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Prospective and randomized clinical trial for the treatment of hepatocellular carcinoma – a comparison of L-TAE with Farmorubicin and L-TAE with Adriamycin (second cooperative study)

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Summary. A randomized clinical trial comparing L-TAE with Farmorubicin (FARM) and L-TAE with Adriamycin (ADR) in the treatment of hepatocellular carcinoma was conducted from October 1989 through December 1990. In all, 192 hospitals participated in this study and 117 patients were entered. The patients were randomly allocated to group A (L-TAE+FARM) or group B (L-TAE+ADR). There was no significant intergroup difference in background factors. Additional treatment consisting of repeated TAE or surgery was given to 66 patients. Four factors were analyzed in this study: the percentage of reduction in tumor size, the change in the AFP level, lipiodol accumulation, and survival. None of these factors differed significantly between the two groups. The final evaluation of this study will be based on differences in survival after a long-term follow-up. Toxic effects manifested less frequently in group A than in group B, and the decrease in the platelet count in the peripheral blood was significantly lower in group A than in group B. These results suggest that FARM exerts a more favorable effect than does ADR in the treatment of hepatocellular carcinoma.

Introduction

In the 1980s, remarkable progress was made in the treatment of hepatocellular carcinoma (HCC) via procedures such as L-TAE (lipiodol transcatheter arterial embolization) and PEIT (percutaneous ethanol injection therapy). There have also been advances in preoperative evaluation, ultrasound-guided surgical intervention, postoperative care, and various perioperative technologies brought by transplantation.

In the first clinical trial of this series [2], L-TAE was performed in the presence or absence of Adriamycin (ADR), and the results suggested that ADR had a favorable effect in the treatment of HCC.

In a previous investigation [1], the effect of intrahepatic arterial infusion of Farmorubicin (FARM) on nonresectable HCC was examined, and FARM was found to be more effective than ADR in terms of survival. The present paper reports the results of a multi-institutional, randomized, controlled clinical trial comparing L-TAE with FARM and L-TAE with ADR in the treatment of HCC (second study), performed by the Cooperative Study Group for Liver Cancer Treatment of Japan at 192 hospitals.

Patients and methods

From October 1989 through December 1990, a group study was conducted to investigate the effects of FARM in the treatment of HCC. Patients with HCC were randomly allocated into two treatment groups, group A and group B, by a telephone registration system at the time of angiography.

Group A received ethiodized oil (lipiodol) and FARM at a dose of 60 mg/m^2 and group B was given ethiodized oil and ADR at a dose of 40 mg/m^2; both drug preparations were dissolved in a contrast medium and injected intra-arterially. Following this procedure, the feeding arteries were embolized with particles of gelatin sponge in both groups.

A total of 117 patients were entered in this trial, and all were eligible. Analysis of endpoints was performed in two ways. First, we used so-

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Table 1. Background factors

Factor		Group A	Group B	
Age (years)	Mean	60	62	N. S.
	Range	37–76	38–79	
Sex (M/F)	M	47	48	N. S.
	F	11	11	
Liver cirrhosis	No	9	6	N. S.
	Yes	47	50	
Clinical stage	I	34	36	
	II	18	22	N. S.
	III	1	0	
Child's classification	A	43	44	
	B	14	15	N. S.
	C	0	0	
PS	0	35	34	
	1	12	18	N. S.
	2	4	0	
Eggel's type	N	38	46	
	M	13	11	N. S.
	D	3	1	
Encroachment	E1	22	32	
	E2	18	13	N. S.
	E3	6	8	
	E4	2	2	
Pre-TAE AFP (ng/ml)	Mean	5,207	16,691	N. S.
Lipiodol (ml)	Mean	6.2	6.9	N. S.
Tumor size (cm^2)	Mean	48	37	N. S.

Table 2. Tumor reduction after L-TAE

Reduction rate	Group A ($n = 42$)		Group B ($n = 45$)	
0– 24%	13		16	
25%– 49%	12	} 11	10	} 13
50%– 74%	9		8	
75%– 99%	2		5	
100%	0		0	
Enlargement	6		6	

A vs B; Wilcoxon
$P = 0.9187$

Table 3. Rate of decrease in serum AFP levels after L-TAE

Group	AFP cutoff level (pre-TAE)	Decrease	
		Number	Mean ± SD (%)
A	≧10 ng/ml	34	58.1 ± 36.1
	≧20 ng/ml	31	58.9 ± 37.4
	≧100 ng/ml	18	63.4 ± 40.4
B	≧10 ng/ml	33	50.3 ± 41.2
	≧20 ng/ml	28	55.2 ± 40.6
	≧100 ng/ml	23	60.4 ± 35.2

Group A vs group B (Wilcoxon test): ≧10, $P = 0.5022$; ≧20, $P = 0.7499$; ≧100, $P = 0.6177$

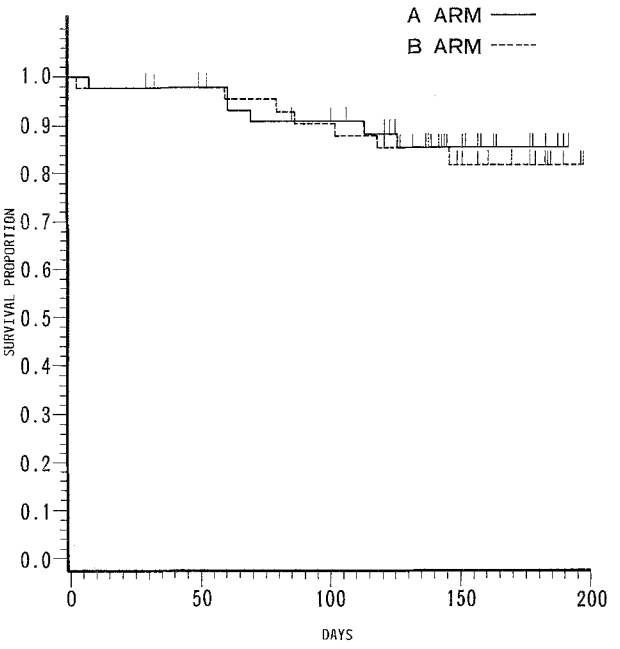

Fig. 1. Survival curves generated for groups A and B

Table 4. Lipiodol accumulation

Accumulation	Group A ($n = 39$)	Group B ($n = 39$)
0%	1	1
<10%	2	1
<50%	6	6
≧50%	15	17
100%	15	14

Group A vs group B (Cochran-Mantel-Haenszel), $P = 0.906$

called "intent-to-treat" analysis, which included protocol-violating patients. Second, we analyzed only protocol-adhering patients. As the differences observed were small, the results reported herein are based on the protocol-adhering patients. The background factors of the patients are listed in Table 1. No statistically significant difference was found between group A and group B.

After the first L-TAE procedure, additional treatment was given to 66 patients; 38 patients were subjected to repeated TAE with ADR or some other agent, 20 underwent surgery, and 8 received some other treatment. No significant intergroup difference was noted in the frequency of additional treatment. At 4 weeks or more after L-TAE, the following four endpoints were compared between the groups to elucidate the effect of FARM in L-TAE: the extent of tumor reduction, the change in AFP levels, the accumulation of ethiodized oil (lipiodol) in HCC nodules, and survival.

Results

Tumor reduction rate

The tumor reduction rate was determined as the percentage of reduction in the two-dimensional size of the largest tumor after L-TAE. No significant difference in the rate was found between the two groups (Table 2).

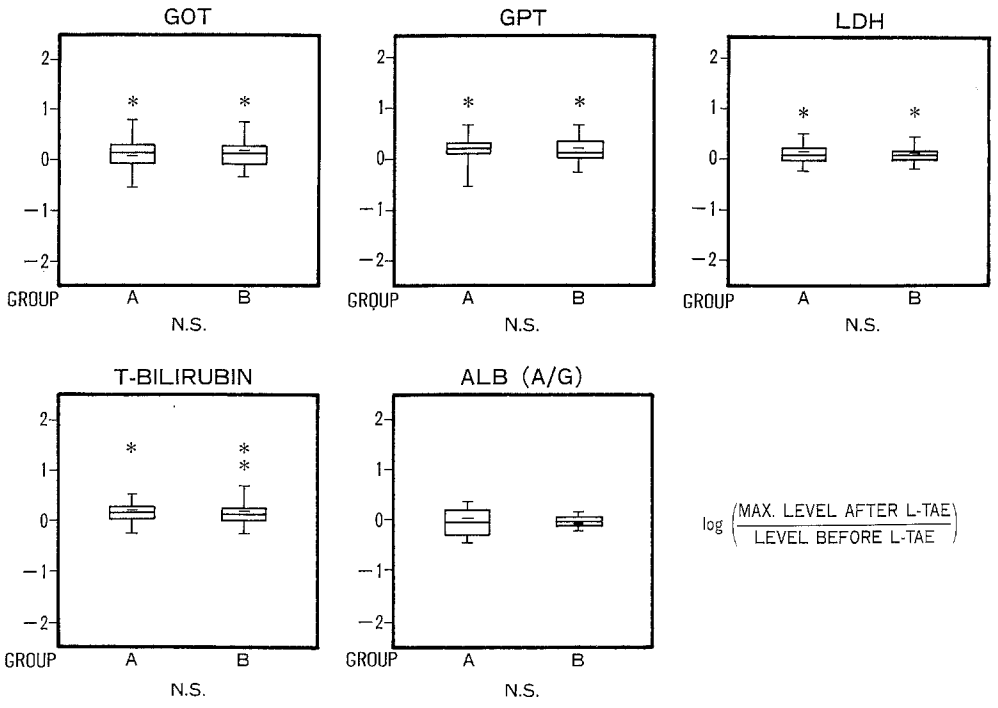

Fig. 2. Comparison of changes observed in GOT, GPT, LDH, T-bilirubin, and albumin (*ALB*) after L-TAE

Percentage of decrease in serum AFP levels

The change in serum AFP levels was determined after the treatment, and the levels of maximal decrease were compared between group A and group B. In all comparisons made using three different cutoff levels, we observed no significant difference between the two groups (Table 3).

Lipiodol accumulation

The accumulation of ethiodized oil in HCC nodules is shown in Table 4. No significant difference was found between group A and group B.

Survival

Survival curves were calculated using the method of Kaplan and Meier. They did not show any significant difference (Fig. 1).

Side effects

Regarding the toxic effects of the treatments, the changes in liver function were not severe in either group A or group B. No significant difference was found in serum GOT, GPT, LDH, total bilirubin, or albumin levels between the two groups (Fig. 2).

The toxic effects on the white cell count, the hemoglobin levels, and the platelet count in the peripheral blood are shown in Table 5. According to short-term analysis performed at less than 1 month after treatment, the toxic effect on the platelet count was observed significantly less frequently in group A than in group B (Table 5).

Discussion

Previous studies have demonstrated the usefulness of L-TAE in the treatment of HCC. Takayasu and co-workers [3] found that lipiodol (ethiodized oil) alone had practically no therapeutic effect but was helpful in differentiating small HCC from regenerative nodules or from minute

Table 5. Toxic effects

Toxicity	Group A Grade					Group B Grade					CMH	
	0	1	2	3	4	0	1	2	3	4	X^2	P^0
WBC	30	12	7	0	0	36	13	3	0	0	1.532	0.216
Hb	35	12	1	0	1	36	11	5	0	0	0.196	0.658
Platelets	44	3	2	0	0	37	11	3	1	0	4.121	0.042[a]
Abdominal pain	17	22	10	0	0	16	24	10	2	0	0.457	0.499
Fever	8	14	25	2	0	5	11	33	2	1	2.322	0.128

[a] Significant difference between group A and group B as analyzed at 1 month after treatment
WBC, Hb, and platelet counts were evaluated according to WHO criteria. CMH, Cochran-Mantel-Haenszel (table scores)

Table 6. Summary of the 192 hospitals participating in the second cooperative study of the Cooperative Study Group for Liver Cancer Treatment of Japan

Hokkaido University
Sapporo Medical College
Asahikawa Medical College
National Sanatorium Dohoku Hospital
Asahikawa City Hospital
Asahikawa Kosei Hospital
Sapporo City Hospital
Kitano Hospital
Sapporo Kosei Hospital
Hakodate City Hospital
TSW Memorial Hospital
Hakodate Goryokaku Hospital
Takigawa City Hospital
Hirosaki University
Keisei Hospital
Aomori Rosai Hospital
Hiraga General Hospital
Akita University
Akita City Hospital
Iwate Prefectural Chuo Hospital
Iwate Medical University
National Sendai Hospital
Tohoku Rosai Hospital
Sendai City Medical Center
Tohoku University
Miyagi Medical Center for Adults
Yamagata Prefectural Chuo Hospital
Yamagata City Saiseikan Hospital
Yamagata University
Takeda General Hospital
Tohoku Kosei Nenkin Hospital
Fukushima Medical College
Hananomaki Kosei Hospital
Niigata Cancer Center Hospital
Niigata University
Niigata Citizen's Hospital
Nagaoka Red Cross Hospital
Shinshu University
Nagano Red Cross Hospital
Yamanashi Prefectural Chuo Hospital
National Sanatorium Nishigunma Hospital
Maebashi Red Cross Hospital
Gunma Cancer Center
Mito Saiseikai Hospital
IHI Hospital
Tsuchiura Kyodo Hospital
Dokkyo University
Jichi Medical School
Utsunomiya Saiseikai Hospital
National Tochigi Hospital
Haga Red Cross Hospital
University of Tsukuba
Saitama Cancer Center
Saitama Medical School
National Defence Medical College
Fukaya Red Cross Hospital
Dokkyo University Koshigaya Hospital
Kimitsu Chuo Hospital
University of Chiba
Jikei University Kashiwa Hospital
National Konodai Hospital
National Matsudo Hospital
Matsudo City Hospital
Kameda General Hospital
National Oji Hospital
Cancer Institute Hospital
Saiseikai Chuo Hospital
National Cancer Center Hospital
National Sanatorium Tokyo Hospital
National Medical Center Hospital
Tokyo Metropolitan Fuchu Hospital
Mitsui Memorial Hospital
Nihon University Surugadai Hospital
Nihon University Itabashi Hospital
Jikei University
Musashino Red Cross Hospital
Tokyo Metropolitan Komagome Hospital
Showa University Fujigaoka Hospital
Yokohama City University
National Yokosuka Hospital
National Yokohama Higashi Hospital
Sagamihara National Hospital
Kanagawa Cancer Center
Kyosai Inada Noborito Hospital
National Tosei Hospital
Shizuoka Red Cross Hospital
Shizuoka Municipal Hospital
Hamamatsu University
Shizuoka Prefectural Hospital
Shimada City Hospital
Seirei Mikatagahara Hospital
Japanese Red Cross Nagoya First Hospital
Shakai Hoken Chukyo Hospital
Nagoya National Hospital
Meitetsu Hospital
Ichinomiya Citizen's Hospital
Toyohashi Citizen's Hospital
Nagoya City University
National Toyohashi Hospital
Nagoya City Hospital
Nagoya University
Aichi Cancer Center
Aichi Medical University
Japanese Red Cross Nagoya Second Hospital
Fujita Health University
Anjo Kosei Hospital
Gifu Prefectural Hospital
Gifu University
Ogaki Municipal Hospital
Yamada Red Cross Hospital
Ise General Hospital
Mie University
National Kanazawa Hospital
Fukui Red Cross Hospital
Fukui Saiseikai Hospital
Fukui Prefectural Hospital
Koseiren Takaoka Hospital
Toyama Red Cross Hospital
Toyama Citizen's Hospital
Ishikawa Prefectural Central Hospital
Kyoto First Red Cross Hospital
National Kyoto Hospital
National Maizuru Hospital
Kyoto University
Kyoto Second Red Cross Hospital
Wakayama Red Cross Hospital
Center for Adult Diseases, Osaka
National Osaka Minami Hospital
Kitano Hospital
Tennoji Hospital
Osaka Red Cross Hospital
Osaka City University
Osaka Prefectural Hospital
Osaka Seamen's Insurance Hospital
Osaka University
Research Institute for Microbial Diseases, Osaka University
Shinsenri Hospital
Ikeda Municipal Hospital
Osaka National Hospital
Osaka Rosai Hospital
Takarazuka City Hospital
Osaka Teishin Hospital
Minoo Municipal Hospital
Sakai Municipal Hospital
Hanwa Hospital
Yao Municipal Hospital
Kinki University
Nishinomiya Municipal Chuo Hospital
Kansai Rosai Hospital
Itami Municipal Hospital
Hyogo Prefectural Nishinomiya Hospital
Tane Hospital
Kobe Municipal Central Hospital
Nara Medical University
Kansai Medical University
Okayama University
Kurashiki Chuo Hospital
Tottori Prefectural Kosei Hospital
Tottori Red Cross Hospital
Tottori University
Shimane Medical University
Hiroshima University
Hiroshima Citizen's Hospital
Hiroshima Red Cross & Atomic-Bomb Survivors Hospital
National Kure Hospital
National Iwakuni Hospital
Yamaguchi Prefectural Chuo Hospital
National Shimonoseki Hospital
National Zentsuji Hospital
Kagawa Medical School
Takamatsu Red Cross Hospital
Kagawa Rosai Hospital
Komatsujima Red Cross Hospital
Ehime Prefectural Central Hospital
Ehime University
University of Tokushima
Shikoku Cancer Center Hospital
Kyushu Cancer Center
Kyushu Rosai Hospital
Omuta City Hospital
National Fukuoka Chuo Hospital
National Saga Hospital
Nagasaki Chuo National Hospital
Nagasaki Municipal Hospital
Isahaya General Hospital
Sasebo City Hospital
National Oita Hospital
Miyazaki Prefectural Hospital
Miyazaki Medical College
National Minami Kyushu Chuo Hospital
University of the Ryukyus
Okinawa Prefectural Nanbu Hospital

intrahepatic foci. However, Uchida et al. [4] demonstrated that the concomitant administration of lipiodol clearly enhanced the effect of TAE on HCC, and segmental L-TAE did not adversely affect normal tissues.

The present clinical trial is the first randomized study on the effects of a combination of chemotherapeutic drugs with L-TAE in the treatment of HCC. Four endpoints were analyzed in this study, and they showed no significant difference between the two treatment groups. The survival of the patients should be the primary endpoint, but the data are premature; further follow-up is required for the final evaluation. However, the incidence of toxic effects observed following therapy with FARM L-TAE was lower than that noted after treatment with ADR L-TAE. These results indicate that FARM provides a more favorable effect than does ADR in L-TAE treatment of HCC. The hospitals that participated in this study are listed in Table 6.

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