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Induction of Long-Term Remission in Advanced Hepatocellular Carcinoma With Percutaneous Isolated Liver Chemoperfusion

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Objective

The aim of this study was to report the long-term results of percutaneous isolated liver chemoperfusion with hepatic venous isolation and charcoal hemoperfusion (HVI-CHP) in patients with multiple advanced hepatocellular carcinoma (HCC).

Summary Background Data

The results of conventional chemotherapy including regional and systemic chemotherapy in patients with HCC remain dismal, and long-term survivors after treatment are rare among patients with multiple advanced HCC. In an effort to improve this situation, we previously developed a novel system of percutaneous isolated liver chemoperfusion with HVI-CHP.

Methods

Doxorubicin (60 to 150 mg/m^2) was administered via the hepatic artery, under conditions of extracorporeal drug elimination by HVI-CHP in 28 consecutive patients with advanced HCC (39 total treatments). Hepatic venous isolation and charcoal hemoperfusion was accomplished mainly by the single catheter technique using a newly developed 4-lumen-balloon catheter, which was used to isolate and capture total hepatic venous outflow and, at the same time, to direct the filtered blood to the right atrium.

Results

Complete remission was achieved in five patients, of which four received repeated treatments (two or three times). Although 1 of 5 patients with complete remission died of pulmonary metastases at 8 months, the other 4 remain healthy and free of disease at 20, 24, 27, and 42 months after the first treatment. Partial responses were observed in 12 patients. Duration of response in responders (complete and partial) with repeated treatments was significantly longer than that with a single treatment ($p = 0.01$). The overall survival rate by the Kaplan-Meier method was 39.7% at 5 years. The treatments were well-tolerated, and the primary side effects were mild to moderate chemical hepatitis and reversible myelosuppression.

Conclusions

The results suggest that percutaneous isolated liver chemoperfusion with HVI-CHP is an effective palliative treatment in the majority of patients and yields long-term complete remission in some patients with multiple advanced HCC.

Hepatocellular carcinoma (HCC) is one of the most common malignant diseases in the Far East and is almost always associated with chronic hepatitis B or C infection.[1,2] Surgical resection remains the mainstay for treatment for HCC and provides the only consistent long-term tumor-free survival. However, because of the underlying cirrhosis or the extent of liver involvement, surgical resection is possible in less than 30% of patients with HCC.[3] For the majority of patients who are not amenable to surgical resection, a variety of targeted or local therapies have been used primarily for disease palliation. These include transcatheter arterial chemoembolization,[4] percutaneous alcohol tumoral injection,[5] and standard intraarterial chemotherapy.[6–8] However, the results of these therapeutic approaches are disappoint-

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ing, especially in patients with extensive tumor involvement of the liver. Therefore, there is a growing necessity for the development of effective alternative treatments for patients with expected survival of only a few weeks or months after diagnosis.

We previously developed a novel system combining complete hepatic venous isolation and charcoal hemoperfusion (HVI-CHP) for delivering dose-intensive chemotherapy only to the liver.[9–11] In a phase I study of HVI-CHP in 15 advanced HCC patients that began in 1989, we found that the hepatic and systemic maximum tolerated dose of doxorubicin when given by hepatic arterial infusion (HAI) was approximately 150 mg/m^2/treatment, and that the tumor response rate reached 64%.[10] We have now expanded our experience with this treatment to 28 HCC patients. The majority had Stage IV-A disease with multiple bilobar lesions, for which no effective therapy otherwise exists. The purposes of this study were to report the effectiveness of percutaneous isolated liver chemoperfusion with HVI-CHP in long-term control of multiple HCC and its impact on survival of such patients.

PATIENTS AND METHODS

Patients

From May 1989 to June 1996, 28 adult patients with advanced HCC were treated by HAI of high-dose doxorubicin under HVI-CHP. Follow-up was complete through December 1996. Two major clinical situations were identified in this study: multiple intrahepatic recurrence after hepatectomy in 8 patients and highly advanced disease at presentation in 20 patients, 5 of whom had a distinctive main tumor accompanied by multiple satellite lesions. These 5 patients were first treated with cytoreduction hepatectomy for the main tumor and subsequently with dose-intensive chemotherapy with HVI-CHP for satellite lesions 3 to 12 weeks after hepatectomy (4 lobectomies and 1 segmentectomy). All but 1 (stage III) of the 28 patients had stage IV-A disease at entry. The staging of HCC was performed according to the International Union Against Cancer macroscopic staging criteria for primary malignant liver cancer.[12] The diagnosis was confirmed histologically in 24 patients. In the remaining 4 patients the diagnosis was based on clinical data including considerably elevated levels of serum alpha-fetoprotein (AFP: 909 ng/mL, 12,500 ng/mL, 51,600 ng/mL, and 450,000 ng/mL, respectively), the proteins induced by vitamin K absence or antagonist II (PIVKA-II), and the characteristic tumor circulation on hepatic angiography.

Patients were eligible for study if they had no clinical or radiographic evidence of extrahepatic disease and no preexisting heart disease. Additional criteria for entry included a Karnofsky score of more than 40%, a serum bilirubin level of less than 2.5 mg/dL, a 15-minute indocyanine green retention rate of less than 35%, a serum aspartate aminotransferase (AST) concentration of less than 300 IU/L, and a platelet count of more than 50,000/mm^3. Informed consent was obtained from all patients before treatments. The study protocol was approved by the institutional review board of the Kobe University Hospital for human investigations.

The patients' characteristics are summarized in Table 1. Data from 15 of these 28 patients were presented in our previous report.[10] The age range was 34 to 78 (mean, 57.3), 25 were men, and all patients had either cirrhosis (68%) or chronic hepatitis (32%). Eleven patients (39%) were hepatitis B surface antigen positive, and hepatitis C virus antibody alone was detected in the sera of 14 other patients. The macroscopic features of HCC were diffused in 1 patient (4%), massive in 4 (14%), and nodular in 23 (82%)., All patients had multiple intrahepatic metastases of more than five tumor foci. Main tumor diameter ranged from 3 to 20 cm (mean, 7.4 cm). Of the 28 patients, 17 (61%) had macroscopic vascular invasion to the portal vein (VP); 7 had VP in the portal trunk or first portal branch (VP3), 5 in second portal branch (VP2), and 5 in third or more distant portal branch (VP1). Vascular invasion to the major hepatic veins and the inferior vena cava was demonstrated in 10 patients by intraoperative venographies performed under hepatic venous isolation.

Percutaneous Isolated Liver Chemoperfusion with HVI-CHP

All patients underwent HVI-CHP under general anesthesia in the operating room. In the first 15 patients, HVI-CHP was performed mainly by the double-balloon technique.[10] After the introduction of a specially designed 4-lumen · 2-balloon (4L · 2B) catheter (24F, 26F), the subsequent 13 patients underwent HVI-CHP using the single catheter technique (Fig. 1), which has been described in detail in our recent paper.[13] In brief, after intravenous infusion of heparin (100 U/kg), a 4L · 2B catheter was placed in the femoral vein through a small cut-down incision on the groin and advanced until the cephalad balloon was at the supra-hepatic inferior vena cava. After initiating blood bypass, the cephalad and caudal balloons were sequentially inflated using two accessory lumina to isolate hepatic venous outflow. The isolated hepatic venous blood was captured through three fenestrations between the balloons which were present on one major lumen of a 4L · 2B catheter and pumped via the extracorporeal system containing CHP filters directly to the right atrium through the other major lumen of the catheter. After ascertaining blood pressure stability in the patient, continuous HAI of doxorubicin was administered. In all patients, HVI-CHP was maintained for at least 10 minutes after the end of HAI. After completion, the 4L · 2B catheter was removed and the femoral vein was repaired as described previously.[13]

Fifteen early patients had a single treatment. In the 13 recent patients treated with the single catheter technique, repeated treatment was assigned, whenever possible, at in-

Table 1. PATIENT CHARACTERISTICS AT ENTRY

Characteristic	Number (%) of Patients
Background factors	
Sex	
Male	25 (89)
Female	3 (11)
Age (yr)*	
<60	15 (54)
≥60	13 (46)
Child's classification	
A	25 (89)
B	2 (7)
C	1 (4)
HBsAG	
Negative	17 (61)
Positive	11 (39)
Anti-HCV	
Negative	11 (39)
Positive	14 (50)
Undetermined	3 11)
Underlying liver disease	
None	0 (0)
Chronic hepatitis	9 (32)
Liver cirrhosis	19 (68)
Serum AST concentration (IU/L)	
<100	20 (71)
100–200	7 (25)
200–300	1 (4)
ICGR 15 (%)	
<10	8 (29)
10–20	13 (46)
20–35	7 (25)
Tumor factors	
Macroscopic tumor type	
Nodular	23 (82)
Massive	4 (14)
Diffuse	1 (4)
Maximum tumor diameter (cm)	
<5	13 (46)
5–10	8 (29)
>10	7 (25)
Portal vein invasion†	
VP_0	11 (39)
VP_1	5 (18)
$VP_{2,3}$	12 (43)
Serum AFP (ng/mL)	
<500	18 (64)
500–1000	1 (4)
>1000	9 (32)

HBsAG = Hepatitis B surface antigen; HCV = Hepatitis C virus; AST = aspartate aminotransferase; ICGR = indocyanine green retention rate; AFP = α-fetoprotein.
* Mean age 57 years; range, 34–78.
† Portal vein invasion: VP_0, present in third or more distant portal branch; VP_2, in second portal branch; VP_3, in portal trunk or first portal branch.

tervals of 3 to 5 weeks. Treatment was not given in five patients. Because of serious damage to the operation facilities caused by an earthquake on January 17, 1995 two patients were not treated. There were technical problems with HAI catheter placement in another two patients and one patient refused treatment. Consequently, 8 of the 13 patients underwent repeated treatments (range, 2 to 4 times) according to the planned course of treatment. In total, 28 patients underwent 39 treatments in this study.

The first dose of doxorubicin averaged 110 mg/m^2 (range, 100 to 150 mg/m^2). For repeated treatment, the dose was reduced to 90 mg/m^2 if the pretreatment leukocyte counts were less than 4,000/mm^3 and to 60 mg/m^2 if the values were less than 3,000/mm^3. In patients with the values below 2,500/mm^3, further treatment was withdrawn. Doxorubicin was diluted with 50 to 200 mL of normal saline solution and was administered as a 5 to 20-minute continuous HAI.

Maintenance Therapy

Among the 17 patients who responded to the treatment, 9 received additional HAI chemotherapy starting 3 to 8 weeks after the last HVI-CHP, by use of the implantable catheter system. In all 9 patients, depending on the side effects, low-dose epirubicin (20 to 50 mg/body) was intermittently given every 2 weeks. The number of infusions ranged from 3 to 13 times.

The reasons for exclusion of the remaining eight responders from maintenance therapy were refusal to the placement

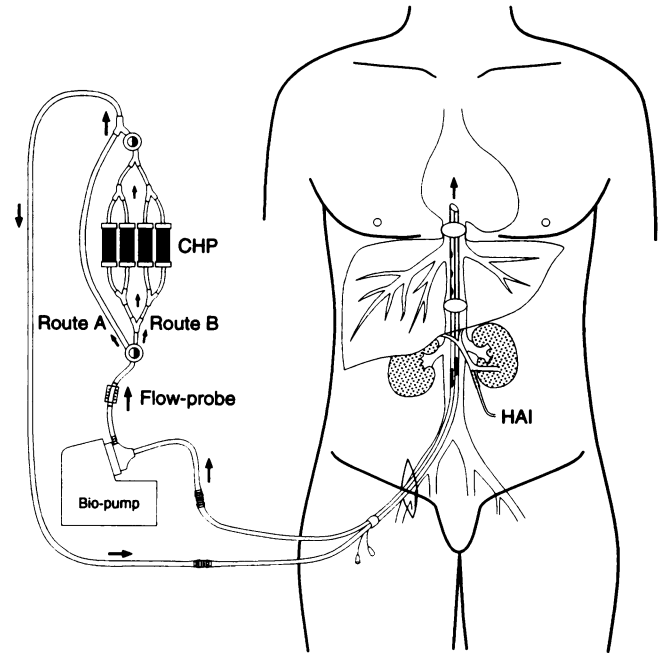

Figure 1. Schematic representation of single catheter technique for percutaneous isolated liver chemoperfusion under hepatic venous isolation and charcoal hemoperfusion. A 4-lumen • 2-balloon catheter was introduced into the inferior vena cava via the femoral vein. Hepatic venous blood was isolated by balloon inflations and captured through three fenestrations between the balloons. After ascertaining blood pressure stability in the patient, hepatic venous blood was directed from the filter-excluded shunt (Route A) to the filter-containing route (Route B), and hepatic arterial infusion (HAI) of a chemotherapeutic agent was initiated.

Table 2. TUMOR RESPONSE AND RESPONSE DURATION

	Response Category					Median Duration of Response in Responders (range) (mo)
	CR	PR	SD	PD	NE	
Single treatment (n = 20)	1	9	6	3	1	6 (2–41)
	53%					
Repeated treatments (n = 8)	4	3	1	0	0	23† (7–25)
	88%*					
Overall (n = 28)	5	12	7	3	1	10 (2–41)
	63%					

CR = complete remission; PR = partial response; SD = stable disease; PD = progressive disease; NE = not evaluable.
* p = 0.09 *vs.* single treatment group by the chi square test.
† p = 0.01 *vs.* single treatment group by the log-rank test.

of the implantable catheter system (3 patients), wound infection or catheter dislocation after placement (3 patients), earthquake damage (1), and other technical problems (1).

Evaluation of Tumor Response

Postoperative examinations and follow-up studies were performed in accordance with the protocol described previously.[10] Serum AFP and PIVKA-II levels were determined monthly during the first 12 months, and thereafter every 3 months. The tumor responses were evaluated by comparing the pretreatment computerized tomographic (CT) findings and serum AFP and PIVKA-II levels with those obtained 1 month after treatment and at 1 to 3-month intervals thereafter.

Complete remission was defined as the disappearance of all measurable hepatic tumors. A partial response was defined as a 4-week reduction of more than 50% in the sum of the products of the cross-sectional diameters of all measurable lesions and the absence of new lesions. Stable disease was defined as a reduction of less than 50% or an increase of less than 25% in the sum of the products of the cross-sectional diameters of all measurable lesions and no clear-cut regression or progression of disease for at least 8 weeks. Progressive disease or relapse was defined as an increase in tumor size.

Statistical Analysis

Categorical data were compared by the chi-square test or by Fisher's exact test.[14] Duration of response (complete and partial response) was measured from the date of response recognition until the time of progression of disease, relapse, death, or the date the patient was last known to be in remission. Survival was measured from the date of the first HVI-CHP treatment until the date of death or most recent follow-up visit. Survival rate and duration of response were calculated by the Kaplan-Meier method,[15] and comparisons were performed with the log-rank test.[16] The data of 1 patient who died 1 month after treatment and was unevaluable for tumor response was included in the overall survival rate. All tests of significance were two-tailed, and a p value of less than 0.05 was considered to indicate statistical significance.

RESULTS

All but one of the 28 patients were evaluable for tumor response (Table 2). Two patients died early — one of necrotizing pancreatitis and the other of hepatic arterial thrombosis — and both deaths were directly related to the HAI catheter. One of these two patients died before the response to treatment could be assessed. Seventeen of the remaining 27 patients responded to treatment under HVI-CHP (5 had a complete remission and 12 had a partial response: response rate, 63%). The median duration of response (complete and partial) was 10 months (range, 2 to 41 months). The duration of response in responding patients with repeated treatments was significantly longer than in those with a single treatment (p = 0.01).

The mean follow-up has now been 19.0 months (range, 1 to 68 months). Of the 17 deaths excluding the 2 early deaths described above, 1 patient died from variceal hemorrhage, and the remaining 14 patients died from tumor progression. The median length of follow-up for the living 11 patients was 25 months (range, 8 to 68 months). The median survival of all 28 patients was 16.0 months. The 1-year, 3-year, and 5-year survival rates of all patients were 67.5%, 39.7%, and 39.7%, respectively (Fig. 2). Nine of the 17 responders are still alive and well 8, 11, 20, 24, 25, 27, 28, and 68 months after treatment, and 6 are still in either partial or complete remission.

Table 3 summarizes data on five patients with complete remission. Four of these five patients underwent repeated

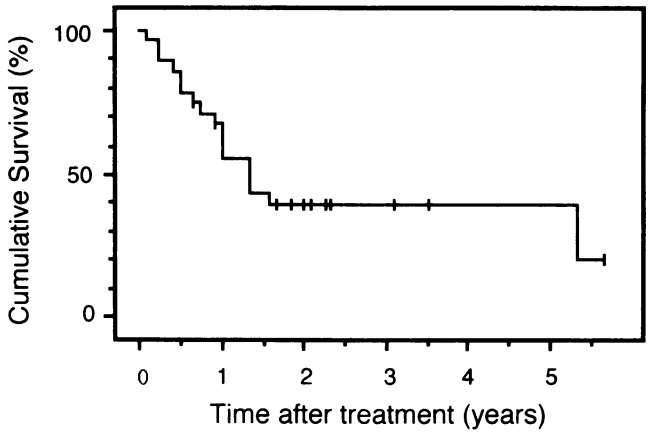

Figure 2. Survival curve for all 28 patients treated with percutaneous isolated liver chemoperfusion with HVI-CHP.

treatments (2 or 3 times in total). Although 1 woman died of pulmonary metastases at 8 months, the other 4 remain well and free of disease with completely normalized values of serum tumor markers (AFP and/or PIVKA-II), at present, 20, 24, 27, and 42 months after the first treatment. Figure 3 shows hepatic angiograms before and 10 months after the first HVI-CHP in a 56-year-old woman, demonstrating complete disappearance of all hepatic tumors. Table 4 summarizes pretreatment factors according to tumor response. No factors predictive of a tumor response were clearly identified in this study. However, our data suggested that patients who have massive tumors and are under age 60 may be good candidates for this dose-intensive chemotherapy.

Complications and toxicities are shown in Table 5. Except for two early deaths, no deaths in this study could be directly or indirectly ascribed to treatment. Chemical hepatitis, as defined by elevations of serum AST levels to more than twice the baseline values, although transient, occurred in most patients. All patients had some degree of leukopenia, but spontaneously recovered without use of granulocyte stimulating agents. Mild to moderate hair loss was observed in 43% of the patients. Leukopenia and hair loss were, in the main, more prominent and frequent after repeated treatments of HVI-CHP. Although gastroduodenal ulcer developed in 2 of 15 early patients, none of the 13 most recent patients with coil embolization of the right gastric artery in addition to the gastroduodenal artery had signs and symptoms of ulcers. It should also be noted that the incidence of hemolysis and hematuria was markedly reduced in patients treated with the single catheter technique of HVI-CHP, in which CHP filters were placed distal to a centrifugal pump in the extracorporeal circuit.

DISCUSSION

In this report, we present the results of percutaneous isolated liver chemoperfusion with HVI-CHP in 28 consec-

Table 3. SUMMARY OF DATA ON FIVE PATIENTS WITH COMPLETE REMISSION

	Unique Patient Number				
	14	**17**	**21**	**24**	**26**
Age at entry (yr)	44	56	45	57	43
Sex	M	F	M	M	F
Underlying liver disease	CH	LC	CH	CH	CH
Viral status	HBV	HBV	HBV	HCV	HBV
ICGR 15	11.7	11.4	10.6	11.3	4.7
Macroscopic tumor type	Nodular	Nodular	Nodular	Nodular	Massive
Maximum tumor diameter (cm)	4	8	13	20	13
Number of doxorubicin HAI under HVI-CHP and dose (mg/m^2)	1 110	2 100,100	2 100,90	2 100,100	3 100,90,60
AFP (ng/mL)					
Pre	12,500	95	59	244	50,901
Post (3 mo)	6	4	4	2	4296
Latest (time from 1st HVI-CHP)	4 (41 mo)	5 (26 mo)	4 (24 mo)	3 (19 mo)	18,070 (6 mo)
PIVKA-II					
Pre	ND	0.165	12.0	<0.06	ND
Post (3 mo)		<0.06	<0.06	<0.06	
Latest (time from 1st HIV-CHP)		<0.06 (26 mo)	<0.06 (24 mo)	<0.06 (19 mo)	
Current status	NED at 42 mo	NED at 27 mo	NED at 24 mo	NED at 20 mo	DOD at 8 mo
Cause of death	—	—	—	—	Lung metastases

HBV = hepatitis B virus; HCV = hepatitis C virus; ND = not determined; HAI = hepatic arterial infusion; NED = no evidence of disease; DOD = dead of disease; AFP = α-fetoprotein.

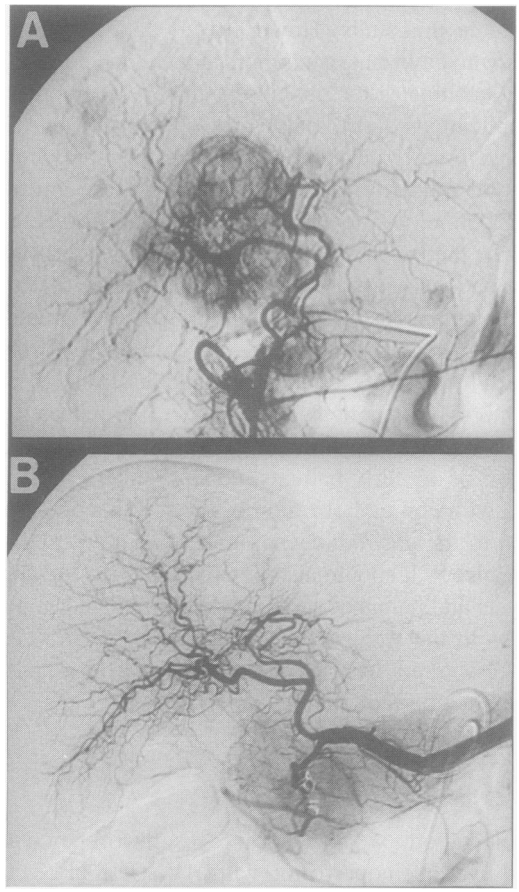

Figure 3. Select hepatic angiogram of Unique Patient No. 17 with multiple bilobar hepatocellular carcinoma. (A) before and (B) 10 months after the first treatment, showing no evidence of tumor recurrence. She remains well and free of disease with normalized serum AFP and PIVKA-II levels 27 months after treatment.

utive patients with advanced HCC who met predefined criteria. These patients had clinical features generally considered to be associated with a poor prognosis, including multiple bilobar metastases (stage IV, 27 patients), a greater incidence of vascular invasion to the portal vein (17 patients), and main tumor diameter of greater than 5 cm (15 patients). Thus, the majority of patients were unsuited for transcatheter arterial embolization. In previous multicenter trials, the median duration of survival for unresectable HCC patients selected for chemotherapy was only approximately 6 months.[17] Other investigators also reported that patients with unresectable HCC have a dismal outcome regardless of therapy, with the median duration of survival ranging from 3.5 to 14.5 months.[6–8,18]

Overall survival rates in this study were 68% at 1 year and 40% at 5 years. The median survival rate of all 28 patients was approximately 16 months. Two early patients died as a result of treatment. Excluding these 2 patients, we found an excellent 5-year survival rate of 43%. Of additional note, 4 of the 5 patients with complete remission are still free of disease with completely normalized serum AFP and PIVKA-II levels and are well at 20 to 42 months after the first treatment currently without maintenance therapy. Once patients with HCC develop extensive intrahepatic metastases, as represented in Fig. 3, the outlook has been poor, and long-term remissions have rarely been reported in such patients with any conventional therapy. Although there are a limited number of patients in this series, it seems clear that this approach can provide long-term complete remission for some patients with otherwise intractable disease.

The refractoriness of HCC to chemotherapy has been explained by tumor heterogeneity,[19] the inducible overexpression of the multidrug resistance gene,[20] and inherent resistance because of unexplained mechanisms. The HAI chemotherapy with cytotoxic agents appears to be partially successful in overcoming such drug resistance, with reported response rates of approximately 40%.[6,8] However, these responses are not usually long lasting. This study addressed two important questions concerning whether dose intensification of doxorubicin improves the response and survival rates for HCC patients and whether repeated treatments further expand the therapeutic index of this approach. First, of the 27 evaluable patients in this study, 17 responded to the treatment, with an overall response rate reaching 63%. The duration of response averaged 10 months. These data altogether suggest a significant tumoricidal impact of high-dose doxorubicin on less sensitive HCC. Furthermore, in 7 responding patients with repeated treatments, the median duration of response was 23 months, which was significantly longer than the duration in the 10 responding patients with single treatment. Notably, all but one of the seven

Table 4. PRETREATMENT FACTORS ACCORDING TO TUMOR RESPONSE

Parameter	Responders (n = 17) CR + PR (%)	Nonresponders (n = 10) SD + PD (%)	p
Age (yr)			
<60	11 (79)	3 (21)	0.08
≥60	6 (46)	7 (54)	
Underlying liver disease			
CH	6 (75)	2 (25)	0.40
LC	11 (58)	8 (42)	
ICGR 15 (%)			
<10	3 (43)	4 (57)	0.20
≥10	14 (70)	6 (30)	
Viral status			
HBsAG positive	6 (60)	4 (40)	0.66
Anti-HCV positive	10 (71)	4 (29)	
Unknown	1 (33)	2 (67)	
Tumor type			
Nodular	13 (59)	9 (41)	0.12
Massive	4 (100)	0 (0)	
Diffuse	0 (0)	1 (100)	
Main tumor diameter			
<5 cm	6 (50)	6 (50)	0.21
≥5 cm	11 (73)	4 (27)	
Portal vein invasion			
Negative	7 (64)	4 (36)	0.95
Positive	10 (63)	6 (37)	

Table 5. COMPLICATIONS AND TOXICITIES

Complications and Toxicities	Single Treatment (n = 20)	Repeated Treatments (n = 8)	Overall (n = 28)
HVI-CHP related			
Hemolysis/hematuria	14 (70)	2 (25)	16 (57)
Thrombocytopenia $<50 \times 10^3/mm^3$	3 (15)	2 (25)	5 (18)
HAI catheter related			
Necrotizing pancreatitis	1 (5)	0 (0)	1 (4)
Hepatic arterial thrombosis	1 (5)	0 (0)	1 (4)
Drug toxicities			
Chemical hepatitis*	15 (75)	5 (63)	20 (71)
Peak AST level			
<300	10	3	13
300–600 IU/L	2	2	4
600–900 IU/L	1	0	1
>900 IU/L	2	0	2
Sclerosing cholangitis	0 (0)	0 (0)	0 (0)
Leukopenia < $2000/mm^3$	9 (45)	6 (75)	15 (54)
Hair loss	7 (35)	5 (63)	12 (43)
Nausea/vomiting	3 (15)	1 (13)	4 (14)
Gastroduodenal ulcer	2 (10)	0 (0)	2 (7)
Cardiac toxicity	0 (0)	0 (0)	0 (0)

Values in parentheses are percentages.
* Chemical hepatitis was defined as elevations of serum AST levels after treatment to more than twice the baseline values.

responding patients with repeated treatments are alive and well, and five are still in remission. Thus, the role of repeated treatments in inducing a long-term remission is becoming clear. We recommend repeated application of this therapy as part of an initial inductive therapy, thereby providing the potential to improve the durability of remission, especially for patients who are responsive to the first treatment.

The surprisingly favorable outcome of percutaneous isolated liver chemoperfusion with HVI-CHP appears to be associated, at least in part, with a significantly reduced liver blood flow. According to our clinical findings,[10,11,13] hepatic venous flow rate ranged from 450 to 720 mL/minute during HVI-CHP, which appears to be approximately one-half to one-third of the physiologic liver blood flow rate. It is well known that liver blood flow is one major parameter that affects the pharmacokinetic advantages of HAI chemotherapy.[21] Therefore, we consider that the phenomenon of reduced liver blood flow under hepatic venous isolation may be beneficial in augmenting the impact of dose-intensity of cytotoxic agents on tumor cells.

However, reduced liver blood flow may increase the risk of endothelial injury to the hepatic artery, enhancing exposure to greater concentrations of doxorubicin. For this reason, in our recent series the drug was diluted at a concentration less than 1 mg/mL and was administered over 20 minutes. Based on the angiographic findings, we feel that these modifications contributed to the reduction of hepatic arterial injury associated with high-dose doxorubicin infusion.

An important issue not directly addressed by this study is to identify patients with HCC who are most likely to benefit from this dose-intensive chemotherapy. Unfortunately, the present series of patients is too small to justify any statement to be made in this respect. However, it is interesting that 4 of 5 patients with complete remission had chronic hepatitis B and were less than 60 years of age. This impression should be clarified by further studies.

In conclusion, this study demonstrated that percutaneous isolated liver chemoperfusion with HVI-CHP has tolerable local and systemic toxicities and a greater efficacy in the majority of patients with advanced HCC. Furthermore, the results suggest a role for repeated treatments in the induction of long-term remission in a subset of patients who are otherwise intractable but still responsive to dose-intensive chemotherapy.

References

1. Colombo M. Hepatocellular carcinoma. J Hepatol 1992;15:225–236.
2. Tsukuma H, Hiyama T, Tanaka S, et al. Risk factors for hepatocellular carcinoma among patients with chronic liver disease. N Engl J Med 1993;328:1797–1801.
3. The Liver Cancer Study Group of Japan. Primary liver cancer in Japan: Sixth report. Cancer 1987;60:1400–1411.
4. Yamada R, Sato M, Kawabata M, et al. Hepatic artery embolism in 120 patients with unresectable hepatoma. Radiology 1983;148:397–401.
5. Livraghi T, Bolondi L, Lazzaroni S, et al. Percutaneous ethanol injection in the treatment of hepatocellular carcinoma in cirrhosis. Cancer 1992;69:925–929.
6. Doci R, Bignami P, Bozzetti F, et al. Intrahepatic chemotherapy for unresectable hepatocellular carcinoma. Cancer 1988;61:1983–1987.
7. O'connell MJ, Hahn RG, Rubin J, et al. Chemotherapy of malignant hepatomas with sequential intraarterial doxorubicin and systemic 5-fluorouracil and semustine. Cancer 1988;62:1041–1043.
8. Atiq OT, Kemeny N, Niedzwiecki D, Botet J. Treatment of unresectable primary liver cancer with intrahepatic fluorodeoxyuridine and mitomycin C through an implanted pump. Cancer 1992;69:920–924.
9. Ku Y, Saitoh M, Nishiyama H, et al. Extracorporeal removal of anticancer drugs in hepatic artery infusion: the effect of direct hemoperfusion combined with venovenous bypass. Surgery 1990;107:273–281.
10. Ku Y, Fukumoto T, Iwasaki T, et al. Clinical pilot study on high-dose intraarterial chemotherapy with direct hemoperfusion under hepatic venous isolation in patients with advanced hepatocellular carcinoma. Surgery 1995;117:510–519.
11. Ku Y, Tominaga M, Iwasaki T, et al. Percutaneous hepatic venous isolation and extracorporeal charcoal hemoperfusion for high-dose intraarterial chemotherapy in patients with colorectal hepatic metastases. Surg Today Jpn J Surg 1996;26:305–313.
12. UICC International Union Against Liver Cancer (ICD-0155). In Hermanek P, Sobin LH, eds. TNM classification of malignant tumors. 4th ed. Berlin, Heidelberg, New York, Springer;1982:53–55.
13. Ku Y, Fukumoto T, Maeda I, et al. Single catheter technique of hepatic venous isolation and extracorporeal charcoal hemoperfusion for malignant liver tumors. Am J Surg 1997;173:103–109.

14. Tables and χ^2 tests. In Armitage P, Berry G. Statistical methods in medical research. 2nd ed. Oxford, England, Blackwell Scientific; 1987:408–420.
15. Kaplan EL, Meier P. Nonparametric estimation from incomplete observation. J Am Stat Assoc 1958;53:457–481.
16. Peto R, Pike MC. Conservation of the approximation $(O-E^2)/E$ in the log-rank test for survival data on tumor incidence data. Biometrics 1973;29:579–584.
17. Falkson G, MacIntyre IM, Moertel CG, et al. Primary liver cancer, an Eastern Cooperative Oncology Group trial. Cancer 1984;54: 970–977.
18. Marcos-Alvarez A, Jenkins RL, Washburn WK, et al. Multimodality treatment of hepatocellular carcinoma in a hepatobiliary specialty center. Arch Surg 1996;131:292–298.
19. Dexter DL, Leith JT. Tumor heterogeneity and drug resistance. J Clin Oncol 1986;4:244–257.
20. Huang C, Wu M, Xu G, et al. Overexpression of the MDR1 gene and P-glycoprotein in human hepatocellular carcinoma. J Natl Cancer Inst 1992;84:262–264.
21. Chen HSG, Gross JF. Intraarterial infusion of anticancer drugs: theoretic aspects of drug delivery and review of responses. Cancer Treat Rep 1980;64:31–40.