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EVALUATION OF INTERMITTENT HEPATIC ARTERIAL OCCLUSION USING DOUBLE LUMEN BALLOON CATHETER IN INFUSION CHEMOTHERAPY FOR UNRESECTABLE HEPATOCELLULAR CARCINOMA

(intermittent hepatic arterial occlusion / infusion chemotherapy / double lumen catheter / unresectable hepatocellular carcinoma)

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As a surgical method for the treatment of unresectable hepatocellular carcinoma (HCC), we developed a new therapy which consists of intermittent hepatic arterial occlusion (IHAO) during infusion chemotherapy by the use of double lumen balloon catheter inserted into the hepatic artery. This therapy was performed in 23 cases with unresectable HCC. Antineoplastic effects judged by Karnofsky's criteria were I-B in 19, I-A in three and 0-0 in one case. It was proved that the anticancer drug remained for a longer period at higher concentrations in the liver during IHAO. With the advance of gradual induction of thrombosis from peripheral hepatic artery by frequent HAO, liver dysfunction, growth of collateral vessels and repatency after induction of thrombosis could be suppressed. We conclude that this new therapy is a safe and more effective procedure for unresectable HCC and will have a wide application.

In recent years, advances in diagnostic methods for hepatocellular carcinoma (HCC) have been striking, and many cases with HCC were found. Furthermore, surgical technique has been well developed. However the resectability of HCC remains to be only 13.3 % in Japan (1). Therefore, treatment for unresectable HCC is of great importance. Since HCC receives its nutritional blood exclusively from the hepatic artery, hepatic artery ligation (HAL), transcatheter arterial embolization (TAE) and infusion chemotherapy have been used for treating unresectable HCC.

We developed a new therapy which consists of intermittent hepatic arterial occlusion (IHAO) during infusion chemotherapy using the double lumen balloon catheter inserted into the hepatic artery (2). The present report describes

to evaluate this new therapeutic method performed in 23 cases with unresectable HCC.

MATERIALES

Experimental studies :

Twenty-four adult mongrel dogs of both sexes, weighing 10 to 12 Kg, were divided into four groups. In Group I, Doxorubicin (DX) (1 mg/kg body weight) was administered through the catheter into the hepatic artery which was not ligated. In other three groups, the catheter was inserted into the proper hepatic artery through the gastroduodenal artery, and then the common hepatic and right gastric arteries were ligated. DX was infused into the hepatic artery immediately (Group Ⅱ), at 5 min (Group Ⅲ) and at 20 min (Group Ⅳ) after hepatic arterial occlusion.

Blood samples were withdrawn from the hepatic vein. Serum DX concentrations were measured by high performance liquid chromatography as described by Masuike et al (3 , 4).

Clinical Studies :

From October 1980 to October 1989, 60 patients with HCC were admitted in our department. They were treated by the following methods ; resection in 9 patients, IHAO with infusion chemotherapy in 23, infusion chemotherapy alone in 13, HAL in 2, TAE in 6 and non-therapy in 7. In IHAO with infusion chemotherapy, as shown in Table 1, there were 19 males and 4 females in this series. They aged from 32 to 77 with an average of 58.2 yr. Alcohol abuse was found in 7 of the 23 cases (30.4 %). Nine cases had a past history of hepatitis or jaundice. Four cases had an episode of intraperitoneal bleeding caused by rupture of HCC. The common complaints were abdominal and/or back pain in 11 and malaise in 6 cases. In two cases distant metastasis was diagnosed before the detection of HCC. One was metastasis of the right hip joint and the other was metastasis of the skull.

Hepatitis B surface (HBs) antigen was detected in 8 cases (34.8 %). Liver cirrhosis was associated in 20 cases (80 %). In the upper gastrointestinal series, 7 cases had esophageal varices. On selective celiac and superior mesenteric angiography, tumor vessels were visualized hypervascularly in 22 cases (95.7 %), arterioportal shunt was detected in 3 cases, arteriovenous shunt in one case and main portal branch occlusion in 2 cases.

Serum albumin levels were lower than 3.5 g/dl in 9 cases. Glutamic oxaloacetic transaminase (GOT) and/or glutamic pyruvic transaminase (GPT) were higher than 100 IU/L in 8 cases. In 50g-oral glucose tolerance test, diabetic

pattern was obtained in 8 cases. The K-value of Indocyanine Green was lower than 0.1 in 6 cases. The serum α-fetoprotein (AFP) level was positive in 19 cases (82.6 %) and higher than 400 ng/ml in 12 cases (52.2 %).

Tumor stage was designated according to the scale described in the general rules for the clinical and pathological study of primary liver cancer in Japan

Table 1 Clinical feature of 23 patients with unresectable hepatocellular carcinoma

case	age	sex	chief complaint	alcohol abuse ※	episode of hepatitis	HBsag	liver cirrhosis	tumor vessel	stage
1	59	M	upper abdominal discomfort	+	−	+	+	hypervascular	Ⅳ
2	66	F	epigastralgia	−	−	−	−	hypervascular	Ⅲ
3	70	M	right hypochondralgia	−	−	+	+	hypervascular	Ⅲ
4	59	M	epigastralgia	+	−	−	+	hypovascular	Ⅲ
5	58	M	anorexia	−	−	−	+	hypervascular	Ⅲ
6	54	M	right hypochondralgia	−	−	−	−	hypervascular	Ⅳ (rupture)
7	48	M	general malaise	−	+ (33yo)	+	+	hypervascular	Ⅳ
8	53	F	general malaise	−	+ (28yo)	−	+	hypervascular (A-P shunt)	Ⅲ
9	51	M	epigastralgia	−	−	+	+	hypervascular (A-P shunt, PV occlusion)	Ⅳ
10	77	M	general malaise	−	+ (69yo)	−	+	hypervascular (A-P shunt, PV occlusion)	Ⅳ
11	51	F	general malaise	−	+ (18yo)	−	+	hypervascular	Ⅳ
12	49	F	arthralgia of right hip joint	−	−	−	+	hypervascular	Ⅳ (bone meta)
13	58	M	hepatomegaly	+	+ (54yo)	−	+	hypervascular	Ⅳ
14	56	M	right hypochondralgia	−	−	+	−	hypervascular	Ⅳ (rupture)
15	74	M	epigastralgia	−	−	−	+	hypervascular	Ⅳ
16	45	M	hoarseness neck pain	−	+ (40yo)	−	+	hypervascular	Ⅳ (bone meta)
17	77	M	general malaise	+	+ (53yo)	−	+	hypervascular	Ⅳ
18	58	M	general malaise	−	+ (48yo)	+	+	hypervascular	Ⅱ
19	57	M	−	+	+ (47yo)	−	+	hypervascular	Ⅱ
20	64	M	right hypochondralgia	+	−	−	+	hypervascular	Ⅳ
21	39	M	epigastralgia	−	−	+	+	hypervascular (A-P shunt)	Ⅳ (rupture)
22	48	M	right hypochondralgia	+	−	−	+	hypervascular	Ⅳ
23	32	M	right hypochondralgia	−	−	+	+	hypervascular	Ⅳ (rupture)

※ Those who consume more than 86g of alcohol every day for more than 10 years.

Table 2 Clinical staging of hepatocellular carcinoma

Stage	T	N	M
I	T1	N0	M0
II	T2	N0	M0
III	T3	N0	M0
	T1-3	N1	M0
IV	T4	N0-1	M0
	T1-4	N0-1	M1

N factor
N1 metastasis of nl lymphnode

M factor
M1 distant metastasis

T factor

T	size	intrahepatic metastasis	vascular invasion
T1	<2cm	solitary	(−)
T2	<2cm	solitary	(+)
	<2cm	multiple (localized in one lobe)	
	>2cm	solitary	(−)
T3	>2cm	solitary	(+)
	<2cm	multiple (localized in one lobe)	
T4		multiple	
			(+) main branch

(5) and determined by the highest stage of each item (Table 2). In our series, stage II was detected in 2 cases, stage III in 5 cases and stage IV in 16 cases. Operative liver biopsy was performed on 9 cases, in which Edmondson II of HCC was detected in 8 cases and Edmondson III in one case.

1. Surgical Method

Median incision was applied to the upper abdomen to study the indication for hepatic cancer resection. When it was impossible to resect the tumor, a double lumen balloon catheter (Swan-Ganz) was inserted into the hepatic artery through the right gastroepiploic artery. The catheter was of 5 french in outer diameter.

In most cases of unresectable liver cancers, tumors were present in both right and left lobes. Therefore, a catheter was designed to insert into the proper hepatic artery. Depending on a location of HCC, it was inserted into either the right or left hepatic artery. After insertion into the selected artery, the catheter was fixed at the cut end of the right gastroepiploic artery. When the preoperative selective celiac and superior mesenteric angiography revealed a collateral artery into the tumor, it was ligated and the tumor was fed by only one feeding artery. When laparotomy was closed, the major omentum was manipulated to surround the catheter.

2. IHAO with infusion chemotherapy

Table 3 shows the protocol of IHAO with infusion chemotherapy. This therapy was begun after a week when the effect of surgical stress on the liver was relieved. In the first step during the initial postoperative 4 or 5 weeks, infusion chemotherapy through the catheter was performed. 5-fluorouracil

(5FU) 250 mg/day and Urokinase 6000 U/day were infused continuously by the use of a portable pump chronofusor. Furthermore, one shot administration of Mitomycin C (MMC) or DX after hepatic arterial occlusion, which is induced by balloon inflation with saline solution 0.15-0.2 ml, was carried out (Fig.1). In this period, if liver or bone marrow dysfunction was found, the treatment was suspended and resumed after its restoration.

3. Induction of thrombosis and additional embolization

In the next step, the induction of thrombosis for the feeding artery was begun when antineoplastic effect was confirmed by hepatic angiography through the inserted catheter and abdominal CT or it was impossible to continue infusion chemotherapy by side effect of anticanser drugs. The administration of Urokinase 6000 U/day was stopped and only 5FU 250 mg/day was administered. IHAO without MMC or DX was carried out every day (30-60 min/day) for about two weeks and the feeding artery was gradually thrombosed and in some cases completely occluded. If the complete occlusion of the hepatic aretry is not observed by hepatic arteriography through the catheter, the embolic agent such as gelatin sponge was used. However, if severe liver dysfunction or main portal branch occlusion was detected, induction of thrombosis and additional embolization were stopped. In this study, additional embolization combined with induction of thrombosis was performed on 18 cases (case numbers 1, 2, 4, 7, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 21, 22 and 23 in Table 1). Finally, the inserted catheter was extracted.

MMC was administered under the following conditions ; unoccluded (Group I) and occluded states by balloon inflation. Under occluded states, MMC was infused into the hepatic artery immediately (Group II), at 5 minutes (Group III) and at 20 minutes (Group IV) after hepatic arterial occlusion. Blood samples were withdrawn from the brachial cephalic vein. Serum MMC concentrations were measured by Miyamura's method (6).

GOT, GPT and total bilirubin (T.Bil) were measured in first week after induction of thrombosis.

During the treatment, histamine H2-receptor antagonist was administered for prevention of peptic ulcer. After extraction of catheter, 5FU (200 mg/day p.o.) was administered and the patients were followed up by serum AFP level and abdominal CT.

The judgement of antineoplastic effect in this study was done by Karnofsky's criteria (7), in which the changes of abdominal CT, ultrasonography, serum AFP level, angiography, clinical symptom and physical findings were evaluated. The survival rate in this study was presented by Kaplan-Meier's method (8).

Statistical significance was evaluated by student's t test.

RESULTS

Experimental Studies :

Fig. 2 shows the DX concentration in hepatic venous blood. The DX concentration in Group Ⅱ was significantly lower than in Group Ⅰ ($p<0.05$). These findings suggest that anticancer agents infused as immediately as possible (at least within 5 minutes) after occlusion of hepatic artery could remain in higher concentration in the liver for a long time.

Clinical Studies :

1. Antineoplastic Effects

The changes in serum AFP level after treatment and the evaluation of treatment based on Karnofsky's criteria are shown in Table 4. A drop in AFP level after the treatment was detected in 16 cases (69.6 %) except in 7 cases (2, 4, 6, 7, 16, 18 and 20), particularly in 8 cases (1, 5, 8, 10, 11, 13, 14 and 17), whose AFP levels were decreased to less than one tenth of preoperative level. In No 2, No 6 and No 20 cases, the AFP level was lower than 5 ng/ml both before and after this treatment.

The results on Karnofsky's criteria were as follows ; I-B in 19, I-A in 3 and 0-0 in one case. The last 0-0 case had a hypovascular tumor.

As shown in Table 5, the factors affecting antineoplastic effects were considered by the duration of the therapeutic responses (I-B) in 19 cases (1, 2, 3, 5, 6, 8, 9, 10, 11, 12, 13, 14, 16, 17, 18, 19, 20, 22 and 23) juged by Karnofsky's criteria I-B. In relation to each factor, this new therapy was more effective in cases with non-cirrhotic liver, hypervascular tumor, early clinical staging, low percent volume of tumor replacement and low value of serum AFP.

2. Survival Period

Except for two cases who are still alive, the longest survival period was 24 months with an average of 12.5 months and no patients died within one month after operation in this series. 21 patients died due to the following causes; acceleration of hepatic tumor (5 cases), hepatic failure (3 cases), gastrointestinal bleeding (4 cases), exacerbation of distant metastasis (5 cases), pneumonia (1 case) and sepsis (1 case).

In 21 cases who were dead, the factors affecting prognosis were evaluated by survival months after beginning of the treatment. In relation to each factor, survival period was longer in cases with non-cirrhotic liver, hypervascular tumor, solitary tumor and low percent volume of tumor replacement (Table 6).

Fig. 3 shows survival rate of two groups obtained by Kaplan-Meier's method.

Table 3 Protocol of IHAO with infusion chemotherapy

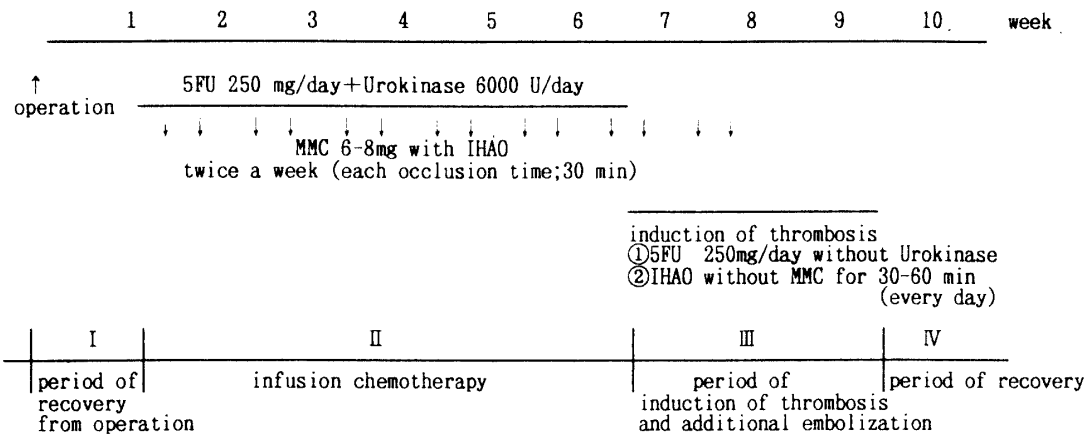

Table 4 Antineoplastic effect and prognosis in 23 patients with unresectable HCC

case	AFP (ng/ml) levels before treatment → after treatment	Karnofsky's criteria	prognosis	survival months
1	27500 → 2100	I－B(16M)	dead (sepsis)	18M
2	5↓ → 5↓	I－B(3M)	dead (pneumonia)	6M
3	25 → 5↓	I－B(12M)	dead (acceleration of hepatoma)	16M
4	200 → 440	0－0	dead (hepatic failure)	2M
5	80 → 5↓	I－B(6M)	dead (acceleration of hepatoma)	9M
6	5↓ → 5↓	I－B(24M)	dead (hepatic failure)	24M
7	1070000 → 1500000	I－A(2M)	dead (acceleration of hepatoma)	5M
8	12800 → 930	I－B(11M)	dead (upper GI hemorrhage)	15M
9	3600 → 1210	I－B(6M)	dead (metastasis of brain and lung)	8M
10	26900 → 1800	I－B(5M)	dead (upper GI hemorrhage)	6M
11	3300 → 330	I－B(14M)	dead (metastasis of lung)	15M
12	27000 → 6700	I－B(8M)	dead (sepsis)	15M
13	1000 → 18	I－B(10M)	dead (upper GI hemorrhage)	13M
14	1370 → 72	I－B(10M)	dead (sepsis)	15M
15	41 → 32	I－A(6M)	dead (acceleration of hepatoma)	9M
16	28 → 30	I－B(15M)	dead (metastasis of brain, lung and bone)	20M
17	760 → 28	I－B(7M)	dead (hepatic failure)	17M
18	11 → 11	I－B(6M)	dead (metastasis of lung)	24M
19	314 → 61	I－B(20M)	alive (26M)	
20	5↓ → 5↓	I－B(7M)	dead (acceleration of hepatoma)	10M
21	359 → 191	I－A(2M)	dead (upper GI hemorrhage)	3M
22	534 → 90	I－B(9M)	dead (metastasis of lung)	12M
23	94800 → 93700	I－B(5M)	alive (10M)	

Table 5 Factors affecting antineoplastic effect

factors		the period (months) of the therapeutic responses (I－B)	
HBs antigen	(+)	9. 1	(7)
	(－)	10. 0	(12)
liver cirrhosis	(+)	9. 3	(15)
	(－)	15. 3	(4)
tumor vessel	hypervascular	10. 2	(19)
	hypovascular		
clinical stage	II	13. 0	(2)
	III	11. 0	(1)
	IV	10. 4	(16)
intrahepatic metastasis	solitary	10. 6	(9)
	multiple	9. 9	(10)
percent volume of tumor replacement	<20%	13. 0	(8)
	<40%	6. 5	(4)
	<60%	9. 8	(5)
	>60%	7. 5	(2)
value of serum AFP(ng/ml) before treatment	<400	11. 6	(8)
	>400	9. 2	(11)

( ) number of cases who were judged as I-B by Karnofsky's criteria

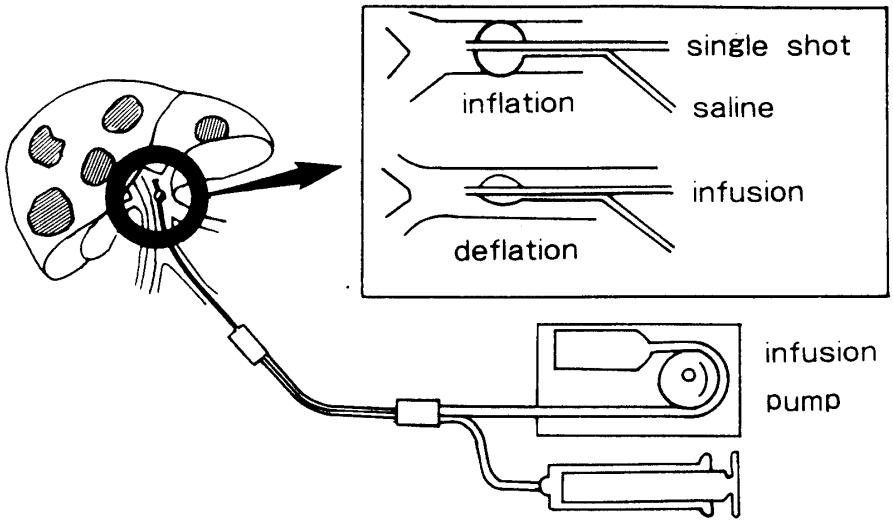

Fig. 1 Scheme of intermittent hepatic arterial occlusion by balloon catheter.

Table 6 Factors affecting prognosis

factors		survival time in month after begining of treatment
HBs antigen	(+)	12.7 (7)
	(−)	12.4 (14)
liver cirrhosis	(+)	12.1 (18)
	(−)	15.0 (3)
tumor vessel	hypervascular	13.0 (20)
	hypovascular	2.0 (1)
clinical stage	II	24.0 (1)
	III	9.6 (5)
	IV	12.7 (15)
intrahepatic metastasis	solitary	15.3 (9)
	multiple	10.3 (12)
percent volume of tumor replacement	<20%	14.6 (8)
	<40%	11.3 (3)
	<60%	11.4 (8)
	>60%	10.0 (2)
value of serum AFP (ng/ml) before treatment	<400	12.3 (10)
	>400	12.6 (11)

( ) number of cases who were dead

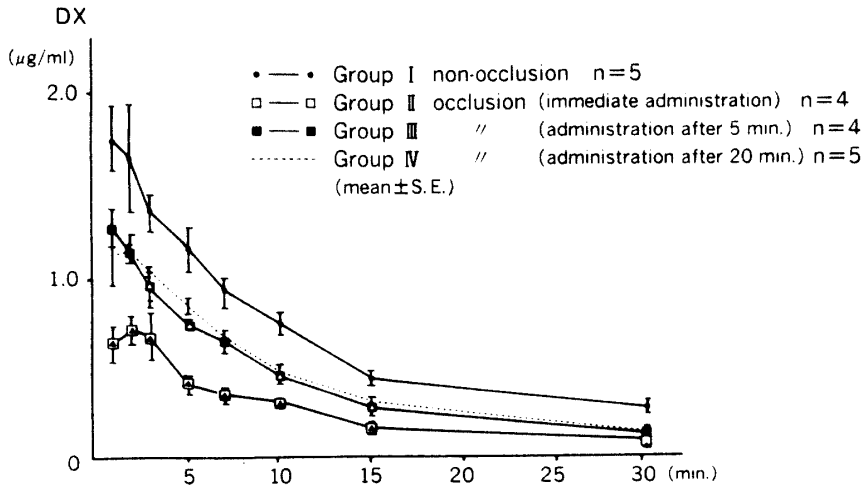

Fig.2 DX concentration in hepatic venous blood in dogs.
Triangle markers indicate statistically significant differences VS. Group I ($p<0.05$).

One group received only infusion chemotherapy, in which the dose of anticancer drugs, period and route of infusion were similar in this study. The group of IHAO with infusion chemotherapy received gradual induction of thrombosis by frequent IHAO in addition to infusion chemotherapy. One year survival rate was 0 % in the group of infusion chemotherapy alone. In the group of IHAO with infusion chemotherapy, one year survival rate was 56.8 % and two year survival rate was 6.9 %. These results suggest that induction of thrombosis after infusion chemotherapy is effective for long survival.

3. Complication

During infusion chemotherapy, bone marrow dysfunction led to suspension of treatment for a time in 11 cases (2, 7, 8, 9, 11, 12, 13, 14, 19, 21 and 23). Peptic ulcer was detected in 2 cases, in which one (case 5) recovered conservatively and the other (case 4) underwent partial gastrectomy successfully. After final induction of thrombosis and/or additional embolization, abdominal pain was detected in 11 cases and high fever (>38 ℃) in 9 cases.

4. MMC concentration in peripheral venous blood

Fig. 4 shows transition of MMC concentration in peripheral venous blood. The MMC concentration in Groups Ⅱ and Ⅲ was statistically lower than that of Group Ⅰ for the initial 3 min ($p<0.05$). Statistically significant differences between Groups Ⅱ, Ⅲ and Ⅳ were not found. Group Ⅳ was similar to Group Ⅰ. From these results, it is considered that the hepatic blood flow after long occlusion reverts to the condition of its unoccluded state by collateral pathways.

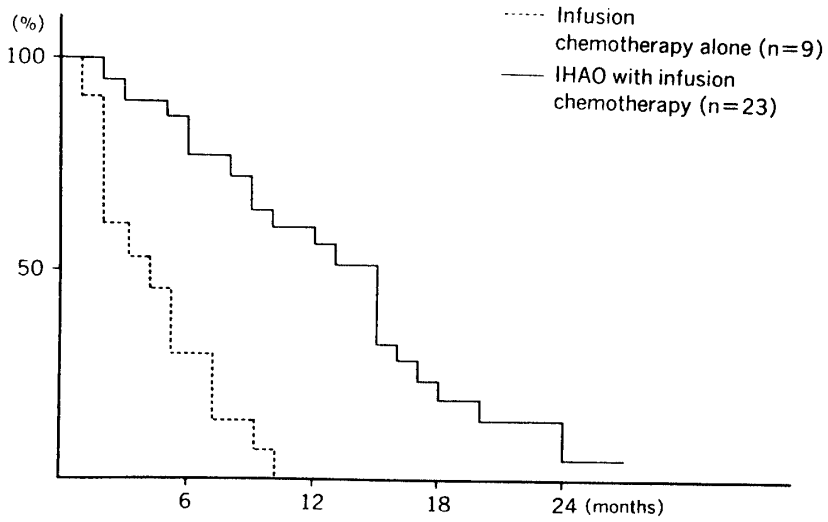

Fig.3 Survival rate (Kaplan-Meier's method).

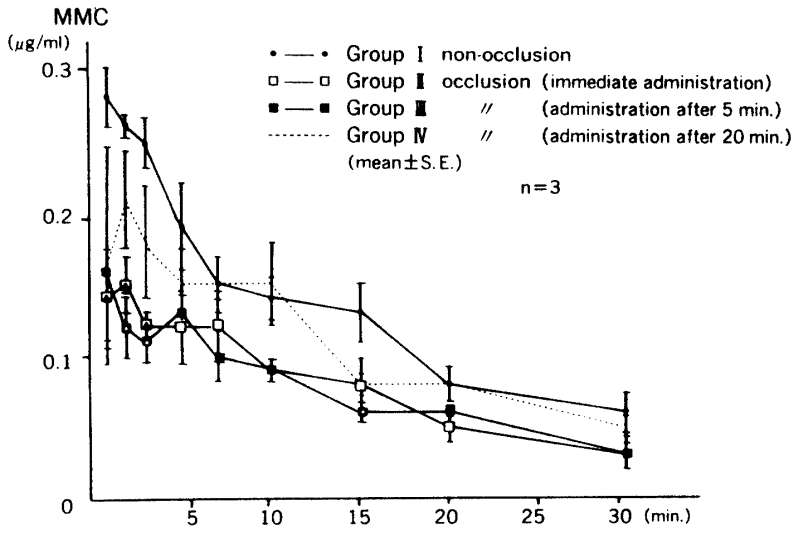

Fig.4 MMC concentration in peripheral venous blood in clinical cases. Triangle markers indicate statistically significant differences VS. Group I ($p<0.05$).

DISCUSSION

As treatment for HCC, the first choice is hepatectomy, but most cases are considered inoperable due to extreme tumor extension or accompanying advanced cirrhosis. As HCC receives its nutritional blood exclusively from the hepatic artery (9), HAL (10-12), TAE (23-27) and infusion chemotherapy (18-21) have been widely tried for unresectable HCC. Our new method makes use of traditional methods such as intra-hepatic infusion chemotherapy, IHAO and TAE. Dose the concurrent use of these techniques mean synthetically to enhance the effect of each therapy as well as to reduce the risk of complications ?

HAL was initiated by Markowitz (10) in 1952. Nilsson (11) and Fortner (12) reported its usefulness. However, as the collateral pathways develop as early as 2 weeks after ligation in many cases (13, 14), antineoplastic effect is maintained for only a short while. Furthermore, as severe damage of the liver after HAL is found in many cases (15) in which an average level of GOT on the first postoperative day was 2076 IU/L in Almersjö's report (16), thirty-day postoperative morbidity was relatively high. In Japan, thirty-day postoperative morbidity was 23.3 % and the 1-year survival rate was 7 % (17). As mentioned above, HAL will have to be avoided as far as possible.

Intra-arterial infusion chemotherapy for malignant tumors was first reported by Kloop (18) in 1950 and produced a greater antineoplastic effect and longer survival than systemic chemotherapy. In 1961, Miller (19) reported intrahepatic arterial infusion for HCC. At present, continuous infusion chemotherapy by infusion pump and as well as one shot administration by Seldinger's method is used. In Nishioka's report (20), its therapeutic effect

was rated as 0-B or better in 48 % and I-B or better in 17 % in Karnofsky's criteria, while it has little influence on normal liver tissue.

IHAO by balloon catheter surgically inserted into the hepatic artery was first introduced by EI-Domeiri (21) in 1967. He reported that IHAO was developed to avoid the risk of massive necrosis produced by HAL and to ensure adequate perfusion of the tumor tissue with the chemotherapeutic agents. In our experimental and clinical studies, anticancer agents remained for a longer period at higher concentrations in the tumor during hepatic arterial occlusion by balloon inflation, and manifestation of systemic side effects was suppressed. Furthermore, as MMC is bioactivated under hypoxic conditions in liver microsomes and nuclei, and is more cytotoxic to chronically hypoxic cells (22), its antineoplastic effect should be increased under IHAO by balloon inflation.

On the other hand, TAE was introduced by Doppman (23) in 1968. Doyon (24) in 1974 and Goldstein (25) in 1976 applied it for HCC. At present, the TAE method is relatively easy and is used in many institutions. Yamada et al (26) reported 120 cases with unresectable HCC treated by TAE. The therapeutic effect of TAE was rated as I-B or better in 75 %. The 1-, 2- and 3-yr cumulative survival rates were 44 %, 29 % and 15 %, respectively. The mean±SD highest serum values of GOT and GPT after TAE were 759±917 IU/L and 265±241 IU/L, respectively (27). But not all of HCCs should be indicated for TAE. HCCs with occluded of main portal branch, distant A-P shunt or V-P shunt are considered as contraindication for TAE. Furthermore, they reported that in this method the prognosis of HCC is poor, if it is fed by plural collateral vessels or makes an invasion upon more than 50 % of the liver. In our new method, IHAO with infusion chemotherapy, the therapeutic effect was rated as I-B or better in 82.6 % and the 1-year survival rate was 56.8 %, 2-year survivalrate 6.9 %. In our clinical study, the serum value of GOT and T.Bil after induction of thrombosis rose in only two cases. In one case, as the intima of the hepatic artery was injured by excessive balloon inflation in the early stage of IHAO, the hepatic artery was occluded rapidly. In another case, as the induction of thrombosis in the hepatic artery after frequent IHAO was not obtained, TAE with gelatin sponge was additionally performed and the hepatic artery was occluded rapidly. Except for these two cases, the highest values of serum GOT and GPT after induction of thrombosis were 48.7±26.3 IU/L and 38.3±17.1 IU/L, respectively. Thus, as these values after induction of thrombosis are distinctly lower than the values after TAE, liver damage should be able to be suppressed after induction of thrombosis. In TAE, the repatency of embolized artery is detected within 4 weeks and the growth of collateral vessels are found in many cases. But, Persson et al (28) reported that gradual induction of thrombosis is more suppressible for the growth of

collateral vessels than hepatic arterial occlusion at a stretch such as TAE and HAL, and repatency is suppressed in many cases.

Following the course of infusion chemotherapy with IHAO, decrease in tumor volume, disappearance of A-P shunt and repatency of occluded portal vein were detected and final induction of thrombosis after frequent IHAO by balloon inflation could be performed safely. Furthermore, during our treatment, hemorrhage caused by the rupture of HCC was sufficiently controlled with arterial occlusion by balloon inflation.

As mentioned above, by gradual induction of thrombosis after frequent IHAO, liver dysfunction, growth of collateral vessels and repatency of the hepatic artery were suppressed, and longer survival can be expected. In our study, this method has a tendency to be more effective for long survival in cases with non-cirrhotic liver, hypervascular tumor, solitary tumor and low percent volume of tumor replacement.

We conclud that this new method combined infusion chemotherapy with induction of thrombosis will find a wide application for unresectable HCC, since it is a safe and more effective procedure.

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