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Intra-arterial administration of epirubicin in the treatment of Nonresectable hepatocellular carcinoma

Epirubicin Study Group for Hepatocellular Carcinoma*, **

Summary. A group study was conducted to investigate the effect of intrahepatic arterial administration of epirubicin in the treatment of nonresectable hepatocellular carcinoma (HCC). Sixty-four patients entered the study. There were 51 men and 13 women. The age range was from 32 to 79 years, with an average of 59.1. Fifty-four patients had associated cirrhosis of the liver. Epirubicin in a dose of 60–90 mg/m^2 was infused as a bolus into the hepatic artery 1–4 times (average 1.8) at intervals of 3 weeks to 3 months. Tumor size was properly evaluated in 53 patients. There were 1 CR (complete responses), 7 PR (partial responses), 34 NC (no change), and 11 PD (progression of disease). Thus, the response rate (CR + PR) was 15.1%. Seventeen patients are still alive 305–730 days (mean 505 days) after the initial treatment. A higher dose and more treatment courses tended to produce a better result. The most common side effects of this drug were bone marrow suppression, gastrointestinal symptoms, and alopecia. Cardiac toxicity was not observed with the doses used in this study. A retrospective comparison of the present result with that of patients treated by intra-arterial administration of doxorubicin demonstrated that epirubicin is more effective than doxorubicin in teams of survival rate.

Introduction

In spite of marked advances in the procedures available for diagnosis the natural course of hepatocellular carcinoma (HCC) has not changed at all over the last few decades [12]. Because of its highly malignant nature and its frequent association with cirrhosis of the liver, the resectability of HCC is still low. Thus, most patients with this tumor are candidates for chemotherapy.

Among numerous anticancer drugs, doxorubicin is one of the most effective agents in the treatment of HCC [1, 3, 6, 9, 10, 14, 16]. The significant side effects of this drug are serious obstacles to its wide clinical use. In particular, cardiac toxicity, which becomes clinically evident after a cumulative dose exceeding 500–550 mg/m^2, limits its prolonged administration. In addition, the frequent complication of alopecia is also an unpleasant problem.

Epirubicin (4'-epi-doxorubicin, 4'-epi-ADM) is a new isomer of doxorubicin, with a different steric configuration at the 4' position of the sugar moiety. Phase I and phase II studies showed antitumor activity against several sorts of human malignancies [4, 8] and also suggested that epirubicin might have a broader spectrum of antitumor activity than doxorubicin and lower toxicity, in particular lower cardiotoxicity.

Recent studies on the pharmacokinetics of this drug have shown that use of the intra-arterial route of administration is rational for epirubicin in the treatment of hepatic malignancies [15, 17]. In this communication, we report the effect of intrahepatic arterial infusion of epirubicin on nonresectable HCCs, verified by a group study at six different institutions.

Subjects and methods

From January 1983 through March 1985, a group study was conducted to investigate the efficacy of intra-arterial administration of epirubicin for the treatment of nonresectable hepatocellular carcinoma (HCC).

The patient group was composed of 51 men and 13 women, their ages ranging from 32 to 79 years with an average of 59.1. HCC and associated liver disease was diagnosed by histological tests in 26 patients, but on the basis of clinical examination only in the remaining 38 patients. Macrosopic typing of the tumors was classified according to the description of Eggel [7]. HCCs were massive in 26, nodular in 27, and diffuse in 11 patients. Tumor stage was decided with reference to the scale of Bengmark and Hafstrom [2]. Eight patients had stage I, 32 had stage II, and 24 had stage III HCC. Underlying cirrhosis of the liver was present in 54 cases. The grade of hepatic dysfunction was decided according to Child's classification [5], Child A being recorded for 32 patients, Child B for 23, and Child C for 9.

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Table 1. Patient characteristics in terms of dose of epirubicin

Dosage (mg/m²)	60–64	65–86	87–90	Significance
No. of patients	28	15	21	
Male/female	26/2	12/3	13/8	$p = 0.029$ (χ^2-test)
Age (years)				
Range	32–79	35–74	36–75	$p = 0.872$
Mean	58.5	58.8	60.1	(analysis of variance)
Child's class				
A	13	6	13	$p = 0.294$ (χ^2-test)
B	11	8	4	
C	4	1	4	
Tumor stage				
I	3	2	3	$p = 0.888$ (χ^2-test)
II	13	7	12	
III	12	6	6	

Indication of epirubicin treatment. Patients with primary HCC who were not indicated for liver resection were included in the present trial. However, the following inclusion criteria had to be met: performance status better than grade 3 (ECOG criteria), leukocyte count more than 3000/mm³, platelet count more than 50000/mm³, absence of serious infectious and cardiac diseases, and age below 75 years. Those who had received prior chemotherapy with other cytostatic agents were included if the preceding treatment had been performed more than 4 weeks before and its effect was already absent at the start of the present trial. The study sample included 14 patients who had been treated with doxorubicin, mitomycin C, or 5-fluorouracil or a combination of these.

Intraarterial injection of epirubicin. In 59 patients the drug was injected into the common or proper hepatic artery using the Seldinger technique at the time of angiography. In the remaining 5 patients, a catheter was surgically inserted into the main hepatic artery via the gastroduodenal artery. The right gastric artery was routinely ligated. Epirubicin in a dose of 60–90 mg/m² was repeatedly infused as a bolus at intervals of 3 weeks to 3 months. We first started with a dose of 60 mg/m², gradually increasing the dose up to 90 mg/m². The patient characteristics in each dose group are summarized in Table 1. No significant differences were found in age, grade of hepatic dysfunction, or tumor stage between the three different groups. However, there were significantly more women in the highest dose group than in the other two. The number of infusions given ranged from 1 to 4, with an average of 1.8.

Evaluation of the treatment. The effects of the treatment with epirubicin were evaluated clinically, biochemically, immunologically, and radiologically. Tumor size was followed up radiologically by computed tomography, ultrasonography, and/or angiography. The antitumor effect was evaluated only by imaging studies and was judged by the criteria of the WHO Handbook for Reporting Results of Cancer Treatment. The result obtained in the present study was compared with those recorded in patients treated during the period from July 1976 to April 1984 with a combination of doxorubicin and other agents (Table 2) or doxorubicin alone (Table 3), which were collected retrospectively from the same institutions.

Table 2. Patient characteristics (1)

	Epirubicin	Positive[a] control	Significance (method)
No. of patients	64	66	
Male/female	51/13	58/8	$p = 0.303$ (χ^2-test)
Age (years)			
Range	32–79	34–82	$p = 0.821$ (T-test)
Mean	59.1	59.5	
Child's class			
A	32	24	$p = 0.127$ (χ^2-test)
B	23	24	
C	9	18	
Tumor stage			
I	8	11	$p = 0.0075$ (χ^2-test)
II	32	46	
III	24	9	

[a] Patients treated with intrahepatic arterial infusion of regimens containing doxorubicin and other cytostatic agents

Table 3. Patient characteristics (2)

	Epirubicin	Doxorubicin	Significance (method)
No. of patients	64	29	
Male/female	51/13	27/2	$p = 0.185$ (χ^2-test)
Age (years)			
Range	32–79	34–72	$p = 0.858$ (t-test)
Mean	59.1	58.7	
Cumulative dose (mg/body)			
Range	79–518	30–170	
Mean	182	84	
Child's class			
A	32	8	$p = 0.118$ (χ^2-test)
B	23	14	
C	9	7	
Tumor stage			
I	8	4	$p = 0.0082$ (χ^2-test)
II	32	23	
III	24	2	

Table 4. Overall response rate to epirubicin treatment

No. of patients evaluated	CR	PR	CR + PR	NC	PD	NE
53	1	7	8 (15.1 %)	34	11	11

Results

Patient mortality

Three patients died within 1 month of treatment, one of hepatic failure, another of variceal bleeding, and the last of bleeding from an acute gastric ulcer. It was uncertain whether or not these complications were related to the treatment with epirubicin.

Antitumor effects

Tumor size was properly followed up in 53 patients. The overall response rates are summarized in Table 4. Complete response (CR) was found in 1 patient with nodular HCC and multiple intrahepatic metastases. This response was confirmed 3 months after a single infusion of epirubicin 60 mg/m^2, and lasted for 9 months, after which the patients died of hepatic failure (Fig. 1). Partial response (PR) was observed in 7 patients. Thus, the overall response rate was 15.1%. It is interesting that there were 34 patients who showed no change (NC), and that 8 of 13 patients who survived longer than 1 year showed NC radiologically (Fig. 2). As shown in Table 5, higher doses of epirubicin tended to produce better response rates ($P=0.075$ according to Kuskal-Wallis test). There seemed to be a positive relationship between the number of courses and response rate, but statistical comparisons were not valid owing to the small number of patients (Table 6). Although CR or PR was found only in the patients without prior chemotherapy, there was no statistically, significant difference between the groups with and without prior chemotherapy (Table 7). Among 50 patients who had initial serum alpha fetoprotein levels higher than 20 ng/ml, a significant fall in this protein was found in 12. At present, 17 patients are still alive 305–730 days (mean, 505 days) after therapy without having received any other anticancer treatments. When the survival rate was compared between 64 patients treated with epirubicin and 66 patients treated with intra-arterial infusion of combinations of doxorubicin with other drugs (Table 2), the 50% survival time was 205 days for the former and 161 days for the latter group ($P=0.069$). The survival rate was significantly better in the epirubicin group after 72 weeks of treatment, although the incidence of stage III cancer was significantly higher in this group (Fig. 3). When the result in the epirubicin group was compared with that obtained in 29 patients treated by intra-arterial administration of doxorubicin only (Table 3), the survival rate was seen to be far better in the former group than in the latter after 32 weeks of treatment (Fig. 4).

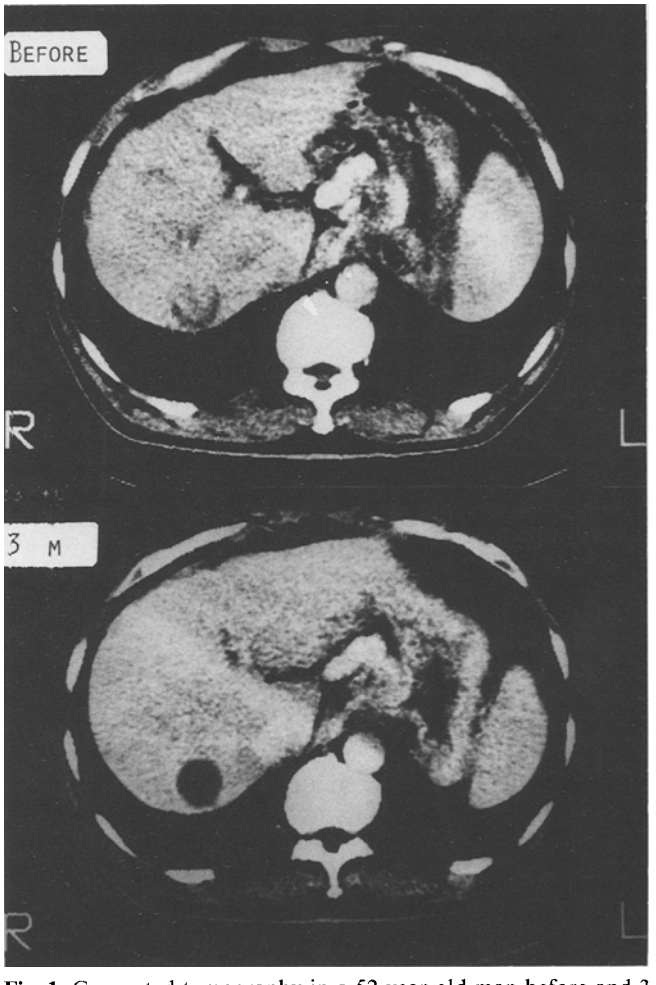


Fig. 1. Computed tomography in a 52-year-old man before and 3 motnhs after a single infusion of epirubicin 60 mg/m^2. Note complete cyst formation and disappearance of intrahepatic metastases. This lasted for another 9 months until the patient died of hepatic failure

Side effects of epirubicin

The overall side effects resulting from the treatment with epirubicin are summarized in Table 8. There was no significant difference in the incidence and severity of each side effect between the low-dose (60 mg/m^2) and high-dose (90 mg/m^2) groups.

Bone marrow. A significant fall in hemoglobin values was seen in 44.8%. The leukocyte count decreased to varying extents in 39 of 56 evaluable patients during the first 2 weeks, but returned to the initial levels 3–4 weeks after the drug infusion. The platelet count also fell in 54.3%, but returned to the initial level within 2 weeks in most of the patients. None of the patients developed any serious infection or bleeding tendency.

Gastrointestinal. Loss of appetite was seen in 30 patients. Diarrhea of several days' duration was noted in four cases. Only four patients developed stomatitis.

Cardiotoxicity. No patients complained of any symptoms indicating cardiac toxicity during or after the drug administration. Chest X-rays and electrocardiograms taken serially showed no cardiotoxic changes in all patients.

Others. Hair loss varying in degree occurred in 64.4% of the patients, but it was reversible. Eight patients had fever of 2–3 days' duration. Transient elevation of serum transaminase activities was found in 11 patients.

Serum concentrations of epirubicin and its metabolites

Serum levels of epirubicin and its metabolites, epirubicinol (13-dihydro-4'-epi-doxorubicin) and doxorubicin agly-

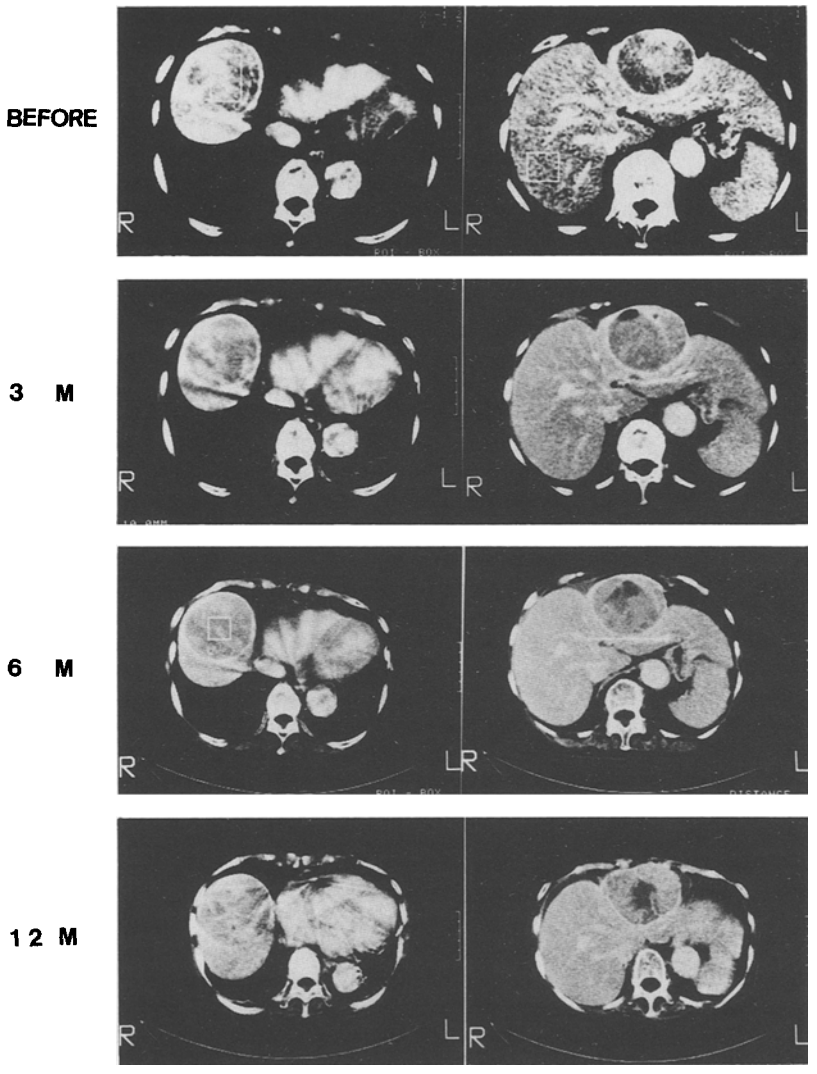


Fig. 2. Computed tomography in a 78-year-old woman. There were two hepatocelluar carcinomas, in the right hepatic lobe and in the medial segment of the left hepatic lobe. After a single infusion of epirubicin 60 mg/m^2, necrotic changes were found in the tumors but their size did not change. The patient lived for 2 years after the treatment

Table 5. Clinical response according to dosage of epirubicin

Dosage (mg/m^2)	No. of patients	Response				Response rate
		CR	PR	NC	PD	CR + PR (%)
60–64	25	1	2	17	5	3/25 (12.0)
65–86	12	0	1	6	5	1/12 (8.3)
87–90	16	0	4	11	1	4/16 (25.0)
Total	53	1	7	34	11	8/53 (15.1)

Level of significance for response rate: $p = 0.0750$ (Kruskal-Wallis test)

Table 6. Clinical response according to courses

No. of course	No. of evaluable casesGar	Response				Response rate
		CR	PR	NC	PD	CR + PR (%)
1	22	1	1	13	7	2 (9.1)
2	22	0	2	16	4	2 (9.1)
3	7	0	3	4	0	3 (42.9)
4	2	0	1	1	0	1 (50.0)

Table 7. Clinical response according to prior chemotherapy

Prior chemotherapy	No. of evaluable cases	Response				Response rate
		CR	PR	NC	PD	CR + PR (%)
Yes	11	0	0	8	3	0 (0)*
With doxorubicin	6	0	0	5	1	0 (0)
Without doxorubicin	5	0	0	3	2	0 (0)
No	42	1	7	26	8	8 (19.1)*
Total	53	1	7	34	11	8 (15.1)

* $p = 0.193$ (U-test)

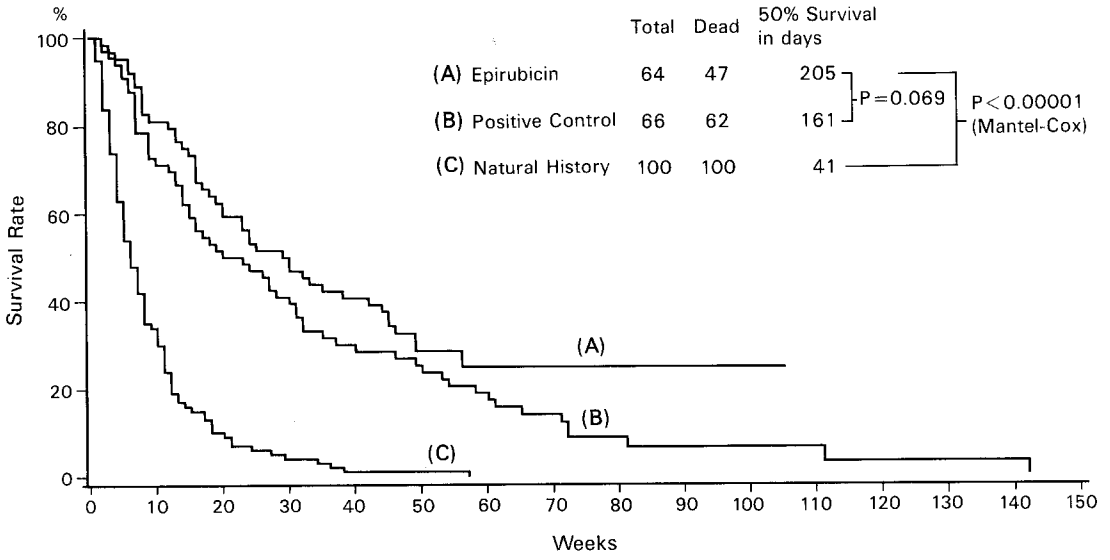


Fig. 3. Cumulative survival curves in 64 patients treated with epirubicin, 66 patients treated with regimens containing doxorubicin, and 100 untreated patients

con, were estimated up to 60 min after injection of eprubicin 60 mg/m^2 in seven patients and 90 mg/m^2 in six patients. The results are illustrated in Fig. 5. Doxorubicin aglycon was not detectable in any of the measurements. The relationship between the drug concentrations and the initial hepatic function or the severity of the side effects was evaluated, but no definitive conclusion was drawn.

Discussion

Hepatocellular carcinoma is one of the most malignant tumors affecting humans. It is well known that HCC is common in Afro-Asian countries but rather rare in Western countries. The incidence of this tumor, however, is increasing steadily all over the world. Despite outstanding advances in diagnostic methods for and a great deal of knowledge about this tumor, its resectability is still generally low.

To date, there has been a wealth of reports concerning the treatment of nonresectable HCCs with various antitumor agents, technical devices, or a combination of the two. Ischemic therapy, such as ligation or embolization of the hepatic artery, combined with cytostatic drugs might be the treatment of choice in selected patients with nonresectable HCCs. Occlusion of the hepatic artery produces tumor shrinkage relatively frequently, but its effects are usually short-lived without additional chemotherapy, probably due to rapid revascularization of the tumor. This type of treatment is apparently not indicated for patients with advanced hepatic cirrhosis, tumor thrombosis of the main portal vein, or severe portal hypertension [11, 13].

Most Japanese patients with HCC have underlying cirrhosis [12], and 30–40% have esophageal varices. Therefore, ligation or embolization is indicated only for selected patients, and development of effective cytostatic agents is necessary, to make it possible to treat as many patients with nonresectable HCCs as possible. Doxorubicin is one of the most effective agents in the treatment of HCC. This drug is cytocidal in nature, and its intra-arterial administration should be more effective than systemic infusion. Theoretically, administration into the hepatic artery

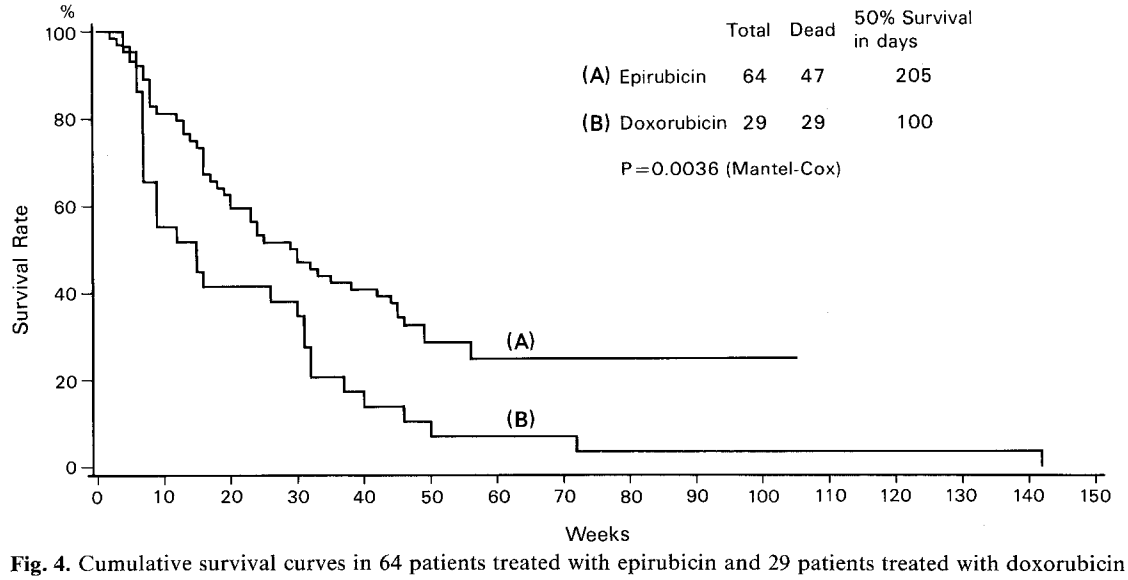


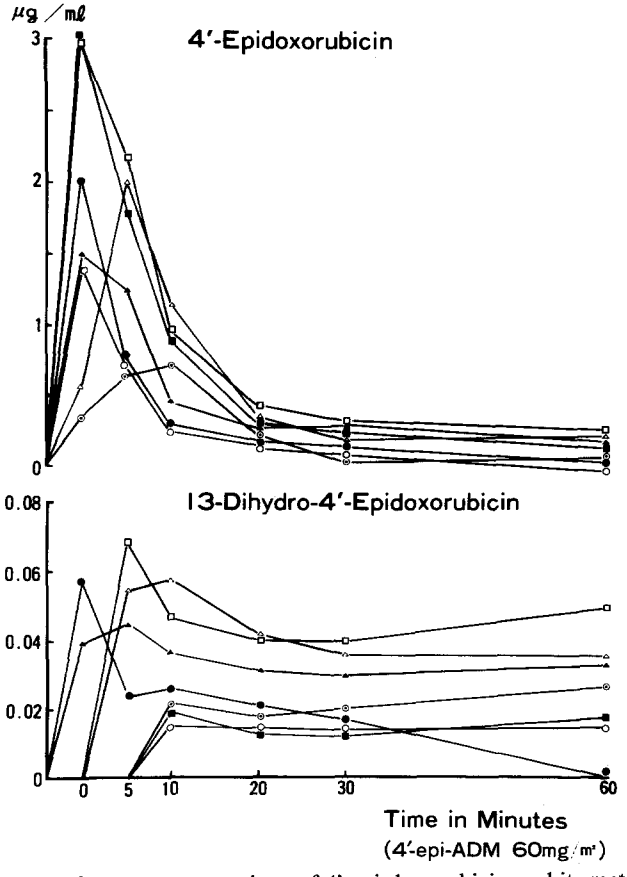
Fig. 4. Cumulative survival curves in 64 patients treated with epirubicin and 29 patients treated with doxorubicin

Table 8. Toxicity of epirubicin

Toxicity	No. of patients evaluated	Frequency
Bone marrow		
Anemia	58	26 (44.8 %)
Leukopenia	56	39 (69.6 %)
Thrombocytopenia	46	25 (54.3 %)
Gastrointestinal		
Anorexia	52	30 (57.7 %)
Nausea, vomiting	55	16 (29.1 %)
Diarrhea	59	4 (6.8 %)
Stomatitis	60	4 (6.7 %)
Cardiovascular		
Tachycardia	60	0
Gardiac dysfunction	60	0
Nervous system		
Conscious	60	1 (1.7 %)
Peripheral	59	0
Others		
Alopecia	59	38 (64.4 %)
Fever	56	8 (14.3 %)
Liver dysfunction	61	11 (18.0 %)
Renal dysfunction	58	3 (5.2 %)
Pain	54	0
Skin eruption	59	1 (1.7 %)
Infection	58	0
Bleeding tendency	57	0
Ear pain	60	1 (1.7 %)
Pollakiuria	60	1 (1.7 %)

should diminish systemic toxicity, but this is not necessarily true for doxorubicin [3]. It is usually agreed that the cardiac toxicity of this drug appears after a cumulative dose exceeding 500–550 mg/m^2. This might be valid in patients with normal hepatic function. According to our experience, patients with HCC and associated liver cirrhosis do not tolerate such high doses.

The present results suggest that epirubicin could be a promising drug in the treatment of HCC. The overall response rate was 15.1% (CR in 1 and PR in 7). This is not very high, but may be acceptable in view of the fact that all our patients had really nonresectable HCCs and 54 of them had advanced cirrhosis. Although many of our patients were therefore treated with limited doses of epirubicin, 17 patients are still alive at 305–730 days after the initial treatment, without having received any other anticancer therapy. Most of the members of the study team felt that the drug had characteristics distinguishing it from all other anticancer agents: epirubicin can induce antitumor



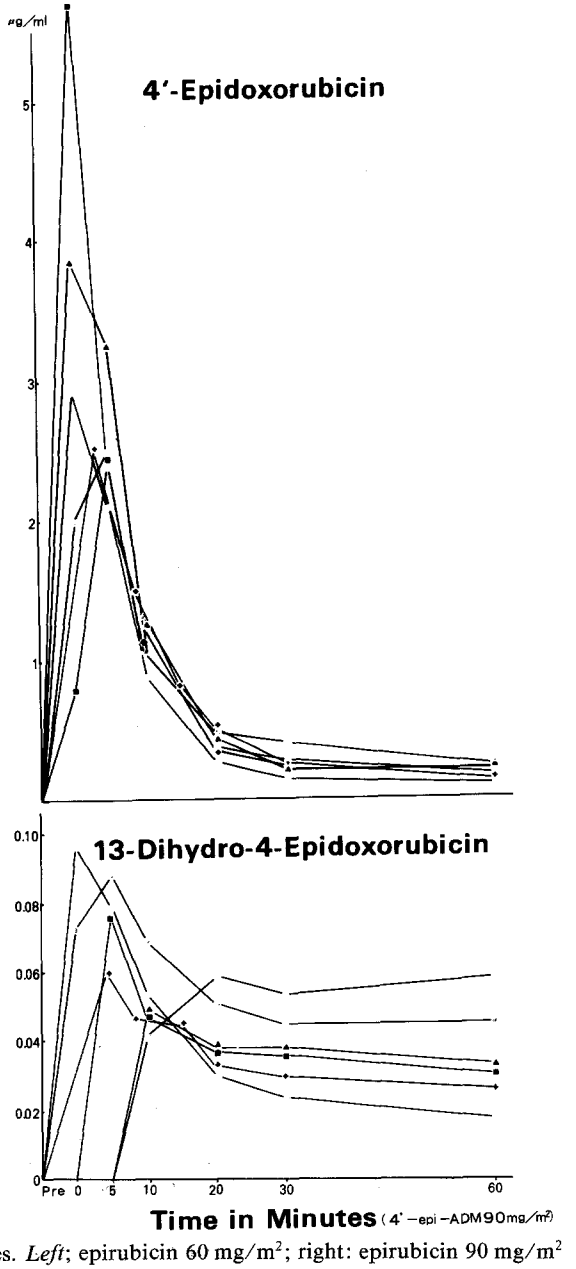


Fig. 5. Serum concentrations of 4'-epi-doxorubicin and its metabolites. *Left*; epirubicin 60 mg/m^2; right: epirubicin 90 mg/m^2

effects much more slowly than expected and it can prolong the survival time in certain patients without inducing any apparent tumor regression. The mechanisms underlying these facts remain to be elucidated. We do not known what dose of epirubicin is equivalent to a known dose of doxorubicin in terms of antitumor activity. Retrospective comparison of the present result with that obtained in patients treated with intra-arterial administration of doxorubicin demonstrated that epirubicin may be more effective than doxorubicin.

The most common side effects of epirubicin were bone marrow suppression, gastrointestinal complaints, and loss of hair. Cardiotoxicity was not observed with the doses used in the present study. We attempted to clarify the relationship between serum concentrations of epirubicin and its metabolites and hepatic function or degree of side effects, but no definitive conclusion was drawn in this regard. The appropriate dose of the drug and the best interval between infusions have yet to be elucidated. Also, combinations of epirubicin and other cytostatic agents can be studied in the treatment of hepatocellular carcinoma.

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