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Prospective and randomized controlled study of chemoembolization therapy in patients with advanced hepatocellular carcinoma

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Abstract. The Cooperative Study Group conducted a study to assess the therapeutic effects of chemoembolization in patients with advanced hepatocellular carcinoma (HCC) using either epirubicin hydrochloride (FARM) or doxorubicin hydrochloride (ADR). A total of 77 patients were enrolled in this study and randomized into 2 groups: 39 patients were treated with a FARM solution as the material for Lipiodol-transcatheter arterial embolization (TAE; FARM group), and 38 patients were treated with an ADR solution as the material for L-TAE (ADR group). For the FARM group, the 1-year survival rate was 69.9% and the 2-year survival rate was 44.5%. For the ADR group, the corresponding survival rates were 74.7% and 44.0%. The differences among the above figures were not statistically significant. As side effects, fever, nausea, and generalized fatigue occurred at almost the same frequencies in the two groups. Changes detected in the liver function and the peripheral blood cell count in both groups were not severe. There was no significant difference between the toxic effects observed in the two groups. In conclusion, there was no significant difference in therapeutic efficacy between the FARM and ADR groups.

Introduction

Recently, we have made remarkable progress in the field of treatment of hepatocellular carcinoma (HCC), but there are no guidelines concerning the treatment of patients with inoperable HCC. Among several therapeutic modalities for HCC, transcatheter arterial embolization (TAE) is an established therapy that embolizes the feeding arteries of HCC [2, 4–6]. Therefore, we have started to use Lipiodol chemoembolization with doxorubicin hydrochloride (abbreviated as L-TAE with ADR) to produce a good therapeutic effect in HCC. The results of a previous study demonstrated a favorable effect in the treatment of HCC with L-TAE with ADR as compared with L-TAE without ADR [4].

The present study was planned to compare the therapeutic effects of L-TAE with epirubicin hydrochloride (FARM) and L-TAE with ADR in the treatment of inoperable HCC.

Patients and methods

This clinical trial was conducted from April 1990 to September 1991. Two university medical schools and two medical school hospitals in the Shikoku area participated in this study. A total of 88 patients with HCC were entered in this trial. There were 9 dropout cases: 6 underwent surgical resection, 2 underwent percutaneous ethanol injection therapy, and 1 patient died due to cardiac tamponade. The patients were randomly allocated to the FARM group and the ADR group by the envelope method at the time of angiography. In all, 41 patients were treated with L-TAE with FARM and 38 patients were treated with L-TAE with ADR. The FARM group received ethiodized oil (Lipiodol) mixed with FARM at a dose of 60 mg/m^2, and the ADR group received Lipiodol mixed with ADR at a dose of 40 mg/m^2. Following this procedure, the arteries feeding the HCC were embolized with gelatin sponge particles in both groups.

The background factors for the two groups, i.e., sex, age, clinical stage, performance status, severity of liver disease (Child's classification), number of tumors, size of the tumors, and the serum α-fetoprotein (AFP) level before treatment, were statistically compared by the nonmatched Wilcoxon test. For measurement of the size of the tumors, we multiplied the long diameter by the short diameter of each tumor, added the value for each tumor, and compared the total value for the tumors before and after the therapy in each group. The tumor reduction rate was determined as the percentage of reduction in the two-dimensional size of each patient's tumors after the therapy.

Results

There was no significant intergroup difference in background factors (Table 1). Also, there was no significant intergroup difference in the frequency of additional treatment.

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Table 1. Background factors

		FARM	ADR	
Sex:				
	M	29	31	NS
	F	12	7	NS
Age (years):				
	Mean	65.4	62.7	NS
	Range	40–85	43–78	
Cause of disease:				
	HBV	9	7	
	HCV	24	25	NS
	Alcohol	3	3	
Clinical stage:				
	I	11	9	
	II	14	14	NS
	III	7	3	
	IV	0	2	
PS:				
	0	7	5	
	1	9	11	NS
	2	10	6	
	3	3	1	
Child's classification:				
	A	20	15	
	B	8	10	NS
	C	6	3	
Number of tumors:				
	1	5	6	
	2	2	4	
	3	3	4	NS
	4	6	5	
	>5	2	2	
Size of tumors (cm^2)		19.9± 2.8	25.2± 5.2	NS
AFP (ng/ml)		6331.2±2959.0	4519.5±2959.0	

NS, Not significant

Tumor reduction rate

The size of the tumors was significantly reduced after L-TAE in both the FARM group and the ADR group (Fig. 1). No significant difference in the tumor reduction rate was found between the FARM and ADR groups (Fig. 2).

AFP level

The AFP levels at 1 and 4 months after L-TAE were compared between the FARM and ADR groups. The level of AFP in the FARM group remained low after 4 months, and both groups showed a significant decrease in levels after the therapy (Fig. 3).

Survival curves of the two groups

Survival curves were calculated using the method of Kaplan and Meier. For the FARM group, the 1-year survival

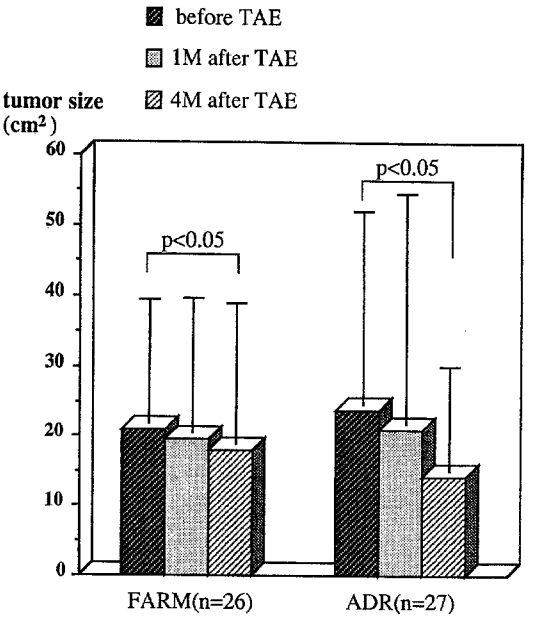

Fig. 1. Size of tumors before and after L-TAE therapy

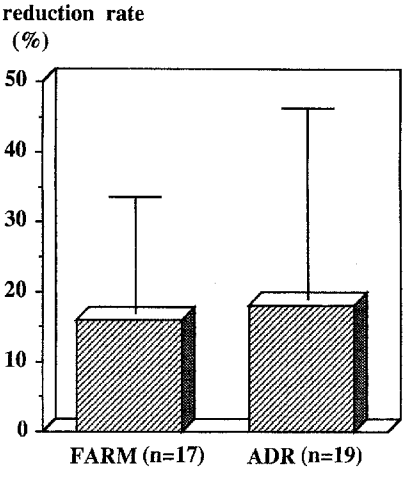

Fig. 2. Tumor reduction at 4 months after L-TAE therapy

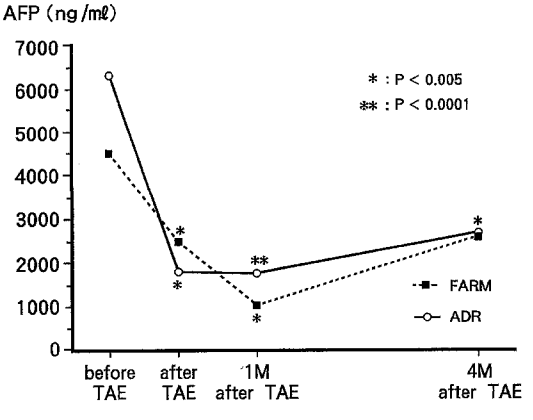

Fig. 3. AFP levels after L-TAE therapy

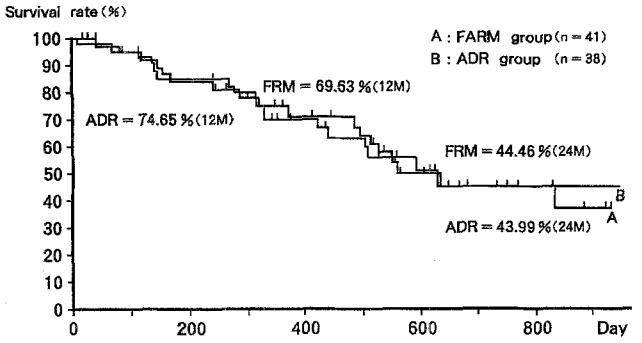

Fig. 4. Survival curves generated for the FARM group and the ADR group

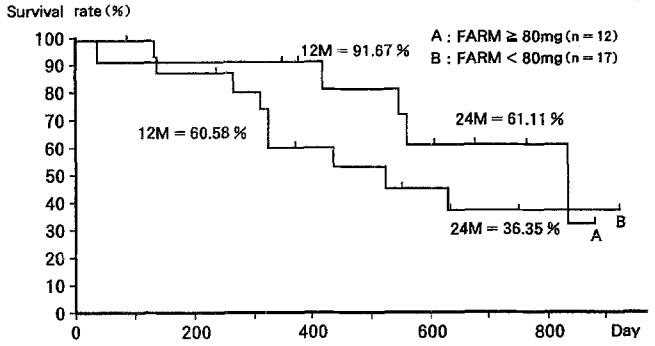

Fig. 5. Survival curves generated for the FARM group. The FARM group was divided into two subgroups of **A** ≥80 mg FARM and **B** <80 mg FARM

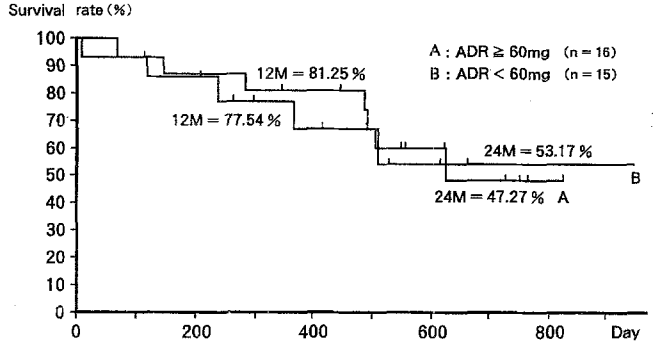

Fig. 6. Survival curves generated for the ADR group. The ADR group was divided into two subgroups of **A** ≥60 mg ADR and **B** <60 mg ADR

rate was 69.9% and the 2-year survival rate was 44.5%. For the ADR group, the rates were 74.7% and 44.0%, respectively. The differences between the corresponding rates were not statistically significant (Fig. 4). The FARM group was divided into two subgroups, one receiving a FARM dose of 80 mg or more and the other receiving a FARM dose of less than 80 mg. The mean survival of patients treated with 80 mg or more of FARM was 684 days, whereas that of patients treated with less than 80 mg of FARM was 565 days. The difference between these survival periods was not significant (Fig. 5). There was no difference in survival between the patients treated with ADR

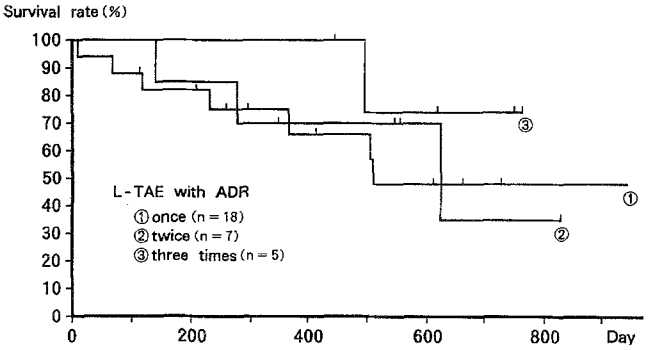

Fig. 7. Survival curves generated for the ADR group. The ADR group was divided into three subgroups according to the number of treatments

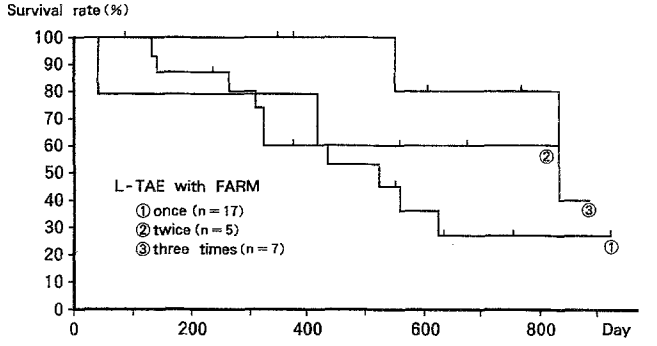

Fig. 8. Survival curves generated for the FARM group. The FARM group was divided into three subgroups according to the number of treatments

at 60 mg or more and those receiving less than 60 mg (Fig. 6). When the ADR group was divided into three subgroups according to the number of L-TAE treatments given, the patients who received three treatments showed the best survival rate. It seems that a greater number of treatments improved the prognosis, but the difference was not significant (Fig. 7). The same tendency in survival was found for the FARM group as a function of the number of treatments (Fig. 8).

Side effects

Side effects such as fever, nausea, and generalized fatigue occurred at almost the same frequency in both treatment groups. Regarding the toxic effects of the treatment, the serum AST, ALT, LDH, total bilirubin, and albumin levels were not seriously changed after the treatment in either group. No significant difference was found in these data between the two groups.

Discussion

HCC patients treated with L-TAE have shown good therapeutic effects [2, 4–6]. The anticancer drugs used in conjunction with the L-TAE therapy have been ADR (20–60 mg) [2, 3], mitomycin C (10–20 mg) [3], and cisplatin (CDDP, 100 mg) [3, 7]. They were used either singly or in

combination, and favorable results were obtained [5, 6]. A retrospective comparison of the intrahepatic arterial bolus administration of either FARM or ADR demonstrated FARM to be more effective than ADR in terms of survival [1]. Recently, Okamura et al. [4] reported a prospective and randomized clinical trial of the treatment of HCC using FARM and ADR, and they found no significant difference between the two treatment groups. Whereas they followed the patients for 200 days, our present study followed the patients for 800 days. Our study also did not demonstrate a clear-cut significant difference in survival between the FARM and ADR groups, and we thus concluded that FARM and ADR exert almost the same efficacy in the treatment of HCC.

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