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Arterial chemotherapy and transcatheter arterial embolization therapy for non-resectable hepatocellular carcinoma

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Summary. An assessment was made on the therapeutic effects of arterial chemotherapy and transcatheter arterial embolization (TAE) therapy on 378 cases with non-resectable hepatocellular carcinoma (HCC). For the 191 cases who had undergone arterial chemotherapy, 22% had a 1-year survival rate, 8.9% survived for 2 years, and 4.0% for 3 years. Of these, for the 128 cases who were compatible with our criteria for patient selection, the three survival rates were 31.4%, 12.2% and 5.9% respectively. However, for the other 63 cases, who were incompatible with our criteria, the 1-year survival rate was 1.6% and it was worse for the cases who had received supportive care alone. For the cases who had undergone arterial chemotherapy, the highest survival rates were obtained by the alternate administration of different anticancer agents, and the three survival rates were 39.0%, 13.1% and 4.9% respectively. For the 187 cases who had undergone TAE therapy, the 1-year survival rate was 66.2%, the 2-year survival rate 36.5%, and the 3-year survival rate 21.9%. For the 124 cases with a tumor progression rate of less than 20% in the liver (E1), the survival rates were 77.8%, 50.1% and 30.8% respectively. The peripheral venous drug concentrations of mitomycin C and adriamycin were lower, but were maintained for a longer period in TAE therapy than in arterial chemotherapy. These results suggest that consideration of the criteria for patient selection and the alternate administration of anticancer agents are necessary in arterial chemotherapy, and that the best therapeutic effects can be obtained by TAE therapy combined with chemotherapy for cases of non-resectable HCC because of the chemotherapeutic and ischemic effects on the tumors.

Introduction

With the recent progress in abdominal real-time ultrasonography, there have been many cases of small hepatocellular carcinomas (HCC) being detected at an early stage [2, 12]. In Japan, however, approximately 80% of the cases with HCC are associated with liver cirrhosis. Indications that a hepatic resection is possible are therefore limited, because the tumor is in a highly advanced state and the liver functions have been impaired as a result of concomitant liver cirrhosis. Thus, HCC often has a poor prognosis [5]. Arterial [3] and systemic [1] chemotherapies, surgery such as the ligation of the hepatic artery [11], and transcatheter arterial embolization (TAE) therapy with anticancer agents [14] have been the main conservative therapeutic modalities for non-resectable HCC.

In the present paper, we discuss the therapeutic effects of arterial chemotherapy by a one-shot injection of anticancer agents and TAE therapy for non-resectable HCC, as well as the criteria for the selection of patients who undergo these therapies. Mention is also made of our pharmacological findings after both therapies were completed.

Material and methods

There were 378 cases with non-resectable HCC from 1970 to March 1987, treated by the Second Department of Medicine at Kurume University School of Medicine. All 378 cases underwent transcatheter treatment, with 191 cases receiving arterial chemotherapy and 187 cases receiving TAE therapy. Arterial chemotherapy was carried out by a one-shot injection of anticancer agents via the hepatic artery through a catheter placed selectively in accordance with Selginger's method. The regimens were MFC or AFC: a combination of 15–20 mg/m^2 mitomycin C, 300 mg/m^2 5-fluorouracil, with 25 mg/m^2 cytosine arabinoside or 30–40 mg/m^2 adriamycin added to the same dose of the latter two agents. For 37 cases, these regimens were alternately administered at intervals of 4–6 weeks.

TAE therapy was carried out using small pieces of Gelfoam mixed with 10–20 mg mitomycin C or 20–40 mg adriamycin. Over the past two years, chemoembolization has been carried out, in which small pieces of Gelfoam are administered following the injection of lipiodol mixed with anticancer agents.

The diagnosis was made by an autopsy, aspiration biopsy with a fine needle under ultrasonography, hepatic angiography and serum α-fetoprotein tests. The tumor progression rate was measured by a planimeter on an angiogram, and the cases were divided into four groups in accordance with the classifications made by the Liver Cancer Study Group of Japan. In class E1 the tumor occupied less than 20% of the whole liver, in E2 more than 20% and less than 40%, in E3 more than 40% and less than 60%, and in E4 more than 60%.

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Table 1. Survival rate after one-shot therapy in 191 Cases (1970 to Mar. 1987)

Therapeutic modality	No. of cases	Survival rate (%)				Median survival (months)
		1 year	2 years	3 years	5 years	
One shot	191	22.0	8.9	4.0	2.0	5.0
	128[a]	31.4	12.2	5.9	2.9	6.8
	63[b]	1.6	0	0	0	2.5
	37[a, c]	39.0	13.1	4.9	4.9	11.3

[a] Compatible with criteria
[b] Incompatible with criteria
[c] Alternate administration of MMC and ADR

The following criteria indicating arterial chemotherapy were established by a retrospective analysis of our results: 1) the absence of jaundice, 2) controllable ascites, 3) the absence of extrahepatic metastasis, 4) bromsulfophthalein or indocyanine green retention rate of less than 30%, 5) a transaminase level of less than 300 U, 6) no tumor thrombus in the main portal vein, 7) a tumor progression rate of less than 70% and 8) peripheral white blood cell and platelet counts of more than 3000/mm^3 and 40000/mm^3, respectively. The former three items are prerequisites for arterial chemotherapy. Concerning the latter five items, if the hepatopetal blood flows through the collateral portal veins in spite of a tumor thrombus into the main portal veins and if an improvement in the peripheral blood cell counts is obtained after splenic arterial embolization, then arterial chemotherapy can be carried out. The therapeutic efficacies were assessed in a comparison between the compatible and incompatible cases in accordance with the criteria for patient selection.

The peripheral venous drug concentrations of mitomycin C and adriamycin were serially measured using high-performance liquid chromatography for a period of up to 3 days after arterial chemotherapy and TAE therapy.

Results

For the 191 cases who underwent arterial chemotherapy, 22% had a 1-year survival rate, 8.9% 2 years, 4.0% 3 years, and 2.0% 5 years (Table 1). Of these, for the 128 cases who were compatible with our criteria, the 1-year survival rate was 31.4%, the 2-year survival rate 12.2%, the 3-year rate 5.9%, and the 5-year rate 2.9%. However, for the 63 cases incompatible with the criteria, the 1-year survival rate was 1.6% and there were no cases who survived longer than 2 years after arterial chemotherapy. For the 37 cases who underwent the alternate administration of AFC and MFC, the highest survival rates were obtained, and the 1-year survival rate was 39.0%, the 2-year survival rate 13.1%, the 3-year rate 4.9%, and the 5-year rate 4.9%.

As for the 187 cases who received TAE therapy, 61 cases were still alive when the statistical analysis was made. The cumulative survival rate for all the cases is shown in Fig. 1. The 1-year survival rate was 66.2%, the 2-year survival rate 36.5%, the 3-year rate 21.9%, the 4-year rate 11.7%, and the 5-year rate 11.7%. According to the classifications made by the Liver Cancer Study Group of Japan, there were 124 cases with E1, 35 cases with E2,

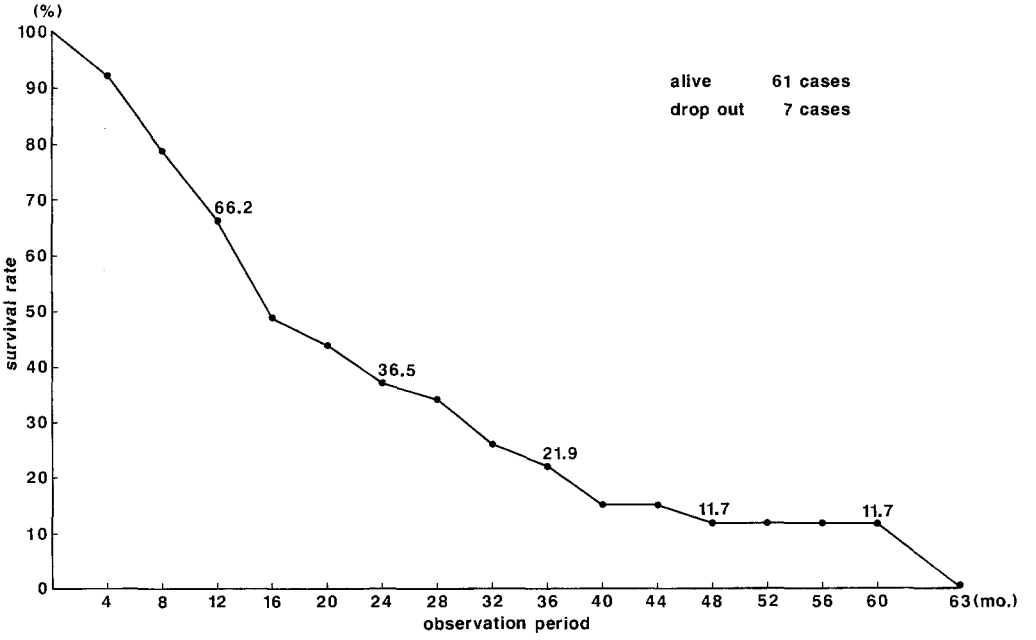

Fig. 1. The cumulative survival rate after TAE treatment for 187 cases (October 1980 to March 1987)

Table 2. Correlation between tumor extension rate and survival rate after TAE

Tumor extension rate[a] (%)	No. of cases	Survival rate (%)				
		1 year	2 years	3 years	4 years	5 years
E_1	124	77.8	50.1	30.8	20.5	20.5
E_2	35	32.2	12.1	8.1		
E_3	16	25.0				
E_4	7	28.6				

[a] E_1 <20%, E_2 20% < ~ <40%, E_3 40% < ~ <60%, E_4 >60%

16 cases with E3, and 7 cases with E4. For the other five cases, the tumor progression rate was not measured. For the 124 cases with E1, the 1-year survival rate was 77.8%, the 2-year survival rate 50.1%, the 3-year rate 30.8%, the 4-year rate 20.5%, and the 5-year rate 20.5%. For the 35 cases with E2, the 1-year survival rate was 32.2%, the 2-year survival rate 12.1%, and the 3-year rate 8.1%. However, there were no cases with E3 and E4 who survived longer than two years (Table 2).

The peripheral venous drug concentrations of adriamycin and mitomycin C were measured for 23 cases, including 5 cases who had undergone arterial chemotherapy with mitomycin C 20 mg/body, 3 cases who had received TAE therapy with the same dose of mitomycin C, 4 cases who had undergone chemotherapy with adriamycin 40 mg/body, and 11 cases who had received TAE therapy with the same dose of adriamycin (Fig. 2). Drug concentrations were high immediately after administration, but rap-

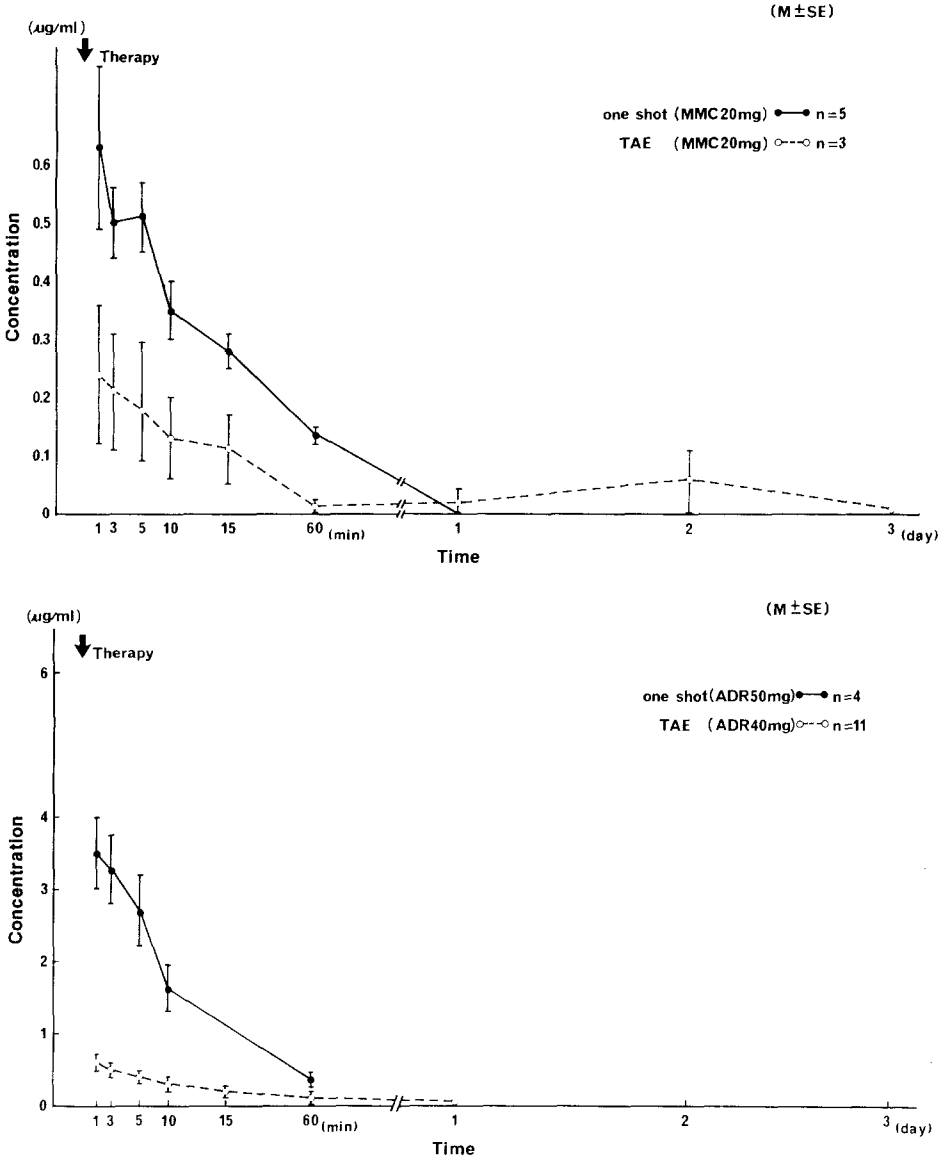

Fig. 2. The peripheral venous drug concentration was lower and remained longer in TAE therapy than in arterial chemotherapy. *Upper:* MMC concentrations; *lower:* ADR concentrations

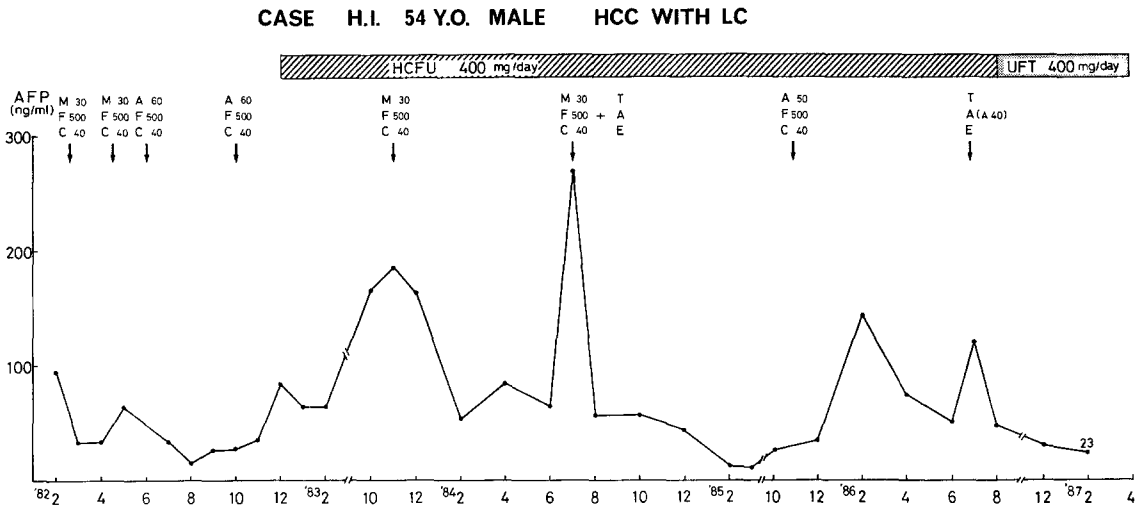

Fig. 3. The clinical course of a 54-year-old male who has survived for more than 5 years after initial arterial chemotherapy

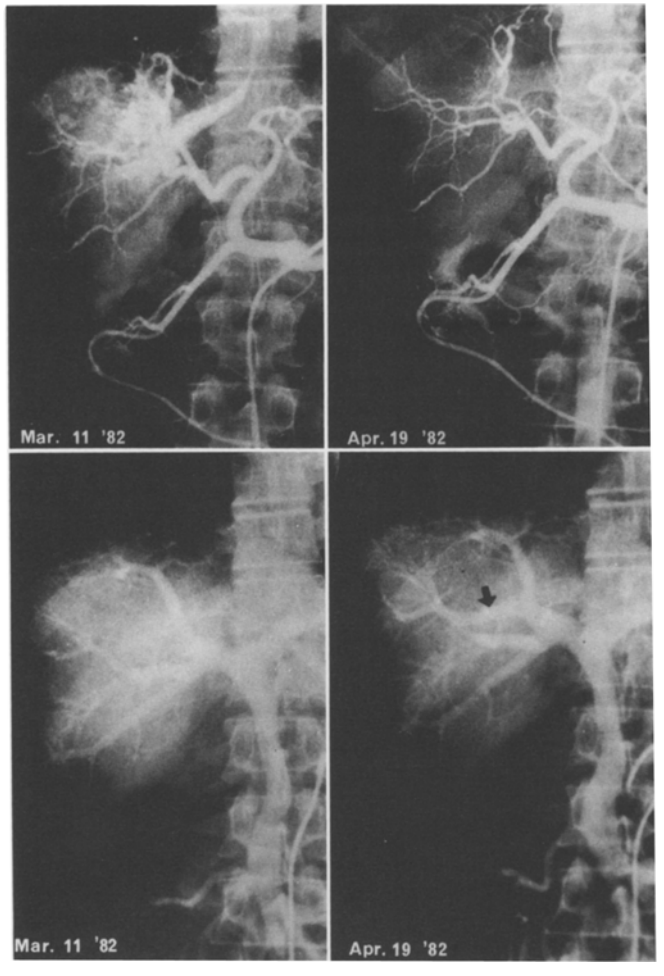

Fig. 4. *Above:* before initial arterial chemotherapy, the hypervascularity and tumor thrombus in the hepatic vein were demonstrated in the arterial phase of the hepatic angiogram (*left*). However, after 1 month they had disappeared (*right*). *Below:* on the arterial portogram, the portal vein was seen to have opacified after 1 month, as shown by the arrow (*right*)

idly decreased within 60 min in the case of arterial chemotherapy. However, in the cases who had undergone TAE therapy, the drug concentration was lower than in those who had received arterial chemotherapy, and remained longer for a period of 3 days.

A representative case

The clinical course of a 54-year-old man who has survived for more than 5 years after initial arterial chemotherapy is shown in Fig. 3. Before initial arterial chemotherapy, an HCC in the right lobe with tumor invasion into the hepatic vein was observed in an angiogram (Fig. 4). After 1 month, the chemotherapeutic effects were seen to have been remarkable, with hypervascularity, thread and streak signs having disappeared. Arterial chemotherapy was carried out five times, and TAE therapy twice. The patient is still alive, but under careful observation for any changes in the serum α-fetoprotein and the tumor size.

Discussion

It is well known that a normal liver has a dual blood supply. However, HCC is mainly supplied with blood from arterial sources, and is thus a hypervascular tumor. Good therapeutic effects can therefore be obtained by obstructing the arterial blood flow without causing an impairment to the liver functions. The arterial administration of a high dose of anticancer agents in a one-shot injection also leads to a high drug concentration in the tumor.

On the other hand, in arterial chemotherapy, a deterioration of the liver functions may occur because the anticancer agents have hepatic toxicity and, moreover, 80% of the cases of HCC are associated with liver cirrhosis. The prognosis for arterial chemotherapy alone is therefore quite poor, while the possibility of hepatic resection is also limited. Nevertheless, many cases of small liver cancer are being detected by ultrasonography these days.

In a previous report from our group, the 1-year survival rate for cases receiving supportive care was 2.8% for 107

cases [13], and 3.0% was reported by Nagasue et al. [6]. These survival rates were better than those of the 63 cases incompatible with the criteria for arterial chemotherapy but who underwent arterial chemotherapy. These results show that it is necessary to consider the criteria when arterial chemotherapy is to be carried out on cases with non-resectable HCC. In arterial chemotherapy, the highest survival rates were obtained by the alternate administration of anticancer agents, and these results suggest that when arterial chemotherapy is carried out several times, alternate administration is better than the repeated administration of the same agents.

Recently there have been many reports on the good therapeutic effects of TAE therapy or chemoembolization. According to Yamada et al. [14], the 1-year survival rate was 44%, the 2-year survival rate 29% and the 3-year rate 15%. By using a mitomycin C microcapsule, the 1-year survival rate was 38% for patients without a tumor cast in the portal vein [9]. However, a complete necrosis of HCC, especially of the tumor nodules invading the surrounding region, is rarely obtained [7], and in many cases there is a recurrence of HCC. Various embolic materials are therefore used, and an oily contrast medium mixed with anticancer agents for selective drug targeting on tumors is commonly used in Japan [4, 10]. In addition, combined hepatic arterial and portal venous embolization is sometimes attempted [8].

The drug concentration in the peripheral venous blood was lower and remained longer in the cases who had undergone TAE therapy than in the cases who had received arterial chemotherapy. This shows that there are both ischemic effects on HCC and continuous chemotherapeutic effects when TAE therapy is used.

The current study suggests that the consideration of the criteria for patient selection in arterial chemotherapy and the alternate administration of anticancer agents are necessary in order to obtain good chemotherapeutic effects, and that the best survival rates can be obtained by TAE therapy for cases of non-resectable HCC because of both the chemotherapeutic effects and the ischemic effects on tumors. TAE therapy is preferable to arterial chemotherapy as the first-choice thrapeutic modality for non-resectable HCC.

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