



Retrospective Study

Transcatheter arterial infusion for advanced hepatocellular carcinoma: Who are candidates?

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Informed consent statement: Written informed consent was obtained from all study participants prior to study enrollment.

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Abstract

AIM: To elucidate anticancer effects of transcatheter arterial infusion chemotherapy (TAI) in patients with hepatocellular carcinoma (HCC).

METHODS: Data from a total of 95 patients with HCC who received TAI were analyzed retrospectively. The efficacy of TAI was evaluated according to the Response Evaluation Criteria in Cancer of the Liver. Overall survival was calculated from the date of initial treatment to the date of death or last follow-up. Survival curves were calculated by the Kaplan-Meier method, and differences in survival were evaluated by the log rank test. Clinical variables that were identified as statistically different by a univariate analysis were included into the Cox proportional hazard regression model for multivariate analysis. A prognostic index based on the regression coefficients derived from variables identified by the multivariate analysis was constructed. Stratification of the patients was conducted using this prognostic index.

RESULTS: The patient group was comprised of 76 men and 19 women with an average age of 68 years (range: 37-82 years). Six patients (6.3%) showed

complete response and 18 patients (18.9%) showed partial response, for an overall response rate of 25.2%. The median overall survival was 27.6 mo, and the proportions of survivors at 1, 2, and 5 years were 67.4%, 54.0%, and 17.4%, respectively. Multivariate analysis demonstrated that no prior transcatheter arterial chemoembolization, lactate dehydrogenase < 230 IU/L, and performance status of 0 were the independent favorable prognostic factors. The development of a 0-3-point prognostic score index was based on the sum of these three prognostic factors. Subsequently, the patients were categorized into three groups: those with a good (prognostic index = 0-1; $n = 54$), intermediate (prognostic index = 2; $n = 26$), or poor (prognostic index = 3; $n = 15$) prognosis. The median survival times in these three groups were 41.0, 21.2, and 6.8 mo, respectively ($P < 0.01$).

CONCLUSION: Our simple prognostic index may be helpful for management of patients in determining treatment strategies for advanced HCC in the era of molecularly targeted therapy.

Key words: Hepatocellular carcinoma; Interventional radiology; Prognostic factor; Survival; Transcatheter arterial infusion

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Core tip: Transcatheter arterial infusion chemotherapy is one of the therapeutic approaches for hepatocellular carcinoma. In this study, multivariate Cox regression analyses demonstrated that no prior transcatheter arterial chemoembolization, lactate dehydrogenase < 230 IU/L, and performance status of 0 were the independent favorable prognostic factors. The prognostic index based on a combination of these three prognostic factors successfully categorized the patients into three groups with good, intermediate, or poor prognoses. This index may assist in the prediction of response to transcatheter arterial infusion chemotherapy in patients with hepatocellular carcinoma.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most common malignancy in the world^[1,2]. Treatment options, such as resection, liver transplantation,

and local ablative treatments, offer a chance of cure and improved life expectancy^[3-7]. Transcatheter arterial chemoembolization (TACE) exhibits a marked antitumor effect in HCC, and meta-analyses have demonstrated that TACE improves the survival of patients with unresectable HCC and preserved hepatic function^[8,9]. Recently, the multikinase inhibitor, sorafenib, has been also established as standard treatment for advanced HCC^[10,11], but the survival rate remains unsatisfactory^[12].

Transcatheter arterial infusion (TAI) is often used for the treatment of intermediate and advanced HCC, especially in Japan, because high concentration of the anticancer drugs can be delivered to tumors with less toxicity^[13,14]. However, there is no evidence within phase III trials that show a survival benefit. In a randomized controlled trial of TACE and TAI with zinstatin stimalamer and lipiodol, TAI yielded results comparable to those of TACE with respect to survival^[15]. In addition, sorafenib has been used in TACE-refractory cases, but the survival advantage of this agent is modest. If TAI can be used as an alternative treatment option, the addition of embolization may not be necessary for HCC patients, and TAI may result in longer survival when compared with sorafenib. Although the identification of prognostic factors might help with appropriate patient selection for TAI, only a few reports have investigated these factors^[16,17].

The present study was conducted to investigate the antitumor efficacy of the treatment, as well as to identify the prognostic factors in patients with advanced HCC receiving TAI. In addition, a prognostic index is proposed to assist with determining treatment strategies in patients with HCC.

MATERIALS AND METHODS

Patients

Between February 2000 and October 2010, 95 patients with advanced HCC were treated with TAI using various chemotherapy regimens at Chiba University Hospital, Japan. HCC was diagnosed on the basis of histologic examination or imaging studies such as distinctive findings on CT and/or angiography, with elevated serum levels of serum alpha-fetoprotein or des- γ -carboxy prothrombin. In principle, to assess the extent and size of the tumors before treatment, chest X-ray, ultrasonography, CT, and angiography of the abdomen were performed. Written informed consent was obtained from all the patients prior to the start of the treatment. This retrospective analysis was approved by the Ethics Committee of Chiba University.

Treatment procedure and assessment of efficacy

TAI was performed by selectively introducing a catheter into the artery feeding the tumor and injecting anticancer drugs in a similar fashion to TACE^[18,19].

Table 1 Patient characteristics (n = 95)

Variables	Value
Sex, male/female	76/19
Age (yr): median (range)	68 (37-82)
ECOG-PS: 0/1/2	62/28/5
Etiology HBV/HCV/Others	72/12/11
Child-Pugh: A/B/C	49/42/4
Maximum tumor diameter (mm): median (range)	30.0 (10.0-160.0)
Tumor distribution: unilateral/bilateral	22/73
Portal vein tumor thrombosis: yes/no	19/76
AFP (ng/mL), median (range)	86.0 (1.9-5856.0)
DCP (mAU/mL), median (range)	117 (0-204030)
Previous treatment	
Surgical resection	4
PEI	25
RFA	8
TACE	34
None	24

ECOG-PS: Eastern Cooperative Oncology Group-performance status; HBV: Hepatitis B virus; HCV: Hepatitis C virus; AFP: Alpha-feto-protein; DCP: Des- γ -carboxy prothrombin; PEI: Percutaneous ethanol injection; RFA: Radiofrequency ablation; TACE: Transcatheter arterial chemoembolization.

Generally, the indication for TAI at our institution was as follows: (1) repeated TACE could not control the HCC progression; and (2) selective TACE could not be performed because of multilobar tumor expansion. Anticancer agents used for TAI were as follows: (1) epirubicin was selected as first-line treatment before cisplatin approval; (2) cisplatin-based regimens were used before miriplatin approval, but not in patients with chronic kidney disease; and (3) miriplatin was selected as first-line treatment after miriplatin approval. The dose of the drug and whether or not the port is implanted, were determined based on the tumor size and liver function. After the treatment, follow-up examinations, including CT, ultrasonography, tumor marker measurement, and serum biochemistry, were generally performed first at 1-3 mo after the treatment completion, and subsequently every 3-4 mo. The transcatheter arterial treatments were repeated when disease progression by imaging studies or clinical deterioration of the patient's general condition occurred.

Evaluation of the antitumor efficacy

The antitumor effect was assessed by CT or magnetic resonance imaging at 3 mo after treatment according to the Response Evaluation Criteria in Cancer of the Liver.^[20] Lipiodol accumulation in the tumor was regarded as representing necrotic tissue. Complete response was defined as 100% size reduction or 100% necrosis of all tumors, and partial response was defined as > 50% reduction and/or necrosis in the sum of all measurable tumors. Progressive disease was defined as more than 25% tumor growth in the sum of all lesions and/or the appearance of any new lesions. Stable disease was considered as any effect that did not qualify for classification as complete or partial response or progressive disease.

Table 2 Chemotherapeutic regimens for hepatocellular carcinoma

Regimen	No. of patients
Cisplatin	35
Carboplatin	21
Epirubicin	13
SMANCS	12
Miriplatin	6
5-fluorouracil	5
Doxorubicin	2
Pirarubicin	1

SMANCS: Poly (styrene-co-maleic acid)-neocarzinostatin.

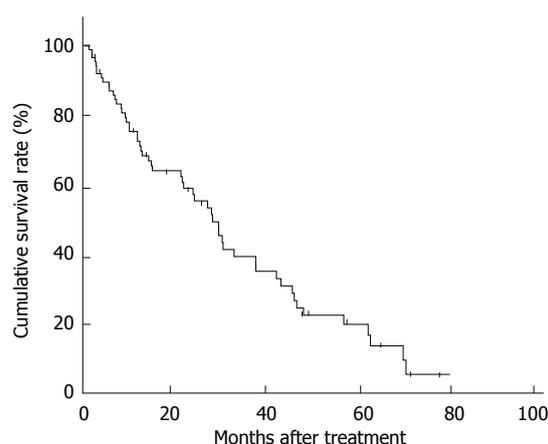


Figure 1 Overall survival curve for all patients with hepatocellular carcinoma treated by transcatheter arterial infusion chemotherapy. Tick marks indicate censored cases.

Statistical analysis

Variables were chosen based on previous investigations or our own clinical experience. Each of the variables was divided into two clinically meaningful subgroups. Overall survival was calculated from the date of initial treatment to the date of death or last follow-up. Survival curves were calculated by the Kaplan-Meier method. Univariate and multivariate analyses were calculated by Cox proportional hazards regression model. Only variables identified as statistically different by a univariate analysis were included in the multivariate analysis. A prognostic index based on the regression coefficients derived from all variables identified by the multivariate analysis was constructed. Stratification of the patients was based on this prognostic index. All *P* values shown in this report are of the two-tailed type. Differences at *P* < 0.05 were considered to be statistically significant.

RESULTS

Patient characteristics

The characteristics of all the 95 patients are shown in Table 1. The numbers of patients with Barcelona Clinic Liver Cancer stage A, B, C, and D were 6 (6.3%), 58 (61.1%), 27 (28.4%), and 4 (4.2%), respectively.

Table 3 Univariate and multivariate analyses of the prognostic factors of hepatocellular carcinoma patients receiving transcatheter arterial infusion chemotherapy

Variable	Univariate analysis		Multivariate analysis	
	HR (95%CI)	P value	HR (95%CI)	P value
Sex (male)	1.20 (0.60-2.37)	0.62		
Age (≥ 70 yr)	0.94 (0.59-1.70)	0.81		
ECOG-PS (1 or 2)	2.81 (1.58-5.02)	< 0.01	2.38 (1.29-4.39)	< 0.01
Platelet count ($\geq 10.0 \times 10^4/\text{mm}^3$)	2.07 (1.22-3.53)	< 0.01		
AST (≥ 70 IU/L)	1.55 (0.92-2.61)	0.10		
ALT (≥ 53 IU/L)	1.23 (0.73-2.09)	0.44		
LDH (≥ 230 IU/L)	1.92 (1.14-3.22)	0.01	2.03 (1.19-3.45)	< 0.01
Total bilirubin (≥ 1.0 mg/dL)	1.88 (1.11-3.18)	0.02		
Albumin (≥ 3.0 g/dL)	0.80 (0.43-1.48)	0.47		
Prothrombin ($\geq 70\%$)	0.48 (0.26-0.88)	0.02		
Maximum tumor diameter (≥ 30 mm)	1.27 (0.74-2.16)	0.39		
Tumor distribution (bilateral)	1.12 (0.62-2.02)	0.71		
Portal vein tumor thrombosis	1.78 (0.45-2.19)	0.14		
AFP (≥ 100 mg/ml)	1.25 (0.74-2.11)	0.40		
DCP (≥ 1000 mAU/mL)	1.20 (0.67-1.45)	0.33		
Prior TACE	2.38 (1.34-4.24)	< 0.01	2.34 (1.28-4.28)	< 0.01

HR: Hazard ratio; CI: Confidence interval; ECOG-PS: Eastern Cooperative Oncology Group-performance status; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; LDH: Lactate dehydrogenase; AFP: alpha-fetoprotein; DCP: Des- γ -carboxy prothrombin; TACE: Transcatheter arterial chemoembolization.

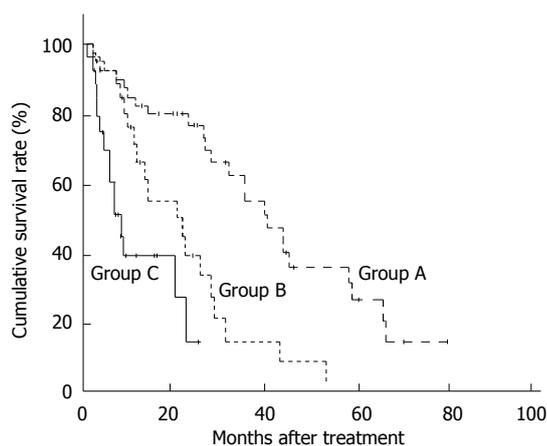


Figure 2 Survival curves for the three groups determined by a prognostic index. Group A: good prognosis; Group B: intermediate prognosis; Group C: poor prognosis. Tick marks indicate censored case.

Chemotherapy regimens of TAI are shown in Table 2. Thirty-five of 95 patients received hepatic arterial infusion chemotherapy using an implanted *port*-catheter system.

Treatment efficacy and survival

Six patients (6.3%) showed a complete response and 18 patients (18.9%) showed a partial response, for an overall response rate of 25.2%. The median survival time was 27.6 mo, and the proportions of survivors at 1, 2, and 5 years were 67.4%, 54.0%, and 17.4%, respectively (Figure 1).

Univariate and multivariate analyses

The results of univariate analysis and multivariate analysis using the Cox proportional hazard model are shown in Table 3. Among the factors, platelet \geq

$10.0 \times 10^4/\text{mm}^3$, total bilirubin < 1.0 mg/dL, lactate dehydrogenase (LDH) < 230 IU/L, performance status (PS) of 0, prothrombin time $\geq 70\%$, and no prior TACE, were significantly associated with longer survival time (all $P < 0.05$). In the multivariate analyses, only those variables identified as significant by the univariate analysis were examined. No prior TACE, serum LDH < 230 IU/L and PS of 0 were significantly associated with favorable survival.

Risk groups based on the regression model

To apply these findings clinically, a prognostic index was evaluated according to the regression coefficients derived from the three significant variables identified by multivariate analysis: prognostic index = score for prior TACE (0 for no, 1 for yes) + score for LDH (0 for < 230 IU/L, 1 for ≥ 230 IU/L) + score for PS (0 for PS 0, 1 for PS 1 or 2). The index values ranged from 0 to 3. The patients were then stratified into three groups according to the prognostic index, as follows: good prognosis group (prognostic index = 0-1; $n = 54$) (equivalent to patients with none or one of the three prognostic factors); intermediate prognosis group (prognostic index = 2; $n = 26$) (equivalent to patients with two of the three prognostic factors); poor prognosis group (prognostic index = 3; $n = 15$) (equivalent to patients with all of the three prognostic factors). The survival curves of these groups are shown in Figure 2. The median survival times in the good, intermediate, and poor prognosis groups were 41.0, 21.2, and 6.8 mo, respectively, with significant differences among the three groups ($P < 0.01$).

DISCUSSION

The aim of this study was to investigate the anticancer

activity of TAI and identify prognostic factors in patients with HCC receiving TAI. In this study, the median survival time and survival rates at two years in the current study were 27.6 mo and 54.0%, respectively. These results were comparable to those of TAI reported previously^[16] and appeared to be favorable in comparison with those in conventional TACE performed approximately ten years ago^[8,21]. However, recent studies^[22-24] revealed that a new chemoembolization technique with drug eluting beads achieved longer survival than was observed in the present study.

Of importance, no prior TACE, LDH < 230 IU/L, and PS of 0 were found to be favorable prognostic factors by multivariate analysis. Many patients receiving TAI already have experienced TACE. One reason for unsatisfactory results is that HCC might acquire resistance to cytotoxic agents. LDH level correlates the tumor burden and the invasive potential of tumor. A high LDH level is associated with poor response to the therapy and recurrence of cancer in many malignancies^[25,26]. PS is widely used as an assessment of the physical condition of the patient and is an important prognostic factor in patients with a variety of cancers^[27,28]. For clinical application of these findings, we proposed a prognostic index based on the independent prognostic factors identified in this study. Patients are classified into three groups: those with good, intermediate, or poor prognoses. The median survival times in these three groups were 41.0, 21.2, and 6.8 mo, respectively. This index is easily calculated. Patients in the good prognosis group may obtain favorable response with TAI alone, with results comparable to those of TACE previously reported in Japan^[29,30]. Even in TACE-refractory cases, TAI may be superior to sorafenib treatment if appropriate candidates are identified. In contrast, patients in the poor prognosis group are recommended for more aggressive treatments or best supportive care because of the extremely short median survival (6.8 mo).

The Barcelona Clinic Liver Cancer staging is widely used worldwide; in this staging system, TACE and sorafenib are the standard treatments for intermediate and advanced HCC, respectively^[5]. Because of the lack of randomized controlled trials, TAI has not been recognized as an effective treatment. The combination of TAI with molecular targeted therapy may improve the survival for patients with advanced HCC.

This study has several limitations. First, the anticancer drugs used in TAI varied because no standard anticancer regimen has been established for TAI. Second, this study was retrospective and therefore has some inherent biases, such as selection criteria.

In conclusion, TAI exhibited antitumor effects and resulted in favorable survival in some patients with HCC. The prognostic factors identified and the proposed index based on these factors may be useful for predicting life expectancy, determining treatment

strategies, and designing future clinical trials for advanced HCC in the era of molecularly targeted therapy.

COMMENTS

Background

Transcatheter arterial infusion chemotherapy (TAI) is one of the therapeutic approaches for hepatocellular carcinoma (HCC).

Research frontiers

In this study, the efficacy of TAI is re-evaluated. Additionally, the prognostic index was developed to determine who are candidates for TAI.

Innovations and breakthroughs

The prognostic index was developed based on the results of multivariate analysis, as follows: prognostic index = score for prior transcatheter arterial chemoembolization (0 for no, 1 for yes) + score for lactate dehydrogenase (0 for < 230 IU/L, 1 for \geq 230 IU/L) + score for performance status (0 for a status of 0, and 1 for a status of 1 or 2).

Applications

The prognostic index described in the current study may be helpful for management of patients via determining treatment strategies for advanced HCC.

Terminology

TAI is an interventional radiologic treatment to deliver anticancer drugs to intrahepatic tumors.

Peer-review

The manuscript reported the efficacy of TAI on advanced HCC and investigated related prognostic factors by Cox regression analyses. The manuscript is well written and is significant to HCC management. As there is no other treatment control, such as TACE, related reports need to be cited and discussed in discussion section.

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