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A randomized trial of intrahepatic arterial infusion of 4′-epidoxorubicin with Lipiodol versus 4′-epidoxorubicin alone in the treatment of hepatocellular carcinoma

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Abstract. We conducted a prospective randomized trial to evaluate the efficacy of Lipiodol in intrahepatic arterial infusion chemotherapy for patients with hepatocellular carcinoma (HCC). A total of 38 patients with unresectable HCCs and underlying cirrhosis were entered in this trial, and 36 of them were evaluable. Every 4 weeks, 17 patients received 70 mg of 4′-epidoxorubicin (epirubicin) alone (group A), whereas 19 patients received a Lipiodol emulsion containing the same dose of epirubicin (group B) through the hepatic artery. A tumor response (CR+PR) was observed in 12% of group A patients and in 42% of group B patients. The group B patients showed a significantly higher response rate than the group A patients. There was a tendency for an increased duration of survival ($P = 0.09$) in the group B patients. These results suggested that the infusion of the Lipiodol emulsion with epirubicin was more effective than epirubicin alone for the treatment of these patients with HCC.

Introduction

Hepatic arterial infusion of anticancer drugs is usually used for the treatment of advanced hepatocellular carcinoma (HCC). In the hepatic arterial chemoinfusion, Lipiodol (Lipiodol Ultra-Fluide; Laboratoire Guerbet, France) is commonly used as an emulsion that is mixed with an anticancer drug in an attempt to retain the anticancer drug in a target tumor [3, 8]. However, the therapeutic efficacy of the Lipiodol emulsion on HCCs has not been clearly investigated. Recently, totally implantable arterial access devices have been used for hepatic arterial chemoinfusion, and they can be implanted in patients under local anesthesia without laparotomy [7]. Using this procedure, we designed a prospective randomized trial to ascertain whether a Lipiodol emulsion mixed with an anticancer drug is more effective than the anticancer drug alone for the treatment of advanced HCCs.

Materials and methods

All patients who had unresectable HCC confirmed by imaging diagnosis were eligible for this study after they had granted their informed consent. The entry requirements included a performance status (PS) of 0 or 1, an age in the range of 20 to 75 years, a macroscopic stage of 3 or 4-A according to the criteria established by the Liver Cancer Study Group of Japan [6], a serum bilirubin level of 3 mg/dl or lower, a platelet count of 30,000/mm^3 or higher, and no evidence of cardiac disease. The evaluation performed before the start of this study included a complete blood count, a chemistry profile, ultrasonography, a computerized tomographic (CT) scan, and angiography to assess the extent of liver involvement and liver function.

Between March 1990 and September 1992, 38 patients were entered in the study. Of the 38 patients who were randomly assigned to the 2 treatment groups, 2 were not evaluable. In group A, the chemotherapy was discontinued within 1 month of the start of the study because of variceal bleeding in one patient and due to catheter trouble in another patient. The patients' characteristics and initial laboratory values are shown in Table 1.

All of the patients had associated liver cirrhosis and were assessed for the severity of this condition by Child's classification. The two treatment groups were well matched in terms of age, sex, macroscopic staging, and the Child's classification. In the initial laboratory values, they were also well matched in terms of the white blood cell (WBC) count, platelet count, and AST, albumin, bilirubin, LDH, and AFP levels. The only difference detected was in the red blood cell (RBC) count. The balance in the two arms was confirmed for all of the randomly assigned patients. We followed these patients through February 1993.

All patients underwent implantation of an arterial catheter (6-F, Anthron P-U; Toray, Tokyo) and a port (PORT-A-CATH; Pharmacia Deltec, St. Paul, Minn.) under fluoroscopic control. We inserted the implantable catheter via the left axillary artery and placed the tip of the catheter in the proper hepatic artery. The gastroduodenal artery was

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Table 1. Patients' characteristics and initial laboratory findings

Characteristics/ laboratory findings	Group A (n = 17)	Group B (n = 19)	P
Age (years)	60.8 (50–70)	58.2 (38–75)	NS
Sex (M/F)[a]	17/0	19/0	NS
Macroscopic staging[c]:			
III[a]	4	3	NS
IV-A[a]	13	16	
Portal vein thrombus (+)[a]	8	4	NS
Child's classification[a]:			
A	5	7	NS
B	5	6	
C	7	6	
WBC ($\times 10^3$/mm^3)[b]	4.58 (2.2–9.2)	4.64 (2.6–8.1)	NS
RBC ($\times 10^6$/mm^3)[b]	3.83 (2.95–4.62)	3.99 (3.04–5.24)	<0.05
Platelets ($\times 10^4$/mm^3)[b]	9.98 (4.5–20.8)	9.63 (4.5–14.6)	NS
AST (U/l)[b]	93.7 (26–154)	94.5 (29–309)	NS
Albumin (g/dl)[b]	3.36 (2.4–4.1	3.52 (2.6–4.4)	NS
Total bilirubin (mg/dl)[b]	1.17 (0.3–2.6	1.28 (0.3–3.0	NS
Lactate dehydrogenase (U/l)[b]	425 (308–588)	467 (264–1,670)	NS
α-Fetoprotein[a]:			
≤20 ng/ml	3	7	NS
>20 ng/ml	14	12	

AST, Aspartate aminotransferase; NS, not significant.
The chi-square test or Student's non-paired t-test was used for statistical analyses
[a] Number of patients
[b] Mean (range)
[c] According to the general rules for the clinical and pathological study of primary liver cancer in Japan established by the Liver Cancer Study Group of Japan

occluded at its origin with steel coils to prevent the chemotherapeutic agents from flowing into nontarget vascular beds. After connection of the catheter and the port, they were totally implanted into a subcutaneous pocket that was created in the region of the left pectoralis major muscle. All procedures were performed with the patients under local anesthesia.

For randomization of each stratum, randomly permuted blocks were used. In group A, 70 mg of 4′-epidoxorubicin (epirubicin) was given as a single bolus injection through the port every 4 weeks. In group B, we infused a Lipiodol emulsion consisting of a mixture of 2–3 ml of Lipiodol and 70 mg of epirubicin (dissolved in 10 ml of iopamidol) through a port under fluoroscopy at 4-week intervals. The infusion of the anticancer drug was stopped if some problem with the arterial device or a severe side effect of the infusion occurred. If the platelet count fell below 20,000/mm^3, the serum bilirubin level exceeded 3 mg/dl, or the serum aspartate aminotransferase (AST) level exceeded 3 times the initial value, the infusion was stopped until the values returned to normal.

The patients underwent alpha-fetoprotein (AFP) measurement, a complete blood count, and a chemistry profile that included the measurement of serum AST, bilirubin, albumin, and lactate dehydrogenase (LDH) levels every 4 weeks. Abdominal CT was performed at 3 months after the start of treatment, and ultrasonography was performed at 1 month after the initiation of treatment; these imaging techniques were repeated thereafter as indicated to assess the response.

The response was assessed as follows: CR, the disappearance of all known lesions; PR, a 50% or greater reduction in the sum of the products of the largest perpendicular diameters of the main tumor for at least 4 weeks and the absence of new lesions; MR, a 25%–50% reduction in the tumor as described above; NC, a 25% reduction cannot be established; PD, a 25% or greater increase in the tumor mass or the appearance of new lesions.

The survival distributions were estimated by the method of Kaplan and Meier, with comparisons being made using the log-rank test. Comparisons of the two treatment groups for their characteristics and findings were made using the chi-square test or Student's t-test. Cox's proportional-hazard model was used to assess the prognostic factors and ascertain whether the use of Lipiodol was a significant factor in the patients' prognosis.

Table 2. Response rates

Response	Group A (n = 17) %	Group B (n = 19) %
CR: complete response	0	0
PR: partial response	12	42
(MR: minor response)	29	21
NC: no change	41	37
PD: progressive disease	18	0
Chi-square test		$P<0.05$

Results

The total number of arterial infusions given during the follow-up period ranged from 1 to 14 (median, 6.0) in group A and from 2 to 30 (median, 8.3) in group B. The total dose of epirubicin ranged from 70 to 980 mg (median, 339 mg) in group A and from 140 to 2,100 mg (median, 483 mg) in group B. There was no difference in these therapeutic background parameters between the two groups. The total dose of Lipiodol in group B ranged from 5 to 127 ml (median, 24.9 ml).

Table 2 compiles the response rates in both groups. The overall response rate (complete and partial responses) was 12% of the 17 patients in group A and 42% of the 19 patients in group B. A higher overall response rate was noted for patients treated with the Lipiodol emulsion mixed with epirubicin as compared with those treated with epirubicin alone. In six patients who achieved a partial response, the initial serum AFP levels were over 20 ng/ml, and these levels decreased after the treatment was initiated.

The overall survival distributions for the two groups of patients are shown in Fig. 1. The cumulative survival rates in group A were 76.5%, 43.3%, 23.1%, and 0 for the per-

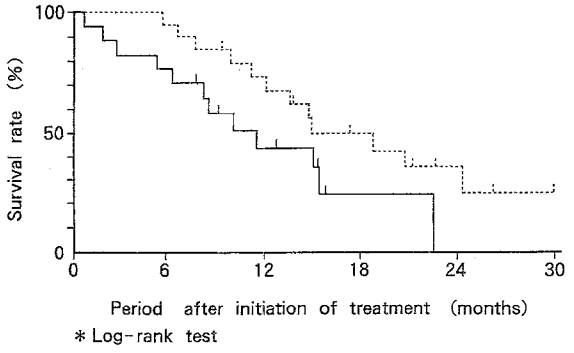

Fig. 1. Survival curves of the patients after the initiation of treatment. A tendency toward an increased duration of survival was seen in patients treated with the Lipiodol emulsion (*group B, n* = 19) as compared with those treated with epirubicin alone (*group A, n* = 17). * $P = 0.09$

iods of 6, 12, 18, and 24 months after the initiation of treatment, respectively. In group B, the cumulative survival rates were 94.7%, 73.0%, 49.4%, and 35.3% for the periods of 6, 12, 18, and 24 months, respectively. There was a tendency toward an increased duration of survival in patients treated with the Lipiodol emulsion mixed with epirubicin in comparison with those treated with epirubicin alone ($P = 0.09$).

During the follow-up period, 11 patients in group A and 12 patients in group B died of various causes. In group A, 1 patient died of hepatic failure with advance of the HCC; 2, of bleeding from the HCC; 4, of hepatic failure due to progress of liver cirrhosis without advance of the HCC; 2, of variceal bleeding; 1, of bleeding from the gastrointestinal tract; and 1, of cerebral hemorrhage. In group B, 2 patients died of hepatic failure with advance of the HCC; 5, of hepatic failure due to progress of liver cirrhosis without advance of the HCC; 4, of variceal bleeding; and 1, of viral meningitis. By statistical analysis using Cox's proportional model, we calculated the risk ratio between the two groups to be 2.65 ($P = 0.03$), and this showed that the use of Lipiodol was a significantly positive factor for the prognosis of these patients.

Table 3 shows the changes in laboratory data occurring within 6 months after the initiation of treatment. In both groups, the WBC and platelet counts dropped slightly 3 or 6 months after the treatment had been initiated, and there was no significant difference between the two groups. The serum bilirubin level gradually increased and the serum

Table 4. Side effects

Side effect	Group A ($n = 17$) %	Group B ($n = 19$) %	P
Nausea/vomiting[a]	24	58	<0.05
Fever[a]	24	68	<0.01
Abdominal pain[a]	18	58	<0.05
Gastritis	12	21	NS
Peptic ulcer	0	11	NS
Cholecystitis	0	0	NS
Others	0	0	NS

The chi-square test was used for statistical analyses. NS, Not significant

[a] For 2 or 3 days after bolus injection

Table 3. Changes in total blood counts and chemical laboratory data

Parameter	Before		3 months		6 months	
	n	Mean ± SD	*n*	Mean ± SD	*n*	Mean ± SD
WBC ($\times 10^3/mm^3$):						
Group A	17	4.58± 1.73	14	4.34± 1.80	12	4.06± 1.97
Group B	19	4.65± 1.55	19	5.01± 1.53	17	5.00± 1.67
RBC ($\times 10^6/mm^3$):						
Group A	17	3.59± 0.44*	14	3.56± 0.56**	12	3.46± 0.62
Group B	19	4.00± 0.57*	19	3.96± 0.51**	17	3.90± 0.70
Platelets ($\times 10^4/mm^3$):						
Group A	17	9.98± 4.04	14	9.95± 4.62	12	9.23± 4.43
Group B	19	9.63± 3.02	19	10.5 ± 3.21	17	11.4 ± 5.00
AST (U/l):						
Group A	17	93.8 ± 32.9	14	80.5 ± 33.6	12	96.5 ± 59.9
Group B	19	94.5 ± 64.3	19	116 ±115	17	113 ± 68.3
Albumin (g/dl):						
Group A	17	3.36± 0.44	14	3.37± 0.55	12	3.34± 0.52
Group B	19	3.51± 0.57	19	3.45± 0.76	17	3.46± 0.76
Total bilirubin (mg/dl):						
Group A	17	1.17± 0.72	14	1.05± 0.61	12	1.71± 2.23
Group B	19	1.28± 0.83	19	1.28± 1.06	17	1.43± 1.28
Lactate dehydrogenase (U/l):						
Group A	17	425 ± 76.0	14	528 ±174	12	446 ±191
Group B	19	467 ±301	19	540 ±442	17	554 ±375

Student's non-paired *t*-test was used for statistical analyses. AST, Aspartate aminotransferase

*, ** $P < 0.05$

albumin level gradually decreased in both groups after the initiation of treatment. The serum AST level did not increase after the initiation of treatment in either group. There was no significant difference in the chemical laboratory data between the two groups.

Table 4 compiles the side effects of the treatments. A higher rate of low-grade fever for a few days after the chemoinfusion was seen in group B. Gastrointestinal toxicity was seen in both groups, but higher rates of nausea and abdominal pain were seen in group B. In both groups, gastritis was seen in several patients, and one patient in group A died of bleeding due to hemorrhagic gastritis. Peptic ulcers were diagnosed in a few group B patients. None of the patients in either group developed severe cholecystitis that required treatment.

Discussion

Pharmacokinetic theory predicts that arterial administration of an anticancer drug as a bolus injection leads to a high drug concentration in the tumor [1]. Lipiodol is commonly used for such an arterial intervention. Lipiodol accumulates in tumors and is retained therein for a long time [3, 8]. By infusion of a Lipiodol emulsion mixed with an anticancer drug via the hepatic artery, microembolization of tumor vessels and slow release of the anticancer drug are expected. Regarding the efficacy of Lipiodol, it was reported that TAE using a Lipiodol emulsion mixed with anticancer drugs produced a significantly stronger therapeutic effect as compared with TAE without Lipiodol [5]. On the other hand, it was also reported that no benefit in terms of the antitumor response or survival was provided by arterial infusion of a Lipiodol emulsion containing epirubicin in comparison with intravenous administration of epirubicin (a historic control) [4].

In our prospective randomized trial, repeated intrahepatic arterial infusion of Lipiodol mixed with epirubicin produced a significantly higher response rate than did epirubicin alone. The total doses of epirubicin were well matched in the two groups, but we repeatedly gave a large dose of Lipiodol (mean, 24.9 ml) to group B. The higher response rate of group B may contribute not only to long-term retention in the tumor and slow release of the drug from the Lipiodol emulsion but also to microembolization of the tumor vessels with Lipiodol.

Leung et al. [4] reported that the toxicity of intraarterial infusion of high-dose epirubicin (90 mg/m^2) was minimal. It was also reported that Lipiodol gradually disappeared from the noncancerous liver parenchyma after hepatic arterial infusion [8]. We followed the total blood cell counts and liver function for 6 months after the initiation of treatment, but we found no significant difference in hematologic or hepatic toxicity between the two groups. These results may be attributable to the repeated administration of a low of epirubicin (70 mg/body) and Lipiodol (2–3 ml) in a single bolus injection every 4 weeks. Gastrointestinal toxicities and low-grade fever were seen at higher rates in group B. Since we placed the catheter tip in the hepatic artery without occlusion of the right gastric artery at its origin in all the patients, the Lipiodol emulsion may have flowed into the gastric region [2]. However, biliary sclerosis, a serious complication of hepatic infusional chemotherapy, was not seen in this study.

We observed a tendency toward an increased duration of survival in the patients treated with Lipiodol. On the other hand, many patients died of hepatic failure due to liver cirrhosis and variceal bleeding. These results suggest that repeated administration of epirubicin for a long time may produce progression of liver cirrhosis. This may have resulted in the absence of a significant difference in survival between the two treatment groups in spite of the higher response rate of the patients treated with the Lipiodol emulsion. Nevertheless, the use of the Lipiodol emulsion was determined to be a significantly beneficial prognostic factor in this study by statistical analysis using Cox's proportional model.

In conclusion, this study shows that repeated intrahepatic arterial infusion of a Lipiodol emulsion mixed with epirubicin is a more effective therapy for HCCs as compared with epirubicin alone. However, close monitoring of the liver function and other side effects is required.

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