Original Article

J Chin Med Assoc
2004;67:602-610

Clinical Effects of Intra-arterial Infusion Chemotherapy with Cisplatin, Mitomycin C, Leucovorin and 5-Flourouracil for Unresectable Advanced Hepatocellular Carcinoma

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Key Words
5-fluorouracil;
chemotherapy;
cisplatin;
hepatocellular carcinoma;
mitomycin C

Background. Intra-arterial infusion chemotherapy (IAIC) can potentially improve survival in some patients with hepatocellular carcinoma (HCC), but the ideal regimen is not yet established. We prospectively evaluated the effects of short-course continuous infusion with the combination of cisplatin, mitomycin C, 5-fluorouracil (5-FU) and leucovorin for unresectable advanced HCC and analyzed their prognostic factors.

Methods. Patients with unresectable advanced HCC and not suitable for other therapy were enrolled. Cannulation via the left subclavian artery with the tip of catheter at the proper hepatic artery was done before initialization of IAIC routinely. The regimen consisted of the daily administration of cisplatin (10 mg/m^2), mitomycin C (2 mg/m^2), leucovorin (15 mg/m^2), and daily infusion of 5-FU (100 mg/m^2) for 5 days. Only the patients that had received at least 2 courses of IAIC were evaluated.

Results. Two-hundred and 11 courses of IAIC were performed, and each patient received at least 2 cycles of chemotherapy. The overall response rate was 28.3%. We observed a complete response in 5 patients (9.4%), a partial response in 10 patients (18.9%), a minimal response in 5 patients (9.4%), no change in 11 patients (20.8%) and a progressive disease in 22 patients (41.5%). The patients with response to treatment survived longer than the patients without response (24.6 ± 14.2 months *vs* 8.7 ± 5.3 months, $p < 0.001$). In univariate and multivariate analysis, absence of main vessel thrombosis and alpha-fetoprotein (AFP) reduction percentage > 50% following treatment showed significance in our study. All side effects subsided after conservative treatment.

Conclusions. Continuous IAIC with cisplatin, mitomycin-C, leucovorin, and 5-FU is effective for patients with severe advanced HCC. Absence of main vessel thrombosis, and AFP reduction percentage > 50% following treatment were good predictors of treatment response in our study. All side effects were mild and tolerable.

Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide. It is a common malignancy in Africa and eastern Asia.[1] In Taiwan, HCC is the leading cause of cancer-related death. Despite the availability of multiple modalities in management of HCC, the prognoses of patients with HCC are still very poor. Surgical resection or liver transplantation seems to be the only possibility for cure. However, low resection rate due to advanced tumors, poor liver reserve, and high recurrence rate following resection bother clinicians. Limited donors also decrease the number of liver transplants. Therefore, transcatheter arterial embolization (TAE) with/or without chemotherapeutic agents, local injection with pure alcohol and thermal therapy, such as microwave coagulation therapy and radiofrequency tumor ablation, have been developed. However, these

Received: May 12, 2004.
Accepted: October 26, 2004.

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treatments are not suitable for patients with bulky tumors, main vessel invasion or multiple tumors involving both lobes of the liver. Intravenous systemic chemotherapy using single agent, such as 5-fluorouracil (5-FU), floxuridine (FUDR), cisplatin, mitomycin C, mitoxantrone, epirubicin, doxorubicin, etoposide, and α-interferon, has been studied and showed only 0-24% response rates and contributed little effect on survival.[2-6] In 1950, Klopp *et al*.[7] firstly reported the results of the intra-arterial infusion chemotherapy (IAIC) for HCC. This form of treatment has been widely used to treat patients with advanced HCC and potentially improved the survival. When compared with systemic chemotherapy, IAIC shows an increased concentration of chemotherapeutic agents locally, and less systemic side effects.[8] Although monochemotherapy or various combinations of chemotherapeutic agents have been studied,[9-13] there is no standard regimen for treatment of patients with advanced HCC. In 1996, Kurth *et al*. reported that the 5-FU, FUDR, mitomycin C and cisplatin significantly reduced the tumor size or inhibited the growth of tumors in animal studies.[14] Other studies showed better responses and survival in combination treatment.[9] However, verification of the most effective drug is still controversial. For patients with advanced HCC receiving IAIC, we must take into account not only the tumor itself, but also the severity of hepatic dysfunction. The prognostic factors related to the response and survival, such as serum alpha-fetoprotein (AFP) level, gender, ascites, icterus, presence of main portal vein thrombosis, Child-Pugh classification, and tumor extension, have been evaluated in some reports,[15,16] but the results were controversial. In this study, we evaluated the therapeutic effects of IAIC using a combination of 5-FU, mitomycin C, cisplatin, and leucovorin in patients with unresectable advanced HCC and analyzed the prognostic factors.

METHODS

Patients and pretreatment evaluation

Patients with advanced HCC who were not eligible for surgical resection or other local treatment such as injection therapy, TAE, or thermal therapy because of multiple tumors in both lobes of the liver, bulky tumor mass, or tumor thrombosis of the main vessels were enrolled. The diagnosis of HCC was confirmed either by results of histological examinations or based on the finding of radiological evidence of hepatic mass with a serum AFP level exceeding 400 ng/mL. The exclusion criteria were serum bilirubin > 3 mg/dL, serum creatinine > 3 mg/dL, white cell count (WBC) < 2500/cumm, platelet count< 60,000/cumm, Eastern Cooperative Oncology Group (ECOG) performance status > 2, and distant metastasis. We recorded the gender and age at enrollment. The characteristics of tumors, including size, location, extension, thrombosis of main vessels and image type, were evaluated using ultrasound (US), computed tomogram (CT) scanning, and angiography, respectively. HCC were classified into nodular type, massive type, and diffuse type, by the images according to the classic gross classification proposed by Eggel in 1901. The degree of liver cirrhosis, serum AFP level, and other biochemical data, including Indocyanide green level, serum albumin, bilirubin, prothrombin time, and platelet count, were recorded before the initial treatment. Tumors were classified according to the staging system proposed by Okuda *et al*. in 1985.[1] The study was approved by the Department of Education and Medical Research Kaohsiung Veterans General Hospital. Written informed consent was obtained from all patients.

Intra-arterial infusion chemotherapy

The left subclavian artery was cannulated with a catheter and the tip of the catheter was placed in the proper hepatic artery under fluoroscopic guidance before each course of chemotherapy. To infuse anticancer agents selectively into the liver and prevent the chemotherapeutic agents from flowing into non-target vascular beds, the main trunk of the gastroduodenal artery was occluded by metallic coil routinely. Continuous infusion of 5000 units (5 cc) heparin solution daily was filled in the catheter for prevention of occlusion by thrombosis. Each course of treatment was 5 days. Cisplatin (10 mg/m^2) and mitomycin-C (2 mg/m^2) were dissolved in 50 mL isotonic sodium chloride solution which was infused for 20 to 30 minutes each time and continued for 5 days. In addition, 100 mg/m^2 of 5-Fluorouracil (5-FU), dissolved in 250 mL of isotonic sodium chloride solution, was administered for 24 hours by infusion pump for 5 days. Leucovorin (15

mg/m^2) was given daily to improve the efficacy of 5-FU during IAIC. The interval between 2 courses of treatment was 3 to 4 weeks.

Follow-up studies

Biochemical tests and serum AFP levels were checked 2 weeks after each session of IAIC. Each evaluated patient received at least 2 sessions. CT scan was done after every 2 sessions to evaluate the tumor responses. The product of the largest perpendicular diameter of the tumor was calculated, and the rate of tumor reduction was calculated according to the equation used by Ando *et al*.[10]

Tumor volume reduction rate (%)
= (Product before chemotherapy — Product after chemotherapy) × 100 / Product before chemotherapy

The maximum tumor reduction rate at the third month and/or the sixth month after chemotherapy was used to evaluate the efficacy. Objective response criteria were defined as follows: Complete response (CR) was defined as complete disappearance of all clinically and radiological evident tumor and no evidence of new lesions; partial response (PR) was defined as more than 50% reduction of tumor volume and no evidence of new lesions; minor response (MR) was defined as more than 25% reduction of tumor volume, but less than 50% reduction of tumor volume; no change (NC) was defined as a decrease or increase of less than 25% of tumor volume and no evidence of new lesions; progressive disease (PD) was defined as more than 25% increase of tumor volume or newly developed lesions. All responses had to have persisted for at least 4 weeks to be recorded. Survival period was defined as the intervals between the first treatment and death. The patients who received "adequate" chemotherapy (at least 2 courses of IAIC) were enrolled for analysis. Patients who received only 1 course of IAIC and were lost for follow-up or not suitable for further IAIC or who refused further IAIC were excluded for analysis due to no evaluation of tumor condition and "inadequate" chemotherapy having been given. According to the treatment responses, we performed univariate and multivariate analysis for all recorded parameters to find the prognostic factors.

Statistical analysis

The results were analyzed using Mann-Whitney test or Fisher's exact test. The relationship between the survival period and prognostic factors was evaluated by using the Kaplan-Meier method. Cox's proportional hazard model was used to estimate the relative risk adjusted for the other factors. A value of p less than 0.05 was regarded as significant.

RESULTS

Patient characteristics

Seventy-eight consecutive patients with unresectable advanced HCC who were admitted to the Kaohsiung Veterans General Hospital from June 1997 to May 2001 were enrolled in this study. Fifty-three patients received at least 2 courses of treatment and were evaluated. Twenty-five patients were excluded from this analysis. The reasons were as follows: 1) 10 patients were lost for follow-up and no further clinical condition could be evaluated (4 patients died within 1 month after IAIC and 6 patients refused further treatment); 2) 15 patients developed repeated bleeding from varices, hepatic encephalopathy, or hepatic failure and chemotherapy was prematurely terminated after 1 course of treatment (6 patients refused further IAIC and 9 patients were not suitable for further treatment due to cirrhotic complications). In addition, 12 of the 53 evaluable patients had received TAE as initial therapy, and IAIC was performed because of multiple recurrent tumors and tumor progression with tumor invasion or thrombi into the main portal vein and/or inferior vena cava. The baseline characteristics and clinical features of the 53 patients are summarized in Tables 1 and 2.

Response and survival

The data on the response to treatment are presented in Fig. 1. After at least 2 courses of chemotherapy, the overall response rate was 28.3%. We observed a CR in 5 patients (9.4%), a PR in 10 patients (18.9%), a MR in 5 patients (9.4%), NC in 11 patients (20.8%) and a PD in 22 patients (41.5%). The overall mean survival in the 53 evaluable patients was 13.2 months, and the 1- and 2-year survival rates were 36% and 18%, respectively.

The duration of survival showed a close relationship with the tumor regression. The mean survival of the 15 responders who achieved CR and PR was 24.6 months, whereas the mean survival of the non-responders, who achieved MR, NC and PD, was only 8.7 months ($p < 0.001$, Mann-Whitney test). The 1- and 2-year survivals of 15 responders were 70% and 57%, respectively, whereas only 2 of the 38 non-responders survived more than 18 months (Fig. 1). Seventy eight percent of non-responders died of repeated gastrointestinal bleeding, liver failure, or cachexia within 1 year of treatment. Tumor shrinkage was found in responders, but persistent viable

Table 1. Clinical characteristics in 53 evaluable patients with advanced hepatocellular carcinoma

Characteristics	
Number of cases	53
Age (mean ± SD; years)	60.7 ± 12.7
Gender	
Male	51
Female	2
Cirrhosis (Yes/No)	50/3
Child-Pugh classification	
A	45
B	5
C	3
Etiology	
HBV	23
HCV	16
Alcohol	2
HBV+HCV	2
Unknown	10
Salvage therapy after TAE	12

HBV = hepatitis B virus; HCV = hepatitis C virus; TAE = transcatheter arterial embolization.

Table 2. Radiological and pathologic features in 53 evaluable patients with advanced hepatocellular carcinoma

Type	
Massive	24
Multi-nodular	26
Diffuse	3
Location	
Bilateral lobe	32
Right lobe	17
Left lobe	4
Diagnostic criteria	
Histology confirmation	48
Images + AFP ≥ 400 ng/dL	5
Histological grading [a] (No = 48)	
Grade I	4
Grade II	34
Grade III	9
Grade IV	1
Okuda classification	
I	22
II	27
III	4
Thrombosis of main vessels	
Yes	14
No	39

[a] Edmondson and Steiner classification.

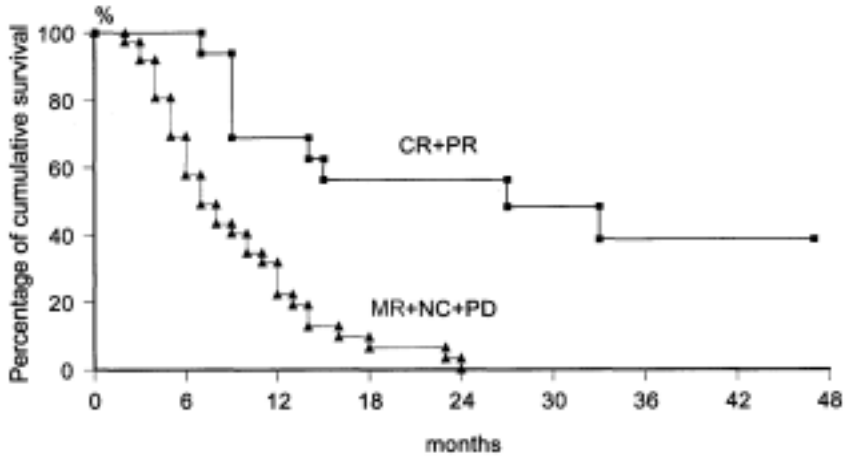

Fig. 1. The overall mean survival was 13.2 ± 11.2 months. Cumulative survival curves were seen in responders (CR+PR), with mean survival 24.6 ± 14.2 months, and nonresponders (MR+NC+PD), with mean survival 8.7 ± 5.3 months. The p value between these 2 groups was less than 0.001. CR = complete response; PR = partial response; MR = minor response; NC = no change; PD = progressive disease.

tumor could not be eradicated by chemotherapy only. Eleven of the 53 patients underwent additional local therapies (10 patients: TAE, 1 patient: percutaneous acetic acid injection). These 11 patients got more promising responses following additional local therapies.

We analyzed 15 parameters related to patients, tumors and the severity of hepatic dysfunction. They were recorded at enrollment, including age, gender, Indocyanide green level, serum AFP level, serum albumin, bilirubin, prothrombin time, platelet count, image type, tumor location, tumor extension, Child-Pugh classification, Okuda's stage, thrombosis of main vessel, and AFP reduction percentage after at least 2 courses of treatment. In univariate and multivariate analysis, AFP reduced by more than 50% following treatment and absence of main vessels thrombosis were the statistical significant factors for tumor response (Tables 3 and 4).

We classified the 53 patients into 2 groups according to their initial treatment. IAIC was the initial therapy in 41 of the 53 patients, and was the salvage therapy in 12 of the 53 patients. There were no statistical significantly differences in survival between these 2 groups (27.3 months and 25.9 months, $p = 0.79$).

Toxicity and catheter-related complications

There were 211 courses of IAIC performed in the 53 patients during 3 years. The treatment-related toxicity and complications are recorded respectively in Table 5. The toxic events were evaluated according to the National Cancer Institute (NCI) Common Toxicity Criteria gradation scale. Gastrointestinal side effects, such as anorexia, nausea or vomiting, were frequently encoun-

Table 3. Factors effecting the response of IAIC between responders (CR+PR) and non-responders (MR+NC+PD) at univariate analysis

Item	Responders	Non-responders	*p* value
ICG test (%)	21.0 ± 7.0	16.0 ± 9.5	NS
AFP (ng/mL)	10978 ± 22845	16378 ± 55218	NS
Albumin (mg/dL)	3.5 ± 0.6	3.6 ± 0.6	NS
Total bilirubin (mg/dL)	1.1 ± 0.5	1.2 ± 0.6	NS
Platelet ($\times 10^3$)/cumm	204 ± 110	196 ± 93	NS
Prothombin time (INR)	1.09 ± 0.20	1.07 ± 0.11	NS
Age (year)	64.9 ± 10.6	59.1 ± 13.3	NS
Gender (male/female)	13/2	38/0	NS
Main vessels thrombosis (Y/N)	1/14	13/25	0.038
Tumor volume < 50% (Y/N)	10/5	19/19	NS
Tumor location (Bil/Rt/Lt)	11/0/4	21/4/13	NS
Okuda classification (I+II/III)	14/1	35/3	NS
Image type (M/N+D)	9/6	15/23	NS
Child-Pugh classification (A/B+C)	13/2	32/6	NS
AFP reduction > 50% after treatment (Y/N)	11/4	6/32	0.001

Data was analyzed by Mann-Whitney test & Fisher's exact test; Value in Mean ± SD.
AFP = α-fetoprotein; Bil = bilateral; CR = complete response; D = diffuse type; ICG test = Indocyanide green test; Lt = left; M = massive type; MR = minor response; N = multi-nodular type; NC = no change; NS = not significant; PD = progressive disease; PR = partial response; Rt = right.

Table 4. Multivariate analysis of prognostic factors in patients receiving IAIC according to treatment response, using Cox's proportional hazard model

Factors	*f* value	*p* value	Favorable Factor	Unfavorable factor	Relative risk
Thrombosis of main vessels	5.77	0.016	Absence	Presence	2.95
AFP reduction > 50% following treatment	3.98	0.046	Yes	No	2.17

Table 5. Adverse effects of IAIC in 211 courses of chemotherapy in 53 evaluable patients (N = 211)

	NCI* Common Toxicity Criteria grade					
Toxicity	0	1	2	3	4	Percentage
Leukopenia	178	20	9	3	1	15.6%
Anorexia	119	57	25	10	0	43.6%
Diarrhea	184	4	19	4	0	12.7%
Vomiting	114	68	21	8	0	46.0%
Liver dysfunction	205	-	5	1	0	2.8%
Infection	210	0	0	0	1	0.5%
Creatinine elevation	189	12	10	0	0	10.4%

* NCI = National Cancer Institute; Percentage = Percentage of Grade 1-4.

tered, which showed good response to intravenous antiemetic drugs, such as metoclopramide. Hematological toxicities such as leukopenia and thrombocytopenia, as well as liver and renal function impairment occurred occasionally and recovered spontaneously without specific treatment about 1 to 2 weeks after treatment in most of the patients. However, 1 patient died of septic shock with severe leukopenia 1 week after IAIC treatment. None of our patients developed thrombosis of hepatic artery or infusion catheter during therapy. In addition, 1 patient developed a large hematoma with fistula formation over the left upper chest wall because of poor compression of the puncture site; the patient received emergent angiography and stenting for closure of the fistula.

DISCUSSION

Because of the progress in diagnostic tools such as CT scan, ultrasonography, and magnetic resonance imaging, many patients with HCC can be found at earlier stage and receive more effective treatments, such as operation, percutaneous injection therapy, and TAE. However, there are still many patients with unresectable advanced HCC receiving only conservative treatment due to poor liver reserve, bulky tumor mass, and thrombosis of main vessels. Systemic chemotherapy of HCC had limited value in clinical practice. The patients gained more toxicity due to chemotherapeutic agents than benefits. The prognosis of untreated HCC was very poor.[1] IAIC offers effective treatments with less systemic chemotherapeutic toxicity for patients with unresectable HCC because of the increase in local concentration of chemotherapeutic agents in the liver.

Hepatic arterial infusion of various anti-cancer drugs has been tried with monotherapy or combination therapy to treat HCC *in vivo* or *in vitro* studies, including doxorubicin, mitomycin C, 5-FU, cisplatin, and methotrexate.[9,12-14,20] Clinical responses in terms of either a decrease in AFP levels or a radiologically proven regression of tumors have been reported in some trials. Mitomycin C showed preferential activation of cytotoxic metabolites at the hypoxic tumor cells and enterohepatic re-circulation.[13] 5-FU has been reported to act as an anticancer agent using 2 mechanisms, (1) the inhibition of DNA synthesis by inactivation of thymidylate synthase (TS), and (2) the occurrence of abnormal metabolism of RNA. 5-FU is a time-dependent drug for anticancer effects and has been reported to show a stronger cell-killing effect *in vitro* when given as prolonged infusion.[14] Prolonged continuous infusion is becoming the standard method for intravenous infusion chemotherapy. Combinations of 5-FU with a modulator can amplify the anticancer effects of 5-FU through biochemical modulation. 5-FU and cisplatin,[17] 5-FU and leucovorin,[2] and 5-FU with interferon[12] have been tried for HCC recently. Cisplatin is an anticancer agent which works using coordinated bonds with 2 guanine bases on the DNA strand and amplifies the cell-killing effects of 5-FU by increasing its potential to produce the complex of 5-fluoro-2'-deoxyuridine 5'-monophosphate and TS. Therefore, we chose mitomycin C, cisplatin, prolonged continuous infusion of low dose 5-FU, and leucovorin as the modulator of 5-FU for patients with advanced HCC.

In our study, the patients with response survived longer than those with little response or progressive disease ($p < 0.001$). IAIC treatments achieved good results in patients with advanced HCC. The tumor regression

showed a close relation with the duration of survival as reported by Nakamura *et al*. in 1992.[18] In evaluating the efficacy of the treatment and analyzing the prognostic factors in patients with advanced HCC, we must take into account not only the tumor itself but also the patient's hepatic reserve and previous treatment such as TAE.[16] We analyzed the prognostic factors including previous cancer treatment, thrombosis of main vessels, severity of hepatic dysfunction, tumor size, initial enrolled serum AFP values, and percentage of AFP change following IAIC treatment. At multivariate analysis, absence of main vessel thrombosis and serum AFP level reduction of more than 50% following treatment were the predictors of tumor response. Even for patients with Child's C, good long-term survival and response were obtained when absence of thrombosis of main vessels and lower serum AFP followed treatment. Measurement of the percentage of tumor volume change using CT scanning is a very good method to evaluate the response at the end of each IAIC, but the cost is expensive. Therefore, we suggest using the percentage of serum AFP change 2 weeks after IAIC to predict the response before images are available. Besides the serum AFP and thrombosis of main portal vein, other prognostic factors, such as tumor type[15] and Okuda classification,[16] did not show any significant differences between the responders and non-responders in our study. Although severity of hepatic dysfunction was important prognostic factor in other reports,[15,16,21] it was not significant factor in our study.

Jang *et al*.[24] reported that multimodal combination therapy using transarterial infusion of epirubicin and cisplatin, systemic infusion of 5-FU and additional PEI for unresectable HCC had higher objective tumor response than traditional TACE (transcatheter arterial chemo-embolization). Portal vein thrombosis and tumor response were the 2 independent factors for survival. Our results were comparable with theirs. In this study, they enrolled patients who underwent at least 2 cycles of transarterial chemotherapy for analysis. For the patients receiving only 1 course of treatment, inadequate chemotherapy was considered and was excluded from analysis. Our study had the same point of view: IAIC should not be considered a regional therapy like TAE or PEI only. It should be considered as series of treatments, just like systemic chemotherapy. Usually, 4 to 6 cycles of IAIC were considered as complete courses. In addition, low cumulative doses of drugs were given within 1 cycle of IAIC. Many other factors, not only the 1 course of IAIC, would interfere with the clinical condition of patients with advanced HCC. We excluded these patients from analysis to prevent the risk of bias.

Recently, selective arterial chemotherapy using implanted reservoirs was utilized for treatment of advanced stages of HCC. Although survival periods showed no definite difference between implanted reservoirs and conventional transcatheter arterial infusion, the advantages of reservoirs over traditional transcatheter arterial infusion appear to be the convenience of frequent infusion of anticancer agents, treatment in outpatient clinics and lower hospital cost.[7] However, complications related to catheters, such as occlusion, tip dislocation, and catheter-induced infections, occur occasionally. The catheter infections and occlusion may be lethal complications to debilitated patients with advanced hepatocellular carcinoma. In addition, some patients cannot receive IAIC or TAE anymore due to occluded common hepatic artery. The catheter cannot be removed by medical methods, except for surgery. Both patency of the implanted catheter and combined therapy after occlusion are important for improving the efficacy of IAIC in these patients.[22,23] In our study, patients had to repeatedly receive arterial catheterization for each course of treatment. Because the catheter was lodged during treatment and removed after treatment, it was easy to keep the patency of the catheter during treatment, and lessen the possibility of catheter infection.

TAE is generally considered an effective form of palliative treatment in patients with inoperable HCC. Recannalization of the embolized arteries and/or presence of extra- and intrahepatic arterial collaterals may result in recurrence of the tumor.[19] In addition, if multiple recurrences of tumors and the presence of main portal vein thrombosis occur in patients receiving TAE, they are usually not suitable for further treatment. IAIC was beneficial for the patients with tumor recurrence after TAE, especially the Child's A and B patients without main portal vein thrombosis.[16] In our study, 12 patients had received TAE as initial treatment and received IAIC as the salvage therapy because of multiple recurrent tu-

mors and/or thrombosis of main vessels. No definite statistical differences in survivals were seen in our study between the group of IAIC as salvage therapy for recurrent HCC after TAE and the group of IAIC as initial therapy. These results may remind us that IAIC is still a useful approach for the treatment of advanced HCC in patients after TAE with damaged feeding artery of tumor.

In addition, effective local therapies other than surgical resection, such as TAE and percutaneous injection therapy, have been widely used for decades because of the anatomical characteristics of HCC. During our present study, if the tumor shrinkage effect was achieved by IAIC, some viable tumors were a bothersome problem because of anti-cancer drug-resistant tumor cells and formation of collateral circulation in viable tumors. Additional local therapy may be capable of inducing marked necrosis of viable tumors. In our studies, when we combined local therapies in patients with PR and MR, more extensive necrosis of the tumors was achieved and the prognoses were relatively good.

In conclusion, continuous intra-arterial infusion chemotherapy with cisplatin, mitomycin-C, leucovorin, and 5-FU was effective for patients with severe advanced HCC. The main goal for treatment is not only complete cure of tumor, but also control of tumor progression and improvement of the quality of life. Absence of thrombosis of main vessels and serum AFP level reduction percentage > 50% following treatment were the good predictors for treatment response. If tumor shrinkage was achieved and viable tumor was present following IAIC, additional combination modalities, such as TAE and percutaneous injection therapy, might be helpful.

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