Studies on the chemotherapy with 5-fluorouracil in transcatheter arterial chemoembolization (TAE) treated patients with resectable or non-resectable hepatocellular carcinoma

Osaka Study Group on Hepatocellular Carcinoma*

Summary. In a prospective clinical trial, 65 patients were studied in an investigation into the effects of the oral administration of 5-fluorouracil on resectable and non-resectable hepatocellular carcinoma. All patients had received initial treatment in the form of transcatheter arterial chemoembolization with adriamycin. No significant effect on the survival periods was demonstrated either in patients with resectabel carcinoma or in those with non-resectable carcinoma, even though the survival rates were too high to reach an accurate conclusion (the lowest survival rate was 80%, 12/15, obtained in non-resectable carcinoma patients without 5-fluorouracil administration). 5-Fluorouracil administration did not significantly prolong the interval before recurrence in patients with resectable carcinoma (P =0.139). However, its favorable effect on the interval up to disease progression was noted in patients with non-resectable carcinoma when a log-rank test was used to carry out a statistical analysis (P = 0.049), though it was not demonstrated by the Wilcoxon test (P = 0.102). Thus, adjuvant chemotherapy with 5-fluorouracil seems to have potential in the palliative effects of transcatheter arterial chemoembolization on non-resectable hepatocellular carcinoma, but further studies are necessary before a final conclusion can be reached.

Introduction

The prognosis of patients with hepatocellular carcinoma has been greatly improved during the past ten years through developments in transcatheter arterial chemoembolization (TAE), hepatic surgery and liver function tests

develop into a state of almost total necrosis [12, 14], has greatly contributed to the palliation of patients with nonresectable hepatocellular carcinoma. Although various chemotherapy trials using anticancer agents like 5-fluorouracil, mitomycin C and adriamycin, or their combinations, have been conducted on patients with hepatocellular carcinoma, [1, 3-6, 10], the effects of chemotherapy are still disappointing. This is partly because the patients studied were so advanced that it was impossible to detect the differences between patients who had undergone chemotherapy and those who had not [1]. On the other hand, there have been no detailed studies on the adjuvant chemotherapy following a hepatic resection or TAE. In the present study, therefore, we investigated the effects of oral 5-fluorouracil administration in patients with resectable or non-resectable hepatocellular carcinoma, who had already received initial treatment by TAE with adriamycin.

[8, 11–13, 16]. In particular, TAE, by which the tumor can

Patients and methods

From June 1985 a total of 74 patients, treated by eleven member institutions of the Osaka Study Group on Hepatocellular Carcinoma, became the subjects of the present study. All patients who had undergone hepatic surgery were histologically confirmed as having hepatocellular carcinoma, while those who had not undergone surgery were confirmed by radiological and biochemical (e.g. α -fetoprotein) examinations. The patients had to meet the criteria set out below: no previous chemotherapy or radiotherapy, absence of active or pre-existing heart disease, a Karnofsky's performance rating of 40% or above, and absence of any liver disfunction (only class A according to the Child classification). The following investigations were carried out prior to the start of treatment: liver function tests (glutamic-oxaloacetic transaminase, glutamic-pyruvic transaminase, alkaline phosphatase, lactate dehydrogenase, γ-glutamyl transpeptidase, total bilirubin, total protein and serum albumin), α-fetoprotein, serum hepatitis B surface antigens and antibodies (HBsAg, HBsAb) and a complete blood picture with platelet counts. The four randomized treatment regimens were as follows.

Resectable cases. Arm A: transcatheter arterial chemoembolization (TAE) with adriamycin (20-50 mg/body) and thereafter surgical resection; oral administration of 5-fluorouracil (100-300 mg/body/day) initiated about 1 month after surgery. Arm B: TAE with adriamycin (20-50 mg/

Offprint requests to: M. Sakon, Second Department of Surgery, Osaka University Medical School, 1-1-50 Fukushima, Fukushimaku, Osaka 553, Japan

^{*}Members of the investigation team: J. Okamura (Osaka Teishin Hospital); M. Monden, M. Gotoh, M. Sakon, K. Kobayashi, W. Endoh, Y. Nakano, T. Mori, C. Kuroda, K. Tokunaga, T. Marukawa (Osaka University); S. Imaoka, Y. Sasaki (Osaka Center for Adult Disease); S. Oshima, H. Watanabe (Kansai Rosai Hospital); T. Kawahara, K. Kobayakawa (Osaka National Hospital); K. Okagawa (Kinki Chuoh Hospital); S. Noguchi, N. Shibata (Nishinomiya Central City Hospital); N. Murai, M. Beppu (Nishinomiya Prefectural Hospital); Y. Matsuda (Ikeda City Hospital); K. Tomita, Y. Maeura (Shinsenri Hospital); Y. Aoki, M. Mizumoto, H. Akashi (Minoo City Hospital)

body) and surgical resection. No 5-fluorouracil administration.

Non-resectable cases. Arm C: TAE with adriamycin (20-50 mg/body) and oral administration of 5-fluorouracil (100-300 mg/body) initiated about 1 month after TAE. Arm D: TAE with adriamycin (20-50 mg/body) only. The 5-fluorouracil dose was reduced when gastrointestinal or hematopoietic side-effects were observed. When patients were treated with TAE, the tumor size hardly decreased even in patients whose α -fetoprotein levels returned to the normal range and whose tumors were found to be completely necrotic upon a histological examination. Therefore, the response criteria for TAE and 5-fluorouracil administration in non-resectable patients were defined as (A) complete response: the normalization of the serum level of α-fetoprotein (normal range less than 20 ng/ml), the absence of any detectable new areas of the malignant disease, and a sufficient accumulation of lipiodol in the tumor (followed by a computerized tomography scan), all of which persisted for more than 4 weeks after TAE; (B) partial response: a reduction by at least 50% of the serum level of α-fetoprotein, the absence of new areas of malignant disease, and an accumulation of lipiodol, that occupies more than half of the tumor mass, all of which persisted for more than 4 weeks after TAE; (C) no change: a reduction by less than 50% or an increase by less than 25% of the α-fetoprotein level, an increase of less than 25% in the tumor size (the sum of the longest perpendicular diameters), the absence of a new area of the disease and/or an insufficient accumulation of lipiodol (less than half of the tumor); (D) progressive disease: an increase in the level of α-fetoprotein or the tumor size (more than 25%) and new areas of the disease. Complete response and partial response together formed the objective response.

The interval to a recurrence or progression (defined as having new areas of the disease and/or a higher level of α -fetoprotein than that before TAE) was obtained. The Student *t*-test, Mann-Whitney U test, X^2 test and Fisher's exact test were used for the statistical analysis. The survival curves were constructed using the Kaplan-Meier

Table 1. Characteristics of patients

Patient	Treatment arm ^a				
characteristic	A B		С	D	
No. Sex (M/F)	15 (13/2)	22 (20/2)	13 (12/1)	15 (10/5)	
Age (years)	56.8 (38–73)	57.7 (46–73)	58.7 (46–72)	61.9 (25 – 72)	
Stage ⁶					
Ĭ	6	9	1	1	
II	5	5	2	4	
III	3	6	3	4	
IV	1	2	6	5	
unkown	0	0	1	1	

^a A: TAE+adriamycin, surgical resection, 5-fluorouracil; B, TAE+adriamycin, surgical resection; C, TAE+adriamycin, 5-fluorouracil; D, TAE+adriamycin

method and were compared by the log-rank test and the Wilcoxon test.

Results

Of the 74 patients who were to be the subjects of study 9 were excluded from analysis because of incorrect treatment and the lack of follow-up. The major characteristics of the 65 patients eligible for evaluation are given in Table 1. No significant difference was observed in the distribution of sex, age and and clinical stage between the patients of arms A and B (resectable cases) and between the patients of arms C and D (non-resectable cases). The patients of arms A and B and the patients of arms C and D were not significantly different with respect to the liver function tests and the counts of red and white blood cells and platelets (data not shown). Table 2 is a summary of the treatments. The patients with non-resectable carcinoma were treated with TAE more often than those with resectable carcinoma. No significant difference in the dose of adriamycin was observed between the patients treated with 5-fluorouracil and those who were not. In the patients with resectable carcinoma, the degree of cirrhosis, the characteristics of the tumor and the types of surgery were further compared (Table 3). No significant differences were observed in these factors. The distributions of the survival periods for different treatment arms were compared as shown in Fig. 1. The survival periods appeared identical between the patients undergoing arms A and B (P = 0.54), even though the number of patients who died in each treatment arm was too small to provide a high assurance of detecting the survival differences (one of the 15 patients of arm A and one of the 22 patients of Arm B). The survival periods of patients of arm C looked longer than those of arm D. However, no significant difference was demonstrated either by the log-rank test (P = 0.137) or by Wilcoxon's test (P = 0.197). Since the survival rate was extremely high (80%, 12/15, for the patients who survived even in arm D of which survival rate was the lowest), the interval from the onset of treatment to a recurrence or progression was evaluated. A significant difference in the interval to recurrence was not seen between the patients of arms A and B (Fig. 2). Even though the interval to progression was significantly prolonged in the patients of arm

Table 2. Profile of treatments

	Treatment arm			
	A	В	С	D
No. of patients	15	22	13	15
Embolization No. (mean)	1.3 (1-3)	1.2 (1-2)	2.3 (1-5)	2.0 (1-5)
Adriamycin (total, mg)	57.7 (20–120)	48.3 (20-100)	89.6 (25 – 160)	83.7 (20-210)
Fluorouracil Duration (days)	333	-	277	-
Dose (total, g)	67	-	41	_

^b According to the general rules for primary liver cancer by Liver Cancer Group of Japan [9]

Table 3. The characteristics of patients with resectable hepatocellular carcinoma

Characteristics		Treatment arm		
		A	В	
Operation				
Resection				
Curative Non-curative		6 9	14 8	
		9	0	
Hepatectomy H0 ^a (partial)		5	9	
Hs (subsegment)		5	4	
H1 (1 segment)	,	4	3	
H2 (2 segments)		1	5	
H3 (3 segments)		0	1	
Distance from tumo	or (>1 cm)	7	14	
	(<1 cm)	8	8	
Cirrhosis				
(-)		1	6	
Mild		12	11	
Moderate		2	4	
Severe		0	1	
Tumor				
Growth Expansive		15	22	
Infiltrative		0	0	
Fc(capsule)	(1)	15	20	
r c(capsule)	(+) (-)	0	20	
Fc infiltration			10	
reminuation	(+) (-)	9 6	9	
Unknown	(-)	0	3	
Tumor thrombi			-	
Portal vein	(+)	0	4	
	(-)	15	17	
Unknown		0	1	
Hepatic vein	(+)	1	2	
-	(-)	14	20	

^a Classified according to the general rules for primary liver cancer by Liver Cancer Group of Japan [9]

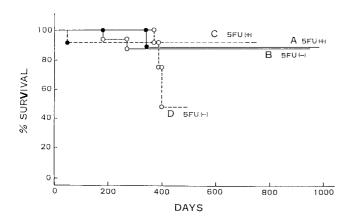


Fig. 1. Survival curves of patients with hepatocellular carcinoma. Arm A, TAE + operation +5-fluorouracil (● — ●); arm B, TAE + operation (○ — ○); arm C, TAE +5-fluorouracil (● - - - ●); arm D, TAE (○ - - - - ○)

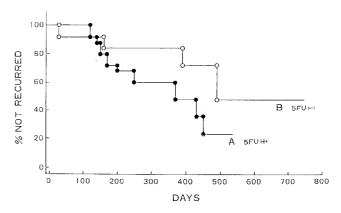


Fig. 2. Interval to recurrence in patients with resectable hepatocellular carcinoma. Arm A, TAE + operation +5-fluorouracil (● —— ●); arm B, TAE + operation (○ —— ○)

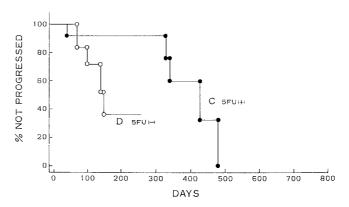


Fig. 3. Interval to disease progression in patients with non-resectable hepatocellular carcinoma. Arm C, TAE +5-fluorouracil (● — ●); arm D, TAE (○ — ○)

Table 4. Response rates in patients with non-resectable hepatocellular carcinoma

ARM	No.	CR^a	PR	CR + PR	NC	PD
С	13	4	6	10 NS ^b (76.9%)	2	1
D	15	3	5	8 NS (53.3%)	5	2

^a CR, complete response; PR, partial response; NC, no change; PD, progressive disease

C (median interval, 432 days), compared with those of arm D (median interval, 148 days) when the log-rank test was used (P=0.049), no statistical significance was observed in Wilcoxon's test (P=0.102) (Fig. 3). The response rates of the patients treated with 5-fluorouracil and those who were not following TAE with adriamycin (arms C and D) were 76.9% (10/13) and 53.3% (8/15) respectively, and no significant difference was observed between them, as Table 4 shows (P=0.184, Fisher's exact test).

b NS, not significant

Discussion

Although the beneficial effects of chemotherapy following the surgical resection of malignant tumors has been reported in the treatment of various malignant diseases [2, 7, 15], studies on adjuvant chemotherapy of hepatocellular carcinoma after hepatic surgery have never been reported.

In the present study, we investigated the effect of oral 5-fluorouracil administration on the survival periods or the response periods (the interval to recurrence or progression) of patients with resectable or non-resectable hepatocellular carcinoma, all of whom had received an initial treatment of TAE using adriamycin. Significant effects of 5-fluorouracil on the survival periods were observed neither in patients with resectable carcinoma nor in those with non-resectable carcinoma. However, it seems difficult to reach a conclusion, because the survival rates of the patients studied were too high to justify the administration of 5-fluorouracil. Further observations are therefore definitely necessary. The interval from initial treatment to recurrence was not significantly different when compared between the resectable patients who received 5-fluorouracil and those who did not. However, favorable effects of 5-fluorouracil on the interval to progression were obtained in patients with non-resectable carcinoma when the logrank test was used for a statistical analysis (P = 0.049). This was not due to the difference in the effectiveness of TAE, since the response rate, which is considered to be mainly affected by TAE rather than by chemotherapy with 5-fluorouracil, was statistically identical for both the unresectable patients who had received 5-fluorouracil and hose who had not. Its effect, however, was not confirmed by Wilcoxon's test (P = 0.102). Thus, adjuvant chemotherapy with 5-fluorouracil is likely to increase the potential of the effects of TAE on patients with hepatocellular carcinoma even though further cooperative group studies are necessary on greater numbers of patients and over longer periods of observation in order to reach a final conclusion.

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