Cancer Chemother Pharmacol (1992) 31 (Suppl I): S77–S81

Cancer Chemotherapy and Pharmacology

Analysis of prognostic factors in patients with hepatocellular carcinoma treated by transcatheter arterial embolization*

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Summary. We studied 240 cases of unresected hepatocellular carcinoma (HCC) using Cox's proportional hazard model to elucidate which factors would be closely related with the survival period after treatment by transcatheter arterial embolization (TAE) in the presence or absence of iodized oil. The results were as follows. The cumulative survival values obtained after TAE were 67.5% for 1 year, 32.0% for 2 years, and 20.5% for 3 years. The most significant prognostic factor was the degree of extension of tumor embolus in the portal vein or its branch. The tumor extension and the tumor type were also important factors. Age, sex, and AFP, HBsAg, and HCV Ab values were not useful as prognostic factors. This study provides a rational background for the selection of treatment for HCC. Furthermore, knowledge of the prognostic factors is useful for the management of patients, particularly in maintaining their good quality of life.

Introduction

In Japan, about 70% of cases of hepatocellular carcinoma (HCC) are complicated with liver cirrhosis such that hepatic resection, which is the first choice of treatment, is possible in only 35% of cases [10]. After the benefit of transcatheter arterial embolization (TAE) for the treatment of abdominal tumors was reported [6], this procedure was applied to unresectable HCC [26]. There have since been many reports that TAE is effective in the treatment of unresectable HCC [2, 14, 23, 26].

As a variation of TAE, transcatheter oily chemoembolization (TOCE) has been developed; in this procedure, hepatic embolization is carried out using a mixture of an iodized oil (lipiodol) and an anticancer drug together with gelatin sponge. TOCE (lipiodol-TAE) has been reported to be more effective than TAE alone, and it has recently been commonly used [8, 16, 17, 21, 28]. Moreover, there have been many reports that percutaneous ethanol injection therapy (PEIT) is effective in the treatment of small HCC [12, 20]. Recently, several nonoperative combination therapies for HCC, including TAE and PEIT, have been reported to be more effective than any one therapy [22, 27].

In the treatment of unresectable HCC, the choice of the most suitable therapy for each case seems to be very important. Since 1985, we have been studying the therapeutic effect and outcome of TAE in unresectable cases of HCC. In the present study, we tried to evaluate the prognostic factors that seemed to be associated with more satisfactory results and to determine the suitable indication for TAE as the main nonoperative treatment modality.

Patients and methods

Patients. The subjects of the present study were 240 patients with unresectable HCC who were treated by TAE from 1985 to 1990 in Osaka National Hospital. Their characteristics are shown in Table 1. The study population included 202 men and 38 women whose ages ranged from 25 to 83 years (mean, 61.3 years). HBsAg was positive in 30 patients (12.5%) and HCV Ab (C100-3) was positive in 188 subjects (78.3%). The numbers of patients associated with alcohol abuse, blood transfusion, and coexistent liver cirrhosis were 68 (28.3%), 52 (21.7%), and 189 (78.8%), respectively. Moreover, 86 (35.8%) patients fit Child's classification A, 92 (38.3%) fit classification B, and 62 (25.9%) fit classification C [1]. None of the patients were considered to be suitable candidates for surgery due to factors including the tumor size, its extension, and the presence of metastasis or advanced liver cirrhosis, among others. The diagnosis in these cases was made by biopsy, autopsy, or clinical examinations such as angiography and serum α-fetoprotein (AFP) assay (RIA).

Variables. The survival period and 34 clinical and laboratory parameters were studied in these patients. Data on these 34 factors were assessed immediately before the initial TAE procedure. Some were evaluated by imaging procedures such as computerized tomography (CT), ultrasonography (US), and angiography. Esophageal varices were assessed by endoscopy, and the presence of ascites was evaluated by CT and US. The tumor types were grouped in conformity with Eggel's classification as follows: massive, nodular, and diffuse types [4].

* Presented at the Second International Symposium on Treatment of Liver Cancer. Taipei, 3–4 February 1991

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Table 1. Patients' background factors

Total number of patients		240
Sex (M/F):		
	M	202
	F	38
Mean age (years)		61.3±9.0 (range, 25–83)
HBsAg:		
	(+)	30 (12.5%)
	(–)	210 (87.5%)
HCV Ab:		
	(+)	188 (78.3%)
	(–)	52 (21.7%)
Alcohol abuse		68 (28.3%)
Blood transfusion		52 (21.7%)
Coexistence of LC		189 (78.8%)
Child's classification:		
	A	86 (35.8%)
	B	92 (38.3%)
	C	62 (25.9%)

LC, Liver cirrhosis

Other clinical and pathological findings were classified as follows according to the General Rules for the Clinical and Pathological Study of Primary Liver Cancer proposed by the Liver Cancer Study Group of Japan [11]. The location of the tumor was indicated using the following abbreviations for liver segments: P, posterior segment; A, anterior segment; M, medial segment; L, lateral segment; and C, caudate lobe. The degree of extension of tumor embolus in the portal vein or its branch was classified as follows: Vp_0, no tumor embolus in the portal vein; Vp_1, tumor embolus distal to the second branch of the left or right portal vein (not including the second branches); Vp_2, tumor embolus in the second branch of the portal vein; and Vp_3, tumor embolus in the first branch or the trunk of the portal vein or in a branch on the opposite side. The tumor extension (the percentage of occupancy of the whole liver by the tumor) was calculated from CT films scanned at 10- or 15-mm intervals and was divided into four groups: E_1, less than 20%; E_2, 20%–40%; E_3, 40%–60%; E_4, more than 60%.

TAE treatment. TAE in the absence of lipiodol was performed as follows. After celiac angiography and portography, the catheter was inserted selectively into the feeding artery of the tumor. Thereafter, we infused gelatin sponge cubes (1- to 2-mm pieces) permeated with 20–50 mg Adriamycin (ADM), mitomycin C (MMC), or cisplatin (CDDP) into the feeding artery. For TAE in the presence of lipiodol, an Adriamycin-in-oil (lipiodol) emulsion was infused first, after which gelatin sponge cubes (1–2 mm in diameter) were infused into the proper hepatic artery or its distal branches.

TAE minus lipiodol was performed in 93 patients using ADM (63 cases), CDDP (25 cases), or MMC (5 cases). TAE plus lipiodol was carried out in 147 subjects using only ADM. At the time of this analysis, 123 patients have undergone 1 TAE procedure, 73 subjects have completed 2 procedures, and 44 patients have undergone more than 3 procedures. The relationship between these variables and the duration of survival was assessed using univariate analysis. Then, multivariate regression analysis was carried out to identify independent variables that would be predictive of a long survival period.

Statistical methods. For statistical analysis, we used the chi-square test and Student's *t*-test. Cumulative survival was determined by Kaplan-Meier's method from the 1st day of the initial TAE procedure. Parameters likely to influence the prognosis were subjected to univariate analysis using the log-rank test. On the basis of the results of the univariate analysis, factors with a *P*-value of less than 0.1 were subjected to multivariate analysis using Cox's proportional hazard regression model [3].

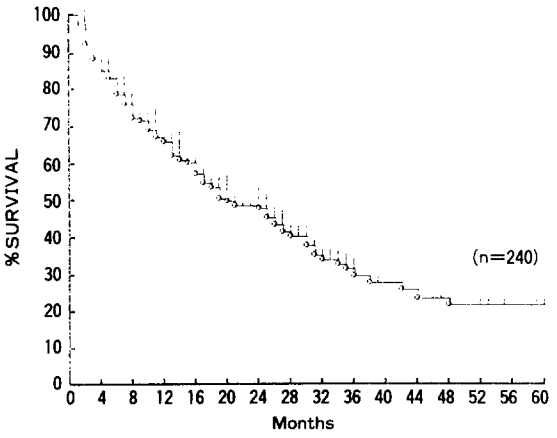

Fig. 1. Cumulative survival of 240 patients with HCC treated by TAE (Kaplan-Meier)

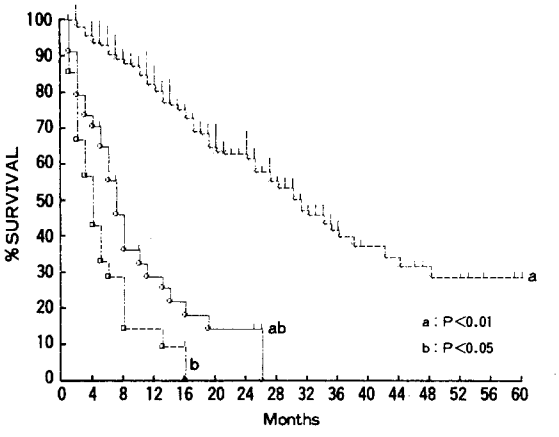

Fig. 2. Cumulative survival following TAE, plotted as a function of the type of HCC (Kaplan-Meier). ———○———, Massive type ($n = 35$); ----x----, Nodular type ($n = 184$); --- □---, Diffuse type ($n = 21$)

Results

Survival

The cumulative survival values obtained after TAE were 67.5% for 1 year, 32.0% for 2 years, and 20.5% for 3 years. The time of 50% survival was 640 days (Fig. 1). Figures 2–4 present the cumulative survival curves obtained using Kaplan-Meier's method, plotted as a function of the type of HCC, tumor embolus in the portal vein, and tumor extension.

Univariate analysis

A total of 34 clinical and laboratory variables were linked to the duration of survival (Table 2). In log-rank tests, several factors, including the tumor type, the tumor extension, the degree of extension of tumor embolus in the portal

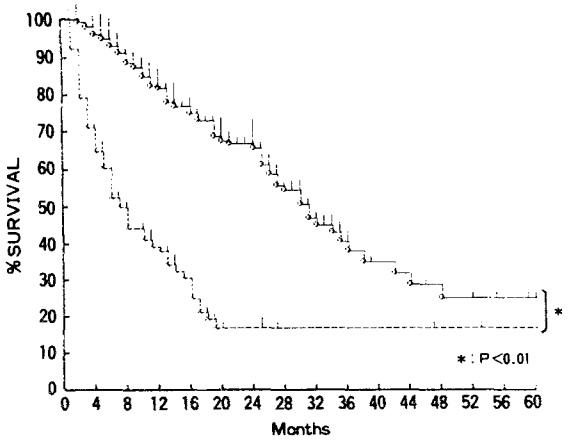

Fig. 3. Cumulative survival following TAE, plotted as a function of the tumor embolus in the portal vein (Kaplan-Meier). ———○———, Vp (–) (n = 155); – – – –x– – – –, Vp (+) (n = 85)

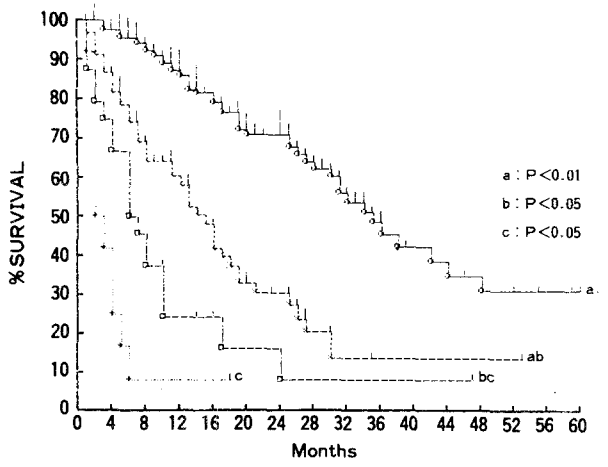

Fig. 4. Cumulative survival following TAE, plotted as a function of the tumor extension (Kaplan-Meier). ———○———, E_1 (n = 131); – – – –x– – – –, E_2 (n = 72); – – –□– – –, E_3 (n = 25); . . . . + ..., E_4 (n = 12)

vein or its branch, the use of lipiodol, and ALP values, showed significant correlation with the outcome (P <0.01). Factors such as Child's classification, the number of TAE treatments, and Ch-E, γ-GTP, LAP, GOT, and T. bilirubin values also had significance (P <0.05). Ascites and LDH and AFP values showed no statistical significance but tended to have some prognostic importance (P <0.1). Other factors such as sex; age; HBsAg and HCV Ab values; alcohol abuse; blood transfusion; the coexistence of liver cirrhosis; esophageal varices; the location of the tumor; anticancer agent; and albumin, γ-globulin, GPT, T. Cho., ICG R_{15}, Hb, platelet, PT, and HPT values had no prognostic significance.

Multivariate analysis

Multivariate analysis was carried out to test the 15 factors shown to be significant or considered to be important in the univariate analysis (Table 3). The degree of extension of tumor embolus in the portal vein or its branch, the tumor

Table 2. Results of the log-rank test on each parameter used in life-table analysis by the Kaplan-Meier method

Parameter	Range	P
Sex	M F	NS
Age	< 60.5 ≧60.5	NS
HBsAg	(–) (+)	NS
HCV Ab	(–) (+)	NS
Alcohol abuse	No Yes	NS
Blood transfusion	No Yes	NS
Liver cirrhosis	(–) (+)	NS
Ascites	(–) (+)	<0.1
Esophageal varices	(–) (+)	NS
Child's classification	A B C	<0.05
Tumor type	Nodular Massive Diffuse	<0.01
Tumor extension	E_1 E_2 E_3 E_4	<0.01
Tumor embolus in portal vein	Vp_0 Vp_1 Vp_2	<0.01
Location of tumor	P A M L C	NS
Anticancer agent	ADM CDDP MMC	NS
Lipiodol	(–) (+)	<0.01
Number of TAE treatments	1 2 ≧3	<0.05
Albumin (g/dl)	< 3.2 ≧3.2	NS
Ch-E (ΔpH)	< 0.38 ≧0.38	<0.05
γ-globulin (%)	< 27.3 ≧27.3	NS
γ-GTP (U/L)	< 131.5 ≧131.5	<0.05
ALP (U/L)	< 151.2 ≧151.2	<0.01

(cont'd)

Table 2. (Continued)

Parameter	Range	P
LAP (G&R)	< 185.7 ≧185.7	<0.05
GOT (U/L)	< 105.3 ≧105.3	<0.05
GPT (U/L)	< 108.5 ≧108.5	NS
LDH (U/L)	< 457.5 ≧457.5	<0.1
T. bilirubin (mg/dl)	< 1.4 ≧1.4	<0.05
T. Cho. (mg/dl)	< 151.4 ≧151.4	NS
ICG R_{15} (%)	< 25.3 ≧25.3	NS
Hb (g/dl)	< 13.1 ≧13.1	NS
Platelets ($\times 10^4$/mm^3)	< 13.4 ≧13.4	NS
PT (sec)	< 13.1 ≧13.1	NS
HPT (%)	< 64.7 ≧64.7	NS
AFP (ng/ml)	< 3.3 $\times 10^4$ ≧3.3 $\times 10^4$	<0.1

NS, Not significant

Table 3. Multivariate analysis of prognostic factors using Cox's proportional hazard model

Variable	Regression coefficient	SE	x^2	P
Tumor embolus in portal vein	0.758	0.213	12.67	0.00037
Tumor extension	0.533	0.163	10.72	0.00105
Tumor type	0.486	0.153	10.07	0.00149
ALP	0.531	0.243	3.012	0.0732
T. bilirubin	0.421	0.257	2.758	0.0967
Lipiodol	0.587	0.342	2.745	0.0981
LAP	0.841	0.371	2.134	0.152
Ch-E	–1.415	0.362	1.209	0.271
GOT	0.392	0.401	0.805	0.341
γ-GTP	0.274	0.387	0.738	0.391
LDH	1.081	0.512	0.684	0.409
Child's classification	0.752	0.405	0.356	0.551
Ascites	–0.563	0.385	0.201	0.653
AFP	2.543	0.412	0.0806	0.776
Number of TAE treatments	0.841	0.545	0.0341	0.935

extension, the tumor type, ALP and T. bilirubin values, and the use of lipiodol had prognostic significance in decreasing order. The number of TAE treatments, AFP values, and ascites had no significance.

Side effects

After undergoing TAE, most patients experienced fever, nausea, abdominal pain, and elevation of transaminase levels. However, most of these symptoms were transient and mild and seldom required additional treatment.

Discussion

Since 1985, we have been studying the therapeutic effect and outcome of TAE in unresectable cases of HCC. In the present study, we tried to evaluate the prognostic factors that seemed to be associated with more satisfactory results and to determine the suitable indication for TAE as the main nonoperative treatment modality. The cumulative survival values obtained after TAE were 67.5% for 1 year, 32.0% for 2 years, and 20.5% for 3 years. The time of 50% survival was 640 days. These values seem to be as high as those reported by other investigators [2, 16, 21].

As about 70% of HCC cases are complicated with liver cirrhosis, the severity of the liver dysfunction seems to be closely related to the duration of the survival of patients. Thus, in the study of prognostic factors for the survival of HCC patients, multivariate analysis of tumor factors, liver-function factors, and other factors is necessary. In the present study, we performed multivariate analysis using Cox's proportional hazard regression model [3, 5]. We first selected 34 parameters that were considered to be likely to influence the outcome in view of the literature and our clinical experience. These parameters included tumor factors such as the tumor type, patient factors such as age and ALP values, and treatment factors such as the use of lipiodol. These 34 parameters were subjected to univariate analysis using the log-rank test. In this analysis, 12 factors were significantly related to the outcome (5 factors, P <0.01; 7 factors, P <0.05), whereas 3 factors were not statistically significant but tended to have some prognostic importance (P <0.1). The other 19 parameters showed no significance.

Multivariate analysis further tested the 15 factors shown to be significant or important in the univariate analysis. The degree of extension of embolus in the portal vein or its branch, the tumor extension, the tumor type, ALP and T. bilirubin values, and the use of lipiodol showed prognostic significance in decreasing order (P <0.1). The number of TAE treatments, AFP values, and ascites had no significance.

There have been several reports that the degree of extension of tumor embolus in the portal vein or its branch is the most important factor as the indication for TAE [7, 9, 13, 15, 25]. These reports also showed that the prognosis for the Vp_3 group was significantly poorer than that for the other groups. In the present study, there was no Vp_3 group because HCC with Vp_3 was determined not to be an indica-

tion for TAE. Despite the exclusion of Vp_3, the degree of extension of tumor embolus in the portal vein or its branch proved to be the most significant prognostic factor in the present study as well. This finding seems to show the necessity for the development of therapy for emboli in the portal vein.

It has also been reported that the tumor extension and the tumor type have prognostic significance [13, 15]. They had significance in the present study as well. We also found that T. bilirubin values had significance, as previously reported elsewhere [19]. In addition, ALP values showed prognostic significance. This may have been related to biliary invasion, although other biliary-tract enzymes such as LAP and γ-GTP had no prognostic significance. This is an interesting finding, which may also have been related to a variant ALP value or to other factors. The use of lipiodol showed prognostic significance; this finding seems to indicate the efficacy of lipiodol-TAE.

Although several investigations have shown that AFP values have prognostic significance [19, 24], we observed no such significance for AFP levels in the present study, perhaps because our study included only a small number of cases with an elevated AFP value. Moreover, because AFP production differs among individual cases of HCC [18], AFP had no prognostic significance for the outcome of HCC.

Considering these results, the prognosis for HCC after TAE seems to depend more on tumor factors than on patient or treatment factors. Apparently, the use of TAE to treat patients with poor risk factors requires more careful consideration, as the optimal therapy in such cases would seem to be a combination of other treatments (e.g., PEIT, thermotherapy) with TAE. Thus, it appears that in cases of unresectable HCC, the best treatment modality would be combination therapy.

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