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

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Abstract. A randomized controlled clinical trial was conducted to compare the use of Farmorubicin (FARM) and Adriamycin (ADR) in Lipiodol transcatheter arterial chemoembolization (L-TAE) as a treatment of hepatocellular carcinoma. In all, 192 hospitals participated, and 415 patients were enrolled in the study during the period from October 1989 through December 1990, and their data were collected. The patients were randomly allocated to group A (FARM) or group B (ADR) by a central telephone registration. Several clinical characteristics were slightly worse in group A than in group B, but there was no statistically significant difference. The actual doses of FARM and ADR were 72 mg/body and 48 mg/body, respectively. Additional treatments, including repeated TAE or surgery, were given to 248 patients. The 1- and 2-year survival rates were 69% and 44% for group A and 74% and 57% for group B, respectively. The difference was marginally significant (*P* value in the log-rank test, 0.038). When each group of patients was classified into two subgroups, i.e., high-risk and low-risk categories, based on the severity index calculated by the Cox regression model from significant prognostic factors, the ADR subgroup was significantly superior to the FARM subgroup in the low-risk category, but there was no significant difference between the subgroups in the high-risk category. The change in the serum alpha-fetoprotein level, the extent of Lipiodol accumulation in the tumor, and the extent of tumor reduction did not show any significant difference between the groups. At the above-mentioned doses, ADR seemed to have efficacy almost the same as or slightly superior to that of FARM in L-TAE for the treatment of hepatocellular carcinoma.

Introduction

Since 1988, the Cooperative Study Group for Liver Cancer Treatment of Japan has conducted two consecutive randomized controlled studies of Lipiodol transcatheter arterial chemoembolization (L-TAE) for the treatment of hepatocellular carcinoma (HCC). The first study [1] was conducted to compare the regimens of L-TAE only and L-TAE with Adriamycin (ADR). The second study [5] compared L-TAE with Farmorubicin (FARM) and L-TAE with ADR and was open for patient entry from October 1989 through December 1990. This paper reports the preliminary results of the second study based on the follow-up through the end of 1992.

Patients and methods

Patients. A total of 192 Japanese hospitals participated in this study (Table 1). A total of 415 patients with hepatocellular carcinoma (HCC) were enrolled in this trial, and their data were collected. The eligibility

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Table 1. List of the 192 hospitals participating in the second cooperative study

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 Cancer Center Hospital
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 City General 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
Chiba University
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
International Medical Center of Japan
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 City Hospital
Toyohashi City 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 City 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 City General 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 City 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

Table 2. Classification of the 415 patients studied

Total	Eligible	Protocol adhering	Complete data	A	B
415	414	390	365	185	180
			Missing information 25	12	13
		Protocol violating 21	Early treatment change 5	2	3
			Early surgery 5	3	2
			Allocation violation 11	4	7
		Early death 3		2	1
	Ineligible 1		Double cancer 1		1

criteria were: (1) a diagnosis of HCC as established on the basis of image findings and the serum alpha-fetoprotein (AFP) level; (2) a Karnofsky performance status (PS) of 0, 1, or 2; (3) laboratory data indicating a WBC count of $\geqq 3{,}000/mm^3$, a platelet count of $\geqq 5\times10^4/mm^3$, and a serum creatinine level of $\leqq 1.5$ mg/dl; (4) a clinical stage of I or II according to the General Rules for the Clinical and Pathological Study of Primary Liver Cancer [4]; (5) an age of over 14 years; and (6) the absence of any previous treatment for HCC. Patients were excluded if there was myocardial damage or obstruction in the stem of the portal vein due to the tumor thrombus.

Allocation of patients. Via a central telephone registration, the patients were randomly allocated to two treatment groups, A and B, at the time of angiography. In all, 208 patients were allocated to group A and 207 were randomized to group B. One patient was ineligible because of double cancers and was completely excluded from the analyses. The remaining 414 eligible patients were classified into 390 patients who adhered to the protocol, 21 patients who violated the protocol, and 3 early deaths that occurred within 4 weeks of the treatment (Table 2). There was no statistical difference between groups A and B concerning the background factors of the patients.

Treatment methods. Using Seldinger's method, Lipiodol mixed with FARM dissolved in a contrast medium was injected into the hepatic arteries feeding the HCC in group A, whereas group B received ADR. Embolization of the tumor-feeding arteries with particles of gelatin sponge was performed following this procedure [5]. The mean actual doses were 71.5 mg/body for FARM and 47.9 mg/body for ADR.

Additional treatment. At 4 weeks or more after the first L-TAE, additional treatments were given to 248 patients. They consisted of 158 patients who received 2 or 3 additional L-TAE treatments with FARM or ADR, 70 patients who underwent surgery, and 20 patients who received some other treatments. There was no significant difference in the frequency of additional treatments between the two groups.

Evaluation of the treatment. The following four factors were used as the endpoints to determine the relative efficacy of the drugs: (1) the maximal decrease in the serum AFP level, (2) the extent of Lipiodol accumulation in HCC nodules as estimated by CT imaging, (3) the extent of tumor size reduction calculated as the percentage of reduction in the two-dimensional size of the largest tumor, and (4) survival.

Statistical analysis. The distribution of clinical characteristics was compared between the two groups by tabulation and statistical tests (χ^2 tests for nominal variables and the Wilcoxon test for ordinal or continuous variables). Three endpoints, i.e., the maximal decrease in the serum AFP level on a log scale, the extent of Lipiodol accumulation, and the percentage of reduction in tumor size, were compared by the Wilcoxon test. Survival curves were estimated by the Kaplan-Meier method, and differences between the groups were tested by the log-rank test. Prognostic factors were screened by log-rank tests with stratification by treatment group. The severity index was calculated by the Cox regression model from selected prognostic factors, and subgroup analysis was carried out using the classification based on this index. Primary analyses were done for 199 patients in group B (ADR) and 204 patients in group A (FARM), excluding 11 allocation-violating cases and 1 ineligible case. There was no essential change in the results if the analyses were restricted to more protocol-adhering patients. Toxic effects were evaluated by comparing the pre- and posttreatment values with paired *t*-tests and the WHO classification.

Table 3. Clinical characteristics of the 416 patients

Characteristic		A (n = 208)	B (n = 208)	P value
Age (years)	Mean	61.6	62.2	0.42
	Range	36–80	38–79	
Sex	M	169	163	0.54
	F	38	43	
Liver cirrhosis	+	166	175	0.35
	–	31	25	
Clinical stage	I	137	129	0.43
	II	59	66	
	III	1	1	
Child's classification	A	151	140	0.24
	B	44	49	
	C	3	7	
PS	0	129	130	0.89
	1	27	31	
	2	11	6	
	3	1	2	
Eggel's tumor type	Nodular	149	152	0.63
	Massive	42	40	
	Diffuse	8	6	
Encroachment[a] (occupation rate of tumor)	E_1	101	113	0.17[b]
	E_2	51	48	
	E_3	22	18	
	E_4	9	5	
AFP pre-TAE	Median	99.8	127.4	0.77
Lipiodol (ml)	Mean	6.5	6.2	0.35
Tumor size (cm^2)	Mean	38.0	31.3	0.15[b]

[a] E_1, <20%; E_2, 20%–40%; E_3, 40%–60%; E_4, >60%
[b] Tendency toward advanced disease

Results

Clinical characteristics of the patients

There was no statistically significant difference between the two groups in the clinical characteristics listed in Table 3. However, there was a tendency for group A to contain more advanced patients than group B in terms of the clinical characteristics, for example, the mean tumor size and the tumor encroachment, i.e., the occupation rate of the HCC nodule [3].

Changes in serum AFP levels

The temporal changes in serum AFP levels after the treatment are shown serially by means of Box Whisker plots

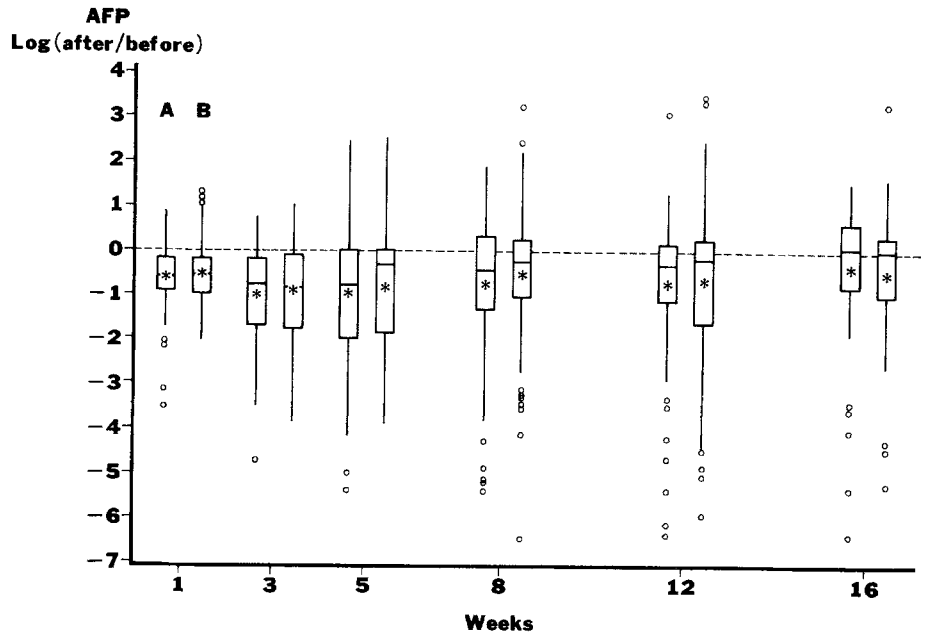

Fig. 1. Changes in serum AFP levels after L-TAE are shown serially in Box Whisker plots. The serum AFP level decreased and continued to be depressed for 8 weeks after the treatment in both groups

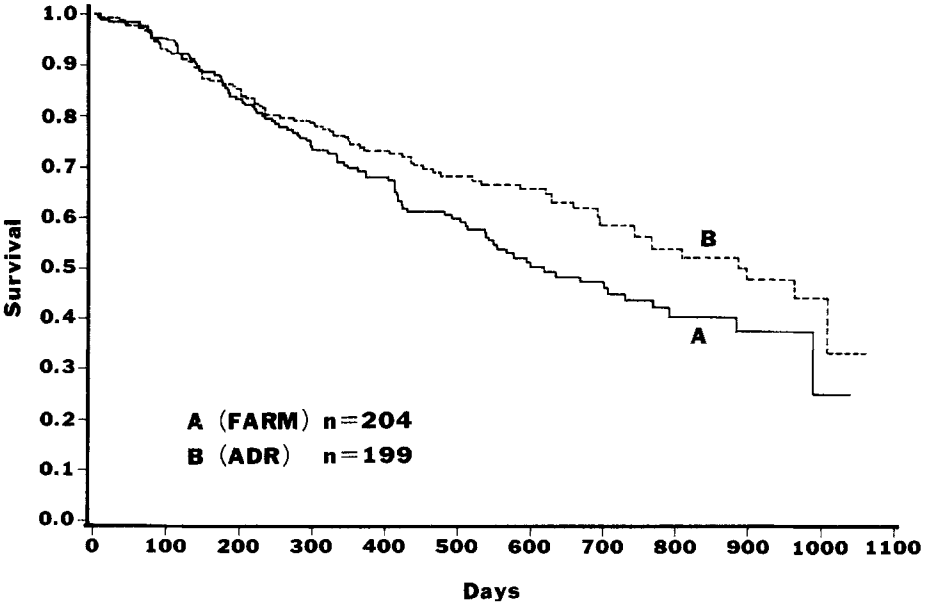

Fig. 2. Survival curves generated for group A (L-TAE + FARM) and group B (L-TAE + ADR). The 1- and 2-year cumulative survival rates for group A were 69% and 44%, and those for group B were 74% and 57%, respectively. The difference between the curves was marginally significant (*P* value of the log-rank test: 0.038)

(Fig. 1). The serum AFP level decreased and continued to be depressed for 8 weeks after the treatment in both groups. The mean maximal decreases in the serum AFP level were 50% in group A and 43% in group B. When the patients were examined at two different cutoff values, 20 and 100 ng/ml of AFP, the mean maximal decreases were 56% and 62% in group A and 51% and 55% in group B, respectively. There was no statistically significant difference between the two groups.

Lipiodol accumulation in the tumor and tumor reduction

The mean Lipiodol accumulation was 67% in group A and 71% in group B. The mean tumor reduction rates were 15% in group A and 22% in group B. There was no significant difference between the two groups.

Survival curves

Figure 2 presents the survival curves generated for the 403 eligible patients, excluding the 11 allocation-violating patients and 1 ineligible patient. In all, 94 patients in group A and 76 patients in group B died during the follow-up period. The 1- and 2-year cumulative survival rates for group A were 69% and 44%, and those for group B were 74% and 57%, respectively. The difference between the curves was marginally significant (*P* value, 0.038; log-rank test).

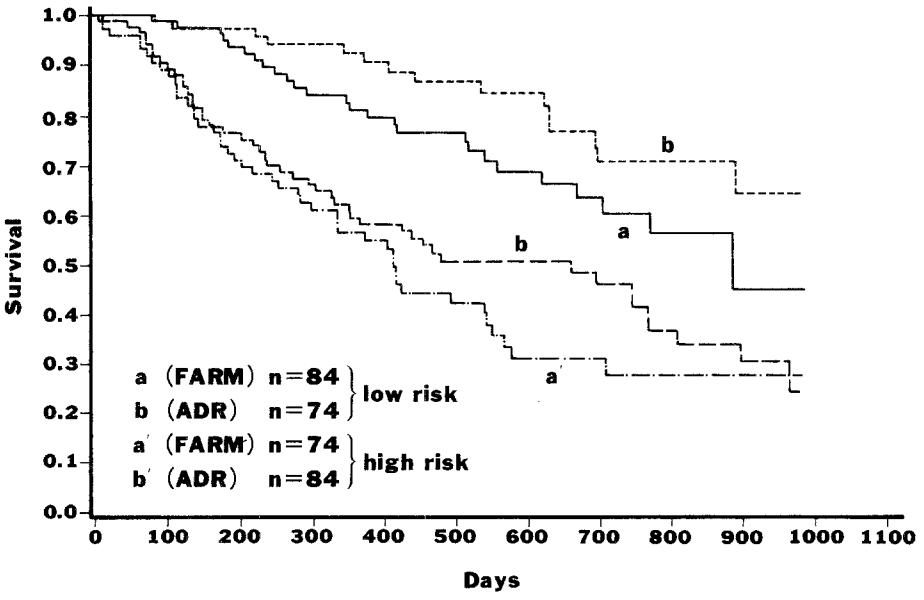

Fig. 3. Survival curves generated for both groups after classification into low-risk and high-risk subgroups. The ADR subgroup was significantly superior to the FARM subgroup in the low-risk category ($P = 0.038$), but the difference was not significant in the high-risk category ($P = 0.326$)

Table 4. Stratification of patients based on the severity index

	Variable (model) selection by Cox regression		
	Coefficient	*P* value	Risk ratio
log (tumor size)	0.26	0.001	
pre: log (AFP)	0.09	0.005	
Encroachment (1, 2-3, 4)	0.87	<0.001	2.38
Child's classification (A-B, C)	0.97	<0.001	2.64

	Distribution of severity index				
	5%	25%	50%	75%	95%
Hazard	0.39	0.56	1	1.50	4.84

Statistical analysis of the survival curves

Four prognostic factors were selected for the calculation of the severity index and the adjustment of heterogeneity among the patients: the pretreatment tumor size on a log scale, the pretreatment AFP level on a log scale, the encroachment (E_1, $E_2 \rightarrow 0$, E_3, $E_4 \rightarrow 1$), and Child's classification (A → 0, B, C → 1). Categorization of classified variables was also determined by the results of the score tests. The significance (risk) of these factors is shown in Table 4 as the coefficients of the Cox regression model stratified by treatment group. The severity index was calculated as the linear combination of these factors with the listed coefficients, and the percentiles of the risk ratio calculated were 0.39 (5%), 0.56 (25%), 1 (50%), 1.50 (75%), and 4.84 (95%). Figure 3 presents the survival curves stratified by this severity index (≧50 percentile or <50 percentile) and by treatment group. The ADR subgroup was superior to the FARM subgroup in the low-risk patients (*P* value of the log-rank test, 0.038), but there was no difference in the high-risk patients.

Table 5. Toxic effects: comparison between pre- and post-TAE observations

		A		B	
		Pre	Post	Pre	Post
WBC count ($\times 10^3$/mm^3)	*n*	199	170	202	170
	Mean	5.02	5.01	5.14	4.87
	SD	1.80	2.37	1.86	2.25
Log post/pre	*t*	−1.98		−3.06[a]	
	P value	0.05		0.00	
Platelet count ($\times 10^4$/mm^3)	*n*	199	167	200	169
	Mean	13.1	17.7	12.5	17.4
	SD	8.5	10.9	5.8	9.6
Log post/pre	*t*	8.92		10.11	
	P value	0.00		0.00	
Hemoglobin (g/dl)	*n*	201	169	201	170
	Mean	13.3	12.2	13.4	12.3
	SD	1.8	1.8	1.8	1.7
Log post/pre	*t*	−7.68		−7.98	
	P value	0.00		0.00	

[a] Tendency toward a decrease post-TAE

Side effects

Regarding the toxic effects of the treatment, changes in liver function were not severe in either group A or group B. No significant difference was found between the two groups in relation to the serum AST, ALT, LDH, total bilirubin, or albumin level. The toxic effects of the drugs on the peripheral blood were evaluated by comparing the WBC counts, platelet counts, and hemoglobin levels determined before and after L-TAE. The WBC counts in group B showed a tendency to decrease slightly more than those in group A after L-TAE, but the difference was not significant (Table 5). The changes in the platelet count and hemoglobin level did not differ significantly between groups A and B.

Discussion

In the first cooperative study, the serum AFP level decreased significantly more in the ADR group than in the control group, but the survival rates were not statistically different [1]. Among several clinical characteristics used as prognostic factors, the most significant factor was the tumor encroachment. The present study yielded results that are very similar to those obtained in the first study. The most important prognostic factor was, again, the tumor encroachment. Further evaluations will be necessary concerning the reliability and objectivity of this factor, because it has been considered to be vague and subjective.

Using a multivariate Cox regression analysis, the severity index of HCC was calculated in this study. The patients in group A and group B were then classified into two categories: a high-risk subgroup and a low-risk subgroup. The ADR subgroup was significantly superior to the FARM subgroup in the low-risk category, but there was no significant difference in the high-risk category. This result probably means that the beneficial effects of anticancer drugs differ according to the extent of tumor progression and to the clinical factors comprising the severity index. Questions will be raised as to whether there are any additional benefits in using anticancer drugs with L-TAE and, if so, as to which group of patients will benefit the most. The clinical characteristics can be classified into two categories: the hepatic functional reserve and the extent of tumor progression. The former may include Child's classification, liver cirrhosis, clinical stage [4], and PS, and the latter may include the tumor encroachment, tumor size, Eggel's type, and pretreatment AFP value. Stratified analyses concerning these factors will be necessary to answer the above questions.

ADR has a more potent cardiotoxicity than FARM [2]. However, as L-TAE is an organ-targeted therapy, ADR can be given at ordinary doses without producing any remarkable cardiotoxicity. Raoul et al. [6] reported that from a pharmacokinetic standpoint, the combination of ADR, Lipiodol, and gelatin sponge can decrease the systemic toxic effects of ADR in chemoembolization for HCC. In the present study, ADR showed a tendency to decrease the WBC count slightly more than FARM after L-TAE.

Although we cannot yet draw a final conclusion because the follow-up period is too short, 48 mg/body of ADR seemed to have a therapeutic efficacy almost the same as or slightly superior to that of 72 mg/body of FARM in L-TAE for the treatment of HCC.

References

1. Kawai S, Okamura J, Ogawa M, Ohashi Y, Tani M, Inoue J, Kawarada Y, Kusano M, Kubo Y, Kuroda C, Sakata Y, Shimamura Y, Jinno K, Takahashi A, Takayasu K, Tamura K, Nagasue N, Nakanishi Y, Makino M, Masuzawa M, Mikuriya S, Monden M, Yumoto Y, Mori T, Oda T, the Cooperative Study Group for Liver Cancer Treatment of Japan (1992) 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). Cancer Chemother Pharmacol 31 [Suppl I]: S1
2. Lahtinen R, Kuikka J, Nousiainen T, Uusitupa M, Lansimies E (1992) Cardiotoxicity of epirubicin and doxorubicin: a double-blind randomized study. Eur J Haematol 46: 301
3. Liver Cancer Study Group of Japan (1987) The general rules for the clinical and pathological study of primary liver cancer (in Japanese). Kanehara & Co., Tokyo, p 18
4. Liver Cancer Study Group of Japan (1989) The general rules for the clinical and pathological study of primary liver cancer. Jpn J Surg 19: 98
5. Okamura J, Kawai S, Ogawa M, Ohashi Y, Tani M, Inoue J, Kawarada Y, Kusano M, Kubo Y, Kuroda C, Sakata Y, Shimamura Y, Jinno K, Takahashi A, Takayasu K, Tamura K, Nagasue N, Nakanishi Y, Makino M, Masuzawa M, Mikuriya S, Monden M, Yumoto Y, Mori T, Oda T, the Cooperative Study Group for Liver Cancer Treatment of Japan (1992) 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). Cancer Chemother Pharmacol 31 [Suppl I]: S20
6. Raoul JL, Heresbach D, Bretagne JF, Bentue Ferrer D, Duvauferrier R, Bourquet P, Messner M, Gosselin M (1992) Chemoembolization of hepatocellular carcinomas. A study of the biodistribution and pharmacokinetics of doxorubicin. Cancer 70: 585