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Evaluation of transcatheter arterial embolization with epirubicin-lipiodol emulsion for hepatocellular carcinoma*

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Summary. A total of 18 patients with hepatocellular carcinoma (HCC) were treated by transcatheter arterial embolization (TAE) with a 4′-epi-doxorubicin (EDX)-lipiodol emulsion. Infusion of the EDX-lipiodol emulsion (EDX-L) via the hepatic artery was followed by the injection of gelatin sponge in 12 cases. The response and survival of these 12 patients following EDX-L treatment were compared with those of 42 subjects treated with a doxorubicin-lipiodol emulsion (DX-L) and those of 23 patients treated by TAE with gelatin sponge (GS) only. In the group treated with EDX-L, nine cases were AFP-positive in sera and four showed a decrease in serum AFP values to less than 10% of the pretreatment level. Seven cases showed a partial response, and nine cases showed no change in the size of the tumor. In the group treated with EDX-L, nine cases are alive, and the oldest has survived for more than 431 days since the treatment. The half-year survival value was 57%, and the 1-year survival value was 49%. These values did not differ significantly from those calculated for the group treated with DX-L. The 1-year survival value determined for patients treated with a lipiodol emulsion (EDX-L or DX-L) followed by GS was 65%, and the 2-year survival value was 39%. These results rates are significantly better than those obtained in patients treated with GS only (1-year survival, 39%; 2-year survival, 13%).

Introduction

The prognosis for patients with HCC has improved as a result of advances in both the diagnosis and the treatment of this disease. TAE using an oily material for unresectable HCC has been performed in many patients, and an improvement in the prognosis has been reported [2, 4, 7]. We have carried out TAE with GS since 1980 and TAE with DX-L since 1986, resulting in an increase in the survival of patients.

New analogs of DX have recently been used for the treatment of HCC. Epirubicin (4′-epi-doxorubicin, EDX) is one such analog, and in randomized clinical studies it has shown less acute toxicity and less cardiac toxicity than DX given at equimolar doses [1].

In the present study, the effectiveness of EDX-L against HCC was compared with that of DX-L and that of TAE with GS alone. The parameters compared were the tumor regression rate after the first treatment and the survival of patients as determined using Kaplan-Meier's method.

Patients and methods

A total of 83 cases of HCC treated by TAE were studied. In all, 18 patients were treated with EDX-L, 42 were treated with DX-L, and 23 were treated with gelatin sponges (GS) only. In 12 patients in the EDX-L group and 27 in the DX-L group, TAE with lipiodol emulsion was followed by GS. The remainder (6 subjects in the EDX-L group and 15 patients in the DX-L group) were treated with lipiodol emulsion alone.

All cases were classified according to the criteria of the Liver Cancer Study Group of Japan [3] on the basis of liver function (Child's classification), clinical staging, staging of progression, and tumor size. The clinical profiles of the three groups are presented in Tables 1 and 2.

The EDX-L emulsion was composed of 60 mg EDX in 2.4 ml distilled water, 7 ml lipiodol, and 360 mg HCO-60. The DX-L emulsion comprised 40 mg DX, 6 ml lipiodol, and 240 mg HCO-60. These emulsions are well suited for the slow release of anticancer drugs. For the DX-L emulsion, the half-dose release time is 150 h [5].

In five patients in the EDX-L group cases and six in the DX-L group, the concentration of EDX and DX in the serum was examined, respectively. The effect of the treatment was evaluated according to the change in serum AFP levels, the tumor regression rate, and the survival after treatment. The tumor regression rates were compared in the following manner. The products of the longitudinal and latitudinal diameters of a slice from the largest tumor on the computed tomograph (CT) prior to and at 1–3 months after TAE were compared to determine the rate of tumor regression. The response criteria were defined as follows: partial

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Table 1. Characteristics of the patients

Treatment	Number of patients	Mean age (years)	Sex (M/F)	Child's classification			Clinical stage			T factor				Tumor size (cm)		
				A	B	C	I	II	II	1	2	3	4	≦2	2<t<5	≧5
EDX-L-TAE	18	60.1 ± 8.4	22/1	9	6	3	8	8	2	2	4	2	10	2	8	8
	(12)	(61.2 ± 5.4)		(7)	(4)	(1)	(6)	(4)	(2)	(0)	(4)	(2)	(6)	(0)	(7)	(3)
DX-L-TAE	42	61.4 ± 10.1)	32/10	11	22	9	10	27	5	2	6	11	23	2	19	21
	(27)	(62.1 ± 8.5)		(9)	(15)	(3)	(7)	(20)	(0)	(1)	(2)	(7)	(17)	(1)	(13)	(8)
GS-TAE	23	59.9 ± 9.0	15/3	4	14	5	3	17	3	0	3	2	18	3	7	13

( ): Lipiodol followed by gelatin sponges

Table 2. Tumor factors and clinical stages of each group

All patients:

Clinical stage	Tumor factors				Totals
	1	2	3	4	
I	2	3	4	13	22
II	2	8	7	34	51
III	1	1	4	4	10
Totals	5	12	15	51	83

GS-TAE:

Clinical stage	Tumor factors				Totals
	1	2	3	4	
I	0	0	0	3	3
II	0	3	0	14	17
III	0	0	2	1	3
Totals	0	3	2	18	23

DX-L:

Clinical stage	Tumor factors				Totals
	1	2	3	4	
I	1 (1)	2 (1)	3 (2)	5 (3)	11 (4)
II	1	3 (1)	6 (5)	16 (14)	26 (20)
III	1	0	2	2	5
Totals	3 (1)	5 (2)	11 (7)	23 (17)	42 (27)

EDX-L:

Clinical stage	Tumor factors				Totals
	1	2	3	4	
I	1	1	1 (1)	5 (3)	8 (4)
II	1	2 (2)	1 (1)	4 (3)	8 (6)
III	0	1 (1)	0	1 (1)	2 (2)
Totals	2	4 (3)	2 (2)	10 (7)	18 (12)

( ): Lipiodol followed by gelatin sponges

response (PR), the reduction rate was more than 50% after therapy; no change (NC), the reduction rate was less than 50%; and progressive disease (PD), the tumor increased by more than 25% in size.

Survival curves were constructed by the Kaplan-Meier method and were compared using the generalized Wilcoxon test, the log-rank test and the Cox-Mantel test.

Results

Plasma levels of EDX and DX after TAE

The maximal concentration of EDX in five patients in the EDX-L group was 0.096 ± 0.040 μg/ml from the time just after injection until 10 min after the injection (Fig. 1). The maximal concentration of DX in six patients in the DX-L group was 0.161 ± 0.063 μg/ml after 5–15 min.

Changes in serum AFP levels

Serum AFP levels in 10 patients in the EDX-L group, 19 in the DX-L group, and 13 in the GS-TAE group were examined weekly. In all, 6 subjects in the EDX-L group, 16 in the DX-L group, and 11 in the GS-TAE group showed more than a 50% reduction (Fig. 2). Moreover, four patients in the EDX-L group and seven subjects in the DX-L group showed more than a 90% reduction in serum AFP levels, but only one patient in the GS-TAE case showed more than a 90% decrease. In addition, serum levels of PIVKA-II were examined weekly in two subjects in the EDX-L group and decreased greatly in both cases.

Change in the tumor size after TAE

In all, 7 patients (47%) in the EDX-L group were classified as showing a PR, and 6 of them had been treated with EDX-L and GS (Table 3). This percentage was almost the same as the PR rate noted in DX-L cases (43%) and was higher than that observed in GS-TAE cases (35%). Furthermore, the PR rate achieved by patients treated with lipiodol emulsion followed by GS was 60% in the EDX-L group and 48% in the DX-L group.

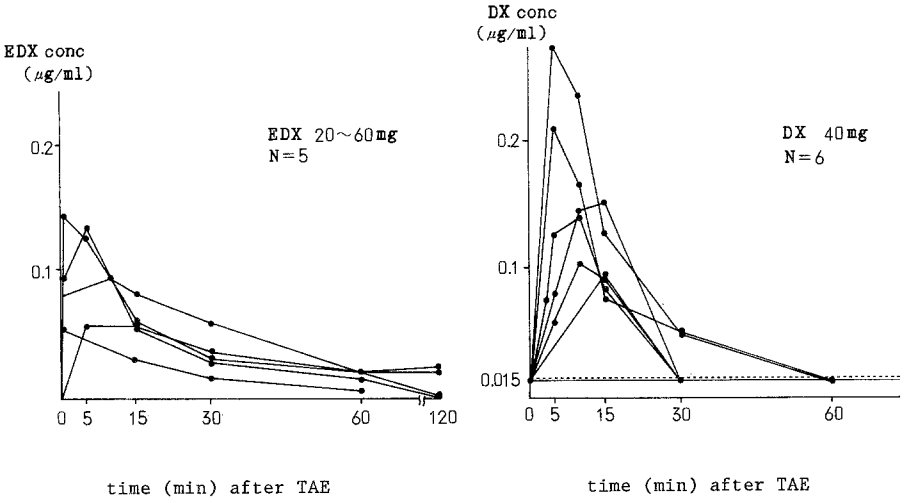

Fig. 1. Plasma levels of EDX and DX after TAE

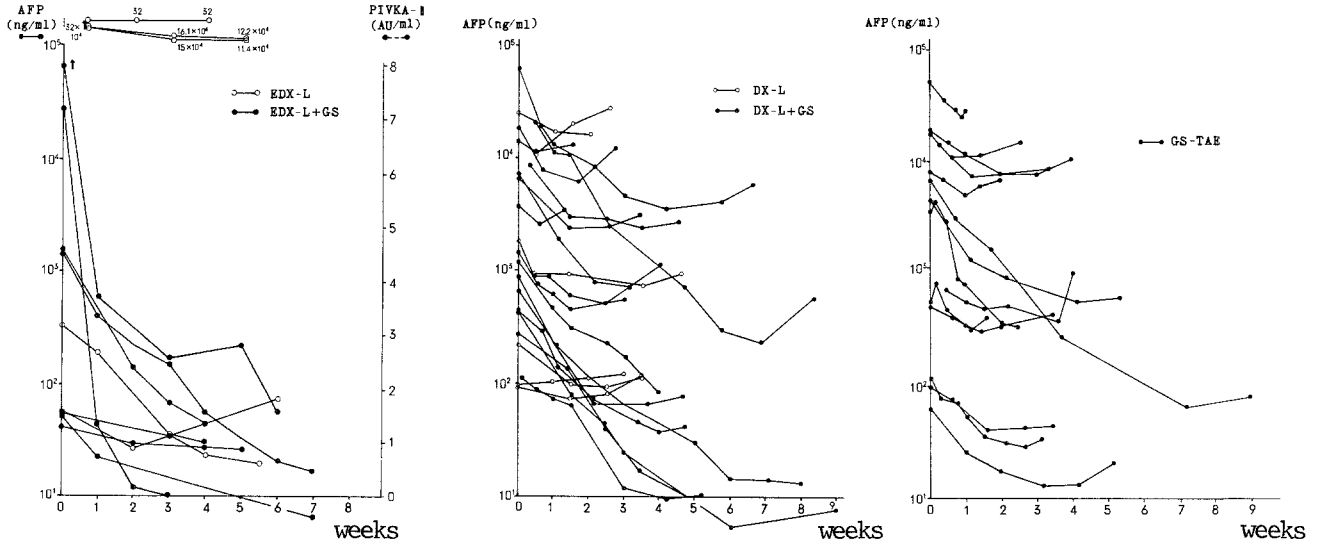

Fig. 2. Changes in AFP levels after treatment

Table 3. Therapeutic response to TAE

Response	EDX-L 18 (12)	DX-L 42 (27)	GS 23
PR	7 (6)	18 (13)	8
NC	7 (4)	18 (14)	14
PD	1 (0)	3 (0)	1
ND	3 (2)	1 (0)	0

( ): Followed by gelatin sponge

Survival of patients

The cumulative survival of patients following TAE is shown in Figs. 3–5. In the EDX-L group, nine cases (50%) remain alive, and the oldest has survived for more than 431 days since treatment. The half-year survival value was 57%, and the 1-year value was 49%. These survival values did not differ significantly from those determined for the DX-L group (half-year survival, 65%; 1-year survival, 51%; Fig. 3). Figure 4 shows a comparison of the survival curves generated for patients treated with EDX-L or DX-L in the presence and absence of subsequent GS-TAE. The 1-year survival values found for the EDX-L plus GS group, the EDX-L minus GS group, the DX-L plus GS group, and the DX-L minus GS group were 53%, 40%, 69%, and 20%, respectively. In both the EDX-L and DX-L groups, patients who had been embolized with lipiodol and GS showed good survival, and a significant difference in survival was found between the DX-L plus GS group and the DX-L minus GS group ($P < 0.05$).

Figure 5 shows a comparison of the survival curve constructed for patients treated with lipiodol emulsion (EDX-L or DX-L) followed by GS and the curve generated for subjects treated with GS alone. The 1- and 2-year survival values calculated for the former were 65% and 39%, respectively. These values were significantly higher than those determined for the latter (1-year survival, 30%; 2-year survival, 13%; $P < 0.05$).

Side effects

The most serious side effects encountered were pulmonary embolism and interstitial pneumonia. Two patients in the

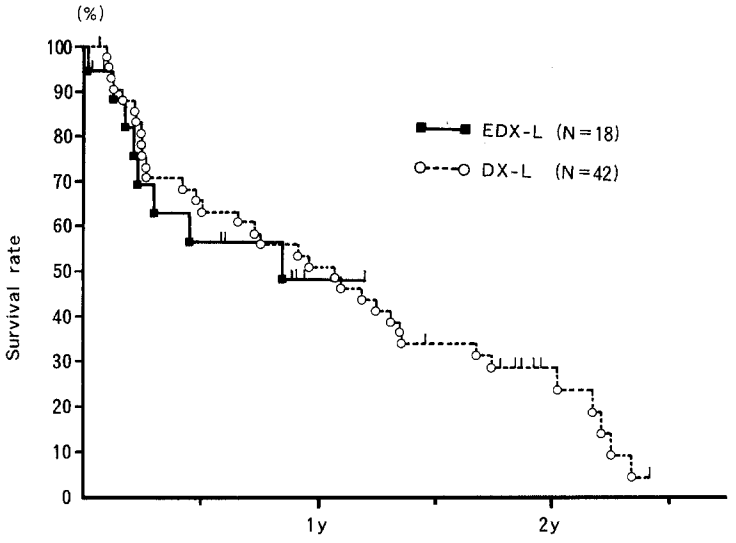

Fig. 3. Survival curves (EDX-L vs DX-L)

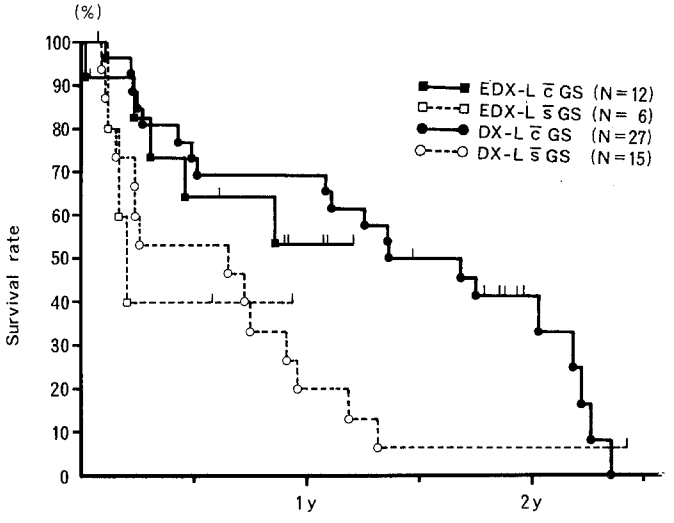

Fig. 4. Survival curves (EDX, DX-L c̄ GS vs EDX, DX s̄ GS)

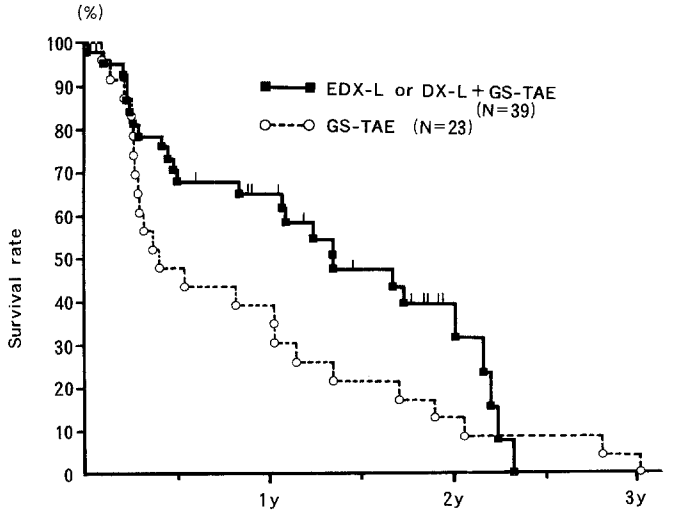

Fig. 5. Survival curves (lipiodol + GS-TAE vs GS-TAE)

EDX-L group and five subjects in the DX-L group suffered from prolonged dyspnea after TAE, and one individual in each group died of respiratory failure. The factors considered to have contributed to these side effects were the amount of lipiodol injected, the size of the HCC, the rate of retention of lipiodol in the tumor, and the history of pulmonary disease. In addition, fever and abdominal pain were commonly observed after treatment. Alopecia and cardiac damage were not seen in any patient in either the EDX-L group or the DX-L group.

Discussion

Recently, there have been many reports concerning the excellent therapeutic effects of TAE therapy or chemoembolization in HCC [6]. Many drug-delivery methods have been applied for the slow release of drugs and for selective targeting of tumors. Especially, suspensions and emulsions containing an oily contrast medium (lipiodol) have been used and have yielded good clinical effects.

In the present study, the survival of patients treated with DX-L or EDX-L followed by GS was superior to that of subjects treated with GS only. This improvement was considered to have been caused by the direct embolization effect of lipiodol and by the anticancer agent slowly released from it. The patients treated with lipiodol alone included those with massive tumors and tumor thrombi in the main portal vein. Furthermore, the amount of lipiodol injected was insufficient to embolize the arteries feeding the large tumors. Therefore, the outcome was poor in these cases.

No significant difference in survival was found between patients treated with DX-L and those treated with EDX-L. EDX-L treatment was carried out for less than 2 years, and only 18 subjects underwent this therapy, of whom 10 are presently alive. Therefore, further study will be needed for an adequate evaluation of the effects of this treatment, and even better therapeutic effects are anticipated.

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