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Prospective and randomized clinical trial for the treatment of hepatocellular carcinoma – a comparison of lipiodol-transcatheter arterial embolization with and without Adriamycin (first cooperative study)*

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Summary. A randomized, controlled clinical trial comparing the use of lipiodol-transcatheter arterial embolization (L-TAE) in the presence versus the absence of Adriamycin (ADR) for the treatment of hepatocellular carcinoma was conducted from August 1988 through September 1989. In all, 125 Japanese hospitals participated in this study and 289 patients were entered in the trial. The patients were randomly allocated into group A (L-TAE) or group B (L-TAE+ADR) by telephone registration. There was no significant difference in background factors between group A and group B. Additional treatment, including repeated TAE or hepatic resection, was given to 189 patients. Among the four endpoints analyzed, the rate of tumor reduction and lipiodol accumulation in the tumor did not significantly differ between the two groups. The 3-year survival values for groups A and B were 33.6% and 34.9%, respectively; the difference was not significant. The serum alpha-fetoprotein level, however, decreased to a significantly greater extent in the group that received ADR than in the group that did not ($P < 0.05$). This result suggests that ADR has some favorable additional effect in L-TAE for the treatment of hepatocellular carcinoma.

Introduction

Transcatheter arterial embolization with an anticancer agent that is suspended in lipiodol and particles of gelatin sponge (L-TAE) has become one of the standard treatments for advanced hepatocellular carcinoma (HCC). Adriamycin (ADR) has been commonly used as an anticancer agent in L-TAE, but its efficacy has not been sufficiently evaluated by a prospective and randomized study.

In the present study, a multi-institutional, randomized, controlled clinical trial was conducted to elucidate the effects of ADR in L-TAE for the treatment of HCC.

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Table 1. Summary of the 125 institutions comprising the Cooperative Study Group for Liver Cancer Treatment of Japan (first cooperative study)

Hokkaido University	National Yokosuka Hospital	Minoo Municipal Hospital
Sapporo Medical College	National Yokohama Higashi Hospital	Sakai Municipal Hospital
Asahikawa Medical College	Sagamihara National Hospital	Hanwa Hospital
National Sanatorium Dohoku Hospital	Kanagawa Cancer Center	Yao Municipal Hospital
Asahikawa City Hospital	National Tosei Hospital	Kinki University
Asahikawa Kosei Hospital	Shizuoka Red Cross Hospital	Nishinomiya Municipal Chuo Hospital
Kitano Hospital	Shizuoka Municipal Hospital	Kansai Rosai Hospital
Sapporo Kosei Hospital	Japanese Red Cross Nagoya First Hospital	Itami Municipal Hospital
Sapporo Hokuyu Hospital	Shakai Hoken Chukyo Hospital	Shinsenri Hospital
TSW Memorial Hospital	Nagoya National Hospital	Ikeda Municipal Hospital
Sapporo City Hospital	Meitetsu Hospital	Hyogo Prefectural Nishinomiya Hospital
Hirosaki University	Gifu Prefectural Hospital	Tane Hospital
Kensei Hospital	Ogaki Municipal Hospital	Kobe Municipal Central Hospital
Hiraga General Hospital	Yamada Red Cross Hospital	Okayama University
Akita University	Ise General Hospital	Kawasaki Medical School
Akita City Hospital	National Toyohashi Hospital	Hiroshima University
Iwate Prefectural Chuo Hospital	Nagoya City University	Yamaguchi Prefectural Chuo Hospital
Iwate Medical University	Nagoya University	Tottori Prefectural Kosei Hospital
National Sendai Hospital	Mie University	Tottori Red Cross Hospital
Tohoku Rosai Hospital	National Kanazawa Hospital	National Iwakuni Hospital
Sendai City Medical Center	Fukui Red Cross Hospital	National Shimonoseki Hospital
Tohoku University	Fukui Saiseikai Hospital	National Kure Hospital
Miyagi Medical Center for Adults	Fukui Prefectural Hospital	National Zentsuji Hospital
Yamagata Prefectural Chuo Hospital	Ishikawa Prefectural Central Hospital	Kagawa Medical School
Yamagata City Saiseikan Hospital	Kyoto First Red Cross Hospital	Takamatsu Red Cross Hospital
Yamagata University	National Kyoto Hospital	Kagawa Rosai Hospital
Takeda General Hospital	National Maizuru Hospital	Komatsujima Red Cross Hospital
Soma Hospital	Wakayama Red Cross Hospital	Ehime Prefectural Central Hospital
Niigata Cancer Center Hospital	Center for Adult Diseases, Osaka	Ehime University
National Sanatorium Nishigunma Hospital	National Osaka Minami Hospital	University of Tokushima
Maebashi Red Cross Hospital	Kitano Hospital	Shikoku Cancer Center Hospital
Mito Saiseikai Hospital	Tennoji Hospital	Kyushu Cancer Center
Saitama Cancer Center	Osaka Red Cross Hospital	National Sanatorium Fukuoka Higashi Hospital
Yamanashi Prefectural Chuo Hospital	Osaka City University	Kyushu Rosai Hospital
National Konodai Hospital	Osaka Prefectural Hospital	Omuta City Hospital
National Matsudo Hospital	Osaka Seamen's Insurance Hospital	National Oita Hospital
National Oji Hospital	Osaka University	Miyazaki Prefectural Hospital
Cancer Institute Hospital	Research Institute for Microbial Diseases,	Miyazaki Medical College
Saiseikai Chuo Hospital	Osaka University	National Saga Hospital
National Cancer Center	Osaka National Hospital	Nagasaki Chuo National Hospital
National Sanatorium Tokyo Hospital	Osaka Teishin Hospital	National Minami Kyushu Chuo Hospital
National Medical Center Hospital	Osaka Rosai Hospital	University of the Ryukyus

Patients and methods

Treatment protocols and allocation. From August 1988 through September 1989, 125 major Japanese hospitals participated in this study (Table 1), and a total of 289 patients with HCC were entered in the trial. Via a telephone registration system, the patients were randomly allocated into two treatment groups, group A and group B, at the time of angiography.

Using Seldinger's method, a catheter was inserted into the tumor-feeding artery of the liver, and the following procedures were performed. In group A, only lipiodol was injected intra-arterially, whereas in group B, lipiodol mixed with 40 mg/m^2 ADR dissolved in a contrast medium was injected. Embolization of the feeding arteries was next performed in both groups using particles of gelatin sponge.

In all, 141 patients were allocated into group A and 148 subjects, into group B. Two ineligible patients were completely excluded from the analyses. The remaining 287 eligible patients consisted of 260 protocol-adhering patients, 23 protocol-violating subjects and 4 cases of early death (within 4 weeks of treatment; Table 2). Analysis of endpoints was performed in two ways. One was "intent to treat" analysis, which included protocol-violating patients, and in the other, we analyzed only the protocol-adhering patients. Differences between the two analyses were so small that we describe herein all results obtained in the protocol-adhering patients except the survival curves.

Table 2. Allocation of the 289 patients studied

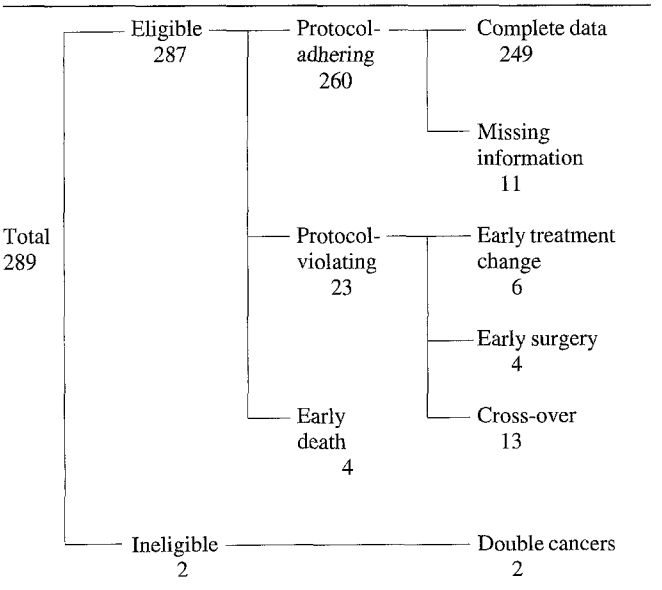

Table 3. Background factors of patients

Background factor		Group A	Group B
Age	Mean	62	61
	Range	41–83	39–83
Sex	M	118	125
	F	21	22
Cirrhosis	+	108	122
	–	24	22
Clinical stage[a]	I	88	87
	II	39	44
	III	2	9
Child's classification	A	102	107
	B	25	33
	C	3	7
PS	0	77	71
	1	36	38
	2	3	10
	3	1	3
	4	1	0
Eggel's tumor type	Nodular	103	96
	Massive	19	28
	Diffuse	5	4
Encroachment[b]	E1	82	83
	E2	30	34
	E3	9	11
	E4	2	6
AFP prior to TAE (ng/ml)	Mean	2,435	3,177
Lipiodol (ml)	Mean	7.3	8.4
Tumor size (cm^2)	Mean	28	33

[a] According to the criteria of the Liver Cancer Study Group of Japan
[b] Rate of encroachment of tumor: E1, <20%; E2, 20%–40%; E3, 40%–60%; E4, >60%

Indications for treatment. L-TAE was indicated when the following criteria were fulfilled: (1) the diagnosis of HCC was established from the serum alpha-fetoprotein (AFP) level and by imaging procedures; (2) the Karnofsky performance status (PS) was 0, 1, or 2; (3) the laboratory data fulfilled the following conditions: WBC, >3000/mm^3, platelet count, >5 × 10^4/mm^3, and serum creatinine, <1.5 mg/dl; (4) the clinical stage [6] was I or II (controllable ascites; serum bilirubin, <3.0 mg/dl; serum albumin, >3.0 g/dl; ICG R_{15}, <40%; and prothrombin activity, >50%); (5) the patient was older than 14 years of age; and (6) the patient had not received any previous treatment for HCC. Patients presenting with myocardial damage or obstruction in the stem of the portal vein due to a tumor thrombus were excluded.

Additional treatment. At 4 weeks or more after the first L-TAE procedure, additional treatment was given to 189 patients, of whom 107 underwent repeated TAE with ADR or some other agent(s), 56 underwent hepatic resection, and 26 received some other treatment. There was no significant difference in the frequency of additional treatment between group A and group B.

Evaluation of treatment. At 4 weeks or more after L-TAE, the following four factors were compared between the groups to elucidate the effect of ADR in L-TAE:

1. The tumor reduction rate as determined by comparing the reduction in the two-dimensional area of the tumors before and after L-TAE
2. The maximal decrease in serum alpha-fetoprotein levels
3. The amount of lipiodol accumulated in the HCC nodules as estimated by CT imaging
4. Survival curves as generated by the method of Kaplan and Meier

Table 4. Tumor reduction after L-TAE treatment

Reduction rate	Group A (n = 109)		Group B (n = 123)	
0 –24%	34		43	
25%–49%	35		40	
50%–74%	22	30 (27.5%)	24	33 (26.8%)
75%–99%	8		8	
100%	0		1	
Enlargement	10		7	

Table 5. Rate of decrease in serum AFP levels after L-TAE therapy

Cutoff level for AFP (pre-TAE)	Group	n	Decrease rate (%)		
			Mean		SD
>10 ng/ml	A	90	49.0	*	63.0
	B	107	66.0		35.4
>20 ng/ml	A	81	51.6	**	65.0
	B	100	69.0		33.9
>100 ng/ml	A	50	70.1		29.3
	B	75	78.4		23.1

* P = 0.0378, ** P = 0.0461

Results

Background factors of the patients

Although there was no statistically significant difference in the background factors listed in Table 3, there was a clear tendency for group B to be classified as being slightly worse or more advanced than group A in many of the background factors, including liver cirrhosis, clinical stage, Child's classification, performance status, Eggel's macroscopic tumor type, encroachment of the mass, pre-TAE AFP levels, and tumor size.

Tumor reduction

The percentage of patients showing a decrease of >50% in the two-dimensional area of the tumor was 27.5% in group A and 26.8% in group B. There was no significant difference between these values (Table 4).

Changes in serum AFP levels

The changes observed in serum AFP levels after the treatment are shown serially in a Box Whisker plot chart in Fig. 1. The mean AFP value was lower in group B than in group A during weeks 2–9 after the treatment, but no significant difference was demonstrated. However, in all comparisons using three different cutoff levels, the rate of decrease was higher in group B than in group A. The between-group differences in cutoff levels of >10 and >20 ng/ml were statistically significant (P <0.05; Table 5).

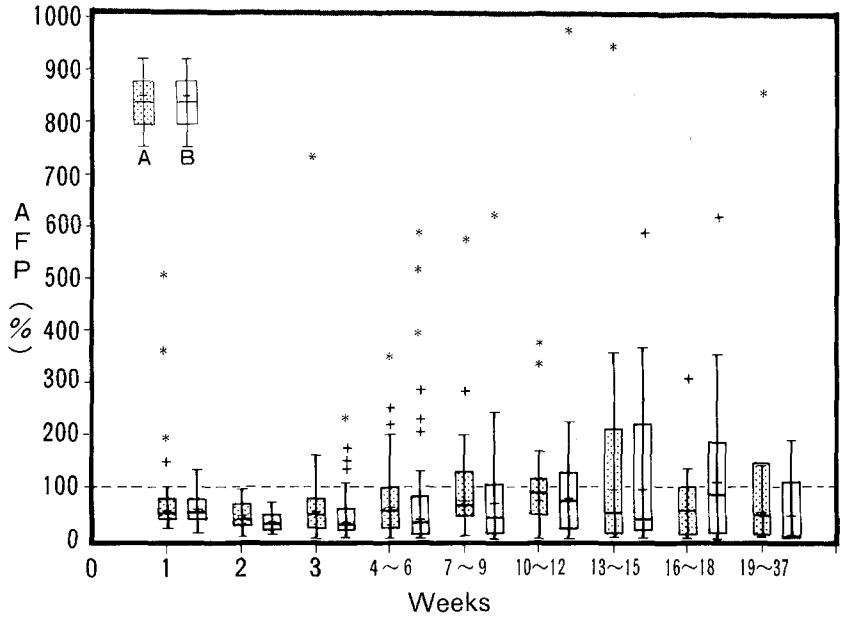

Fig. 1. Changes in serum AFP levels after L-TAE are shown serially in a Box Whisker plot chart. The mean AFP values were lower in group B than in group A during weeks 2–9 after the treatment

Table 6. Lipiodol accumulation following L-TAE treatment

Rate of accumulation	Group A ($n = 110$)		Group B ($n = 127$)	
0	1		0	
<10%	6		9	
<50%	25		25	
≧50%	49	78 (70.9%)	53	93 (73.2%)
100%	29		40	

Lipiodol accumulation in the tumor

The percentage of patients showing lipiodol accumulation amounting to >50% was 71% in group A and 73% in group B, respectively. There was no significant difference between these values (Table 6).

Survival curves

Of the 287 eligible cases, 62 group A patients and 82 group B patients died during the observation period. The 1-, 2-, and 3-year cumulative survival values for group A were 74.4%, 51.3%, and 33.6%, respectively, and those for group B were 65.1%, 42.4%, and 34.9%, respectively. The survival curves did not show any significant difference (Fig. 2).

Side effects

Regarding the toxic effects of the treatment, changes in liver function were not severe in either group A or group B. There was no significant difference in serum GOT, GPT, LDH, total bilirubin, or albumin levels (Fig. 3). A significant difference was observed in the hemoglobin level, whereas no significant difference in the WBC, the platelet count in the peripheral blood, abdominal pain, or fever was

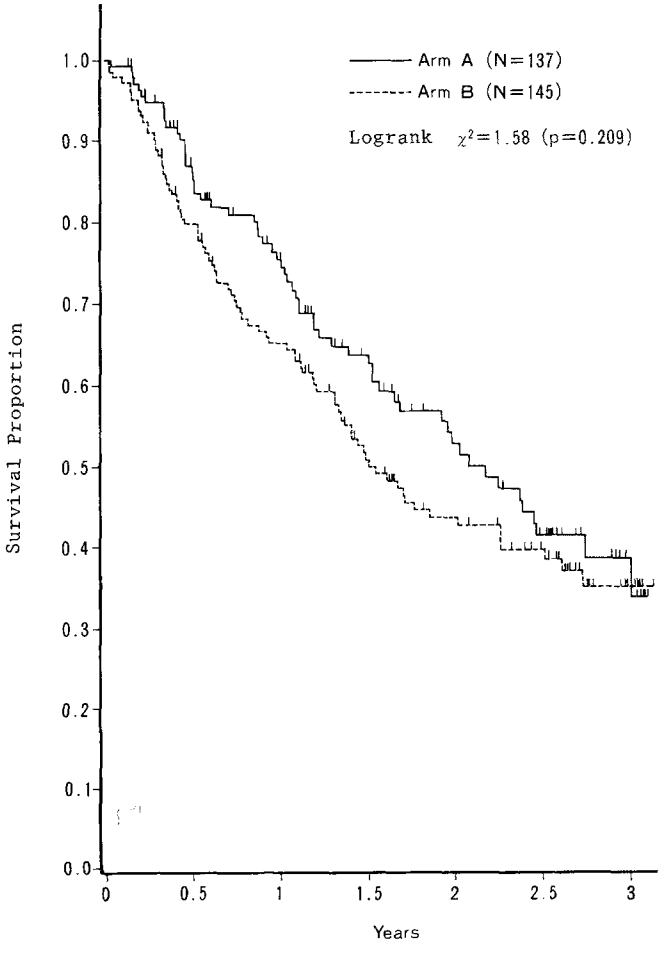

Fig. 2. Survival curves for groups A (L-TAE) and B (L-TAE+ADR). The 1-, 2-, and 3-year cumulative survival values for group A were 74.4%, 51.3%, and 33.6%, respectively, and those for group B were 65.1%, 42.4%, and 34.9%, respectively. The survival curves did not show any significant difference

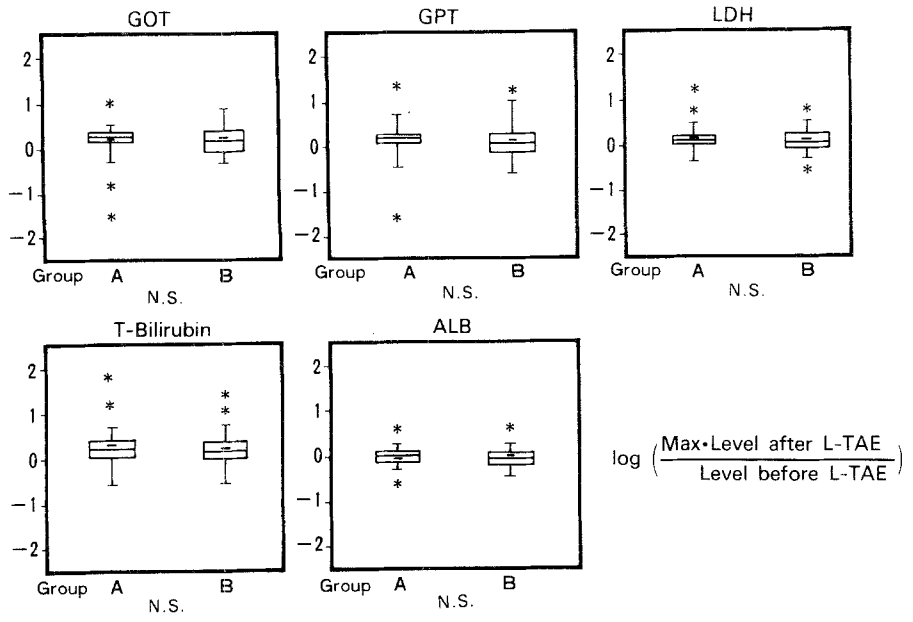

Fig. 3. Comparisons of changes in serum GOT, GPT, LDH, total bilirubin, and albumin levels observed after L-TAE treatment in groups A and B. *N. S.*, Not significant

Table 7. Incidence of toxic effects

Toxic effect	Group A, $n = 115$ (%)	Group B, $n = 134$ (%)	Total, $n = 249$ (%)
WBC decrease	20 (17.4%)	34 (25.4%) *	54 (21.7%)
Hb decrease	11 (9.6%)	30 (22.4%)	41 (16.5%)
Platelet decrease	22 (19.1%)	19 (14.2%)	41 (16.5%)
Abdominal pain	74 (64.3%)	87 (64.9%)	161 (64.7%)
Fever	92 (80.0%)	108 (80.6%)	200 (80.3%)

WBC, hemoglobin (Hb), and platelet decreases were evaluated according to WHO criteria
* $P = 0.002$

found between the groups. The percentage of patients showing a decreased hemoglobin level was 9.6% in group A and 22.4% in group B (Table 7).

Discussion

Since the first report on the selective accumulation of lipiodol in HCC nodules in 1983 [4], a combination of lipiodol, ADR, and particles of gelatin sponge has frequently been used in embolization therapy of HCC. Intravenous or single arterial administration of ADR has not been shown to be effective in the treatment of inoperable HCC [1, 5]. On the other hand, L-TAE with ADR has been reported to be effective, with 2-year survival values ranging from 22% to 43% [7, 9, 14–16]. L-TAE with ADR has been demonstrated to provide the best therapeutic effects, especially in terms of the tumor necrosis rate in resected specimens, whereas the administration of lipiodol alone has not been shown to have a necrotizing effect on HCC nodules [11].

We conducted a multi-institutional, randomized, controlled trial to clarify the additional effects of ADR on L-TAE of HCC. This is the first time such a prospective and randomized study of a great number of patients has been performed. For this kind of trial, it is desirable that there be little difference in the background factors of the patients. However, we could not prepare two groups of patients with exactly the same background factors because L-TAE has a very broad spectrum of indications for the treatment of HCC. Factors such as functional hepatic reserve, performance status, and tumor stage were slightly worse in group B than in group A, although there was no significant between-group difference in background factors. It is well known that some background factors can influence the survival of patients with HCC [12, 13]. Yamashita et al. [15] have reported that the tumor type, AFP value, ascites, treatment protocol, and tumor involvement are important factors affecting the survival of patients after L-TAE. Nomura et al. [8] have observed poor survival for patients with a high pretreatment serum AFP level. An analysis of the background factors and survival values obtained in this study revealed that encroachment of the tumor and the pretreatment serum AFP level significantly affected the survival of the patients. Even slight differences in background factors should be kept in mind in the analysis of differences in survival values.

Some findings obtained after L-TAE have been described as indicators of favorable effects of the treatment. Kawai et al. [3] observed prolonged survival in patients who had received L-TAE, showing greater accumulation of lipiodol in the tumor or a greater decrease in serum AFP levels. Kanematsu et al. [2] reported that a high lipiodol-deposition rate in the tumor correlated closely with a decrease in serum AFP levels as well as a reduction in the tumor size after L-TAE. Of course, the survival value was the primary endpoint of this comparative study, and we did not observe any difference between the two treatment groups.

When the three factors discussed above were compared in this study, only a greater decrease in serum AFP levels was observed in group B. The addition of ADR to L-TAE may have had a favorable antitumor effect as compared

with treatment by lipiodol and gelatin sponge alone. However, it did not result in a significant difference in survival, partly because some of the background factors for group B had a tendency to be classified as being slightly worse or more advanced than those for group A. The rates of reduction in tumor size and the lipiodol accumulation did not differ between the groups. Our follow-up period might have been too short for evaluation of the tumor reduction.

To date, L-TAE therapy has not been reported to produce any serious side effects [2, 10]. In this study, no significant difference in toxicity was observed except for a slight difference in the hemoglobin level. The reason for this side effect cannot be adequately explained, but temporary hypersplenism after the treatment would probably be one factor contributing to the decrease observed in group B.

In conclusion, we surmise that ADR provides some additional anticancer effects when combined with L-TAE in the treatment of HCC. However, the greater part of the effects derive from embolization of the tumor-feeding arteries by the particles of gelatin sponge.

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