefulness of HAIC with low-dose cisplatin and 5-FU in patients with advanced HCC with portal vein tumor thrombosis. The response rate and median survival duration of 48 patients were 48% and 10.2 months, respectively. The regimen of low-dose cisplatin and 5-FU was given daily 5 days a week for 4 consecutive weeks. Itamoto et al.[14] reported outcomes in 7 patients with unresectable or recurrent HCC with portal vein thrombosis. The overall response rate of patients to their chemotherapy was 33%, and the median survival duration was 7.5 months. Tanioka et al.[15] reported that HAIC with low-dose cisplatin and 5-FU achieved a response rate of 47% in patients with advanced HCC. However, these therapeutic schemes, which were performed for the most part in an area that is endemic for hepatitis C virus, were comprised of the protracted infusion of low-dose cisplatin and 5-FU for relatively long periods. Protracted infusion of chemotherapeutic agents may have a negative impact on a patient's quality of life (QOL). It is desirable to tailor the treatment scheme to a shorter duration without compromising tumor response as well as the incidence of adverse events. The practical chemotherapy strategy is to use the most active drugs at maximum doses over a relatively short period. In addition, cytotoxic drugs display a steep dose-response curve, resulting in a significant increase in tumor response. In contrast to previous reports, we assessed the efficacy of repetitive HAIC using high-dose 5-FU and cisplatin during a short treatment course in an area that is endemic for hepatitis B virus. In the current study, the overall response rate was 22.0%. The median survival was 12.0 months and the median TTP was 7.0 months. Patients had fewer side effects and generally tolerated the chemotherapy well. Although efforts to improve disease remission using dose escalation and a shorter treatment period would most likely result in increased chemotherapy-related toxicity, there did not appear to be a clinical limit to repetitive HAIC with high doses of 5-FU and cisplatin in the current study. In addition, compared with previous reports, patients received HAIC during a short treatment course and demonstrated satisfactory results. Unlike potentially curative treatment, the objectives of administering HAIC in patients with advanced HCC are survival benefits with palliative therapy and improvement of the patient's QOL. QOL is an important measure in patients undergoing palliative therapy. If the chemotherapy treatment period is longer, it might deteriorate the QOL. A shorter treatment period can benefit patients by reducing the cost of treatment and by improving QOL.

Recently, improvements in an implantable drug delivery port system have made possible repetitive HAIC for patients with advanced HCC. Use of the implanted catheter and port system has simplified the repetitive, long-term administration of chemotherapy[17] and may contribute to improved patient prognosis and QOL.

In the current study, univariate analysis showed 6 significant prognostic factors that were correlated with survival: ECOG performance status ($P = .001$), Child-Pugh score ($P = .004$), the presence of ascites ($P = .003$), the serum albumin level ($P = .044$), the serum AFP level ($P = .038$), and successful disease control after chemotherapy ($P < .001$). However, portal vein tumor thrombosis did not appear to influence the prognosis in patients with advanced HCC who were treated with HAIC ($P = .340$). Multivariate analysis revealed successful disease control to be the only independent predictor of survival ($P = .005$). Several investigators reported that hepatic reserve function and therapeutic objective response after HAIC were significant prognostic factors in patients with advanced HCC who were treated with HAIC.[13,18,19] The results of the current study were similar to those in the previous reports but, in contrast to other reports, we considered that the successful disease control group contained patients with SD. There was no significant difference noted in overall survival between the patients with PR and those with SD in the current study. Even patients in whom there was no measurable tumor regression but in whom disease remained stable during the period of infusion appeared to fare better symptomatically. The majority of these patients demonstrated a decrease in tumor vascularity without any apparent tumor regression. In addition, if these patients had elevated baseline AFP levels, all patients had a correspondingly significant decrease in the serum AFP level, which supported evidence of a response to HAIC with 5-FU and cisplatin. Considering the natural doubling time of HCC, an inhibition of tumor growth in patients with SD was predicted, indicating the relative efficacy of this method, even in patients with SD. The precise mechanism awaits further investigation, but perhaps chemotherapeutic agents may produce a loss of tumor vascularity in addition to anticancer effects. HAIC appears to be effective in controlling tumors, or at least helps to retard tumor progression. In addition, previous reports have demonstrated that the pretreatment serum AFP level was an independent prognostic predictor, regardless of the treatment adminstered.[18,19] It is interesting to

note that Patt et al.[20] suggested that the better response of patients with low serum AFP to 5-FU may be due to the lower expression of thymidylate synthase, making the tumor more sensitive to fluoropyrimidines. In the current study, the patients who achieved successful disease control had a correspondingly significantly low serum AFP level. This therapeutic approach is worthy of clinical consideration in patients with advanced HCC who have a good performance status, preserved hepatic function, and low serum AFP level, even though portal vein tumor thrombosis is noted.

The results of the current study demonstrate the clinical efficacy of repetitive HAIC with high-dose 5-FU and cisplatin given for 3 days in patients with unresectable advanced HCC. With regard to toxicity, the majority of patients tolerated the therapeutic approach well and only mild or transient adverse reactions were reported. Further comparative randomized controlled trials are needed to confirm the survival outcome of patients with advanced HCC who are treated with repetitive HAIC.

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