Significance of trans-hepatic arterial chemotherapy for advanced hepatocellular carcinoma with portal vein tumor thrombus

MOTOHISA AKIYAMA, HISAMITSU MIYAAKI, SATOSHI MIUMA, HIDETAKA SHIBATA, MASUMI FUJIMOTO, SHIGEYUKI TAKESHITA, EISUKE OZAWA, TATSUKI ICHIKAWA, KAZUHIKO NAKAO and KATSUMI EGUCHI

The First Department of Internal Medicine, Unit of Translational Medicine, Graduate School of Biomedical Science, Nagasaki University, Nagasaki, Japan

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Abstract. Portal vein tumor thrombus (PVTT) is observed in a considerable number of hepatocellular carcinoma (HCC) cases. It is an exacerbating factor for patients afflicted with HCC. The sequelae of PVTT are considered to be a contra-indication for the treatment of HCC in such patients. The survival of 10 HCC patients with PVTT treated with trans-hepatic arterial continuous injection chemotherapy was compared to 13 HCC patients with PVTT, who received best supportive care only, as a control to validate the efficacy of continuous trans-hepatic arterial injection chemotherapy using an implanted catheter for HCC with PVTT. There were no differences in the liver function and HCC stage between the two groups. The survival was significantly different between the two groups (P=0.01 by the log-rank test). The median survival time was 106 days in the treatment patients, whereas it was 65 days in the control patients. Multivariate analyses showed the therapy to be the only predictor for survival (risk ratio 0.144, P=0.016). The therapy was strongly associated with the PVTT prognosis. In conclusion, the importance of trans-arterial chemotherapy was demonstrated even in advanced dysfunctional cirrhotic HCC patients with PVTT. It is therefore necessary to develop a basic protocol to treat HCC with PVTT.

Correspondence to: Dr Tatsuki Ichikawa, The First Department of Internal Medicine, Graduate School of Biomedical Sciences, Nagasaki University, 1-7-1 Sakamoto, Nagasaki 852-8501, Japan
E-mail: ichikawa@net.nagasaki-u.ac.jp

Abbreviations: HCC, hepatocellular carcinoma; PVTT, portal vein tumor thrombus; PEIT, percutaneus ethanol injection therapy; RFA, radiofrequency ablation; TACE, transcatheter chemo-embolization; LT, liver transplantation; TTP, time to progression; MST, median survival time; HCV, hepatitis C virus; HBV, hepatitis B virus

Key words: hepatocellular carcinoma, portal vein tumor thrombus, trans-arterial chemotherapy, liver cirrhosis

Introduction

Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide (1). The treatment of HCC is more difficult when HCC develops in association with advanced cirrhosis. Progress in imaging techniques has permitted the diagnosis of HCC at an early stage (2-4), and therapeutic procedures, such as surgical resection, percutaneous ethanol injection therapy (PEIT), radiofrequency ablation (RFA), transcatheter chemoembolization (TACE) and liver transplantation (LT), have all improved the prognosis of patients afflicted with HCC (5-9). However, portal vein tumor thrombus (PVTT) is still found in a considerable number of cases (10,11) as an exacerbating factor for patients afflicted with HCC. PVTT leads to extensive spread of the tumor throughout the liver and increases portal venous blood pressure, thus resulting in the fatal rupture of esophageal varices, and it can also decrease the portal flow thus leading to hepatic failure (12-15). These sequelae of PVTT are thus considered to be a contraindication for the treatment of HCC in such patients. Previous studies have reported that the median survival time (MST) of HCC patients with PVTT was 2.7-4 months if left untreated after surgical resection; TACE, radiation and systematic infusion of chemotherapeutic agents have been reported to be ineffective (16-23). However, hepatic arterial infusion chemotherapy for advanced HCC has been reported to effectively increase the survival of such patients (24). The trans-hepatic arterial injection of anti-HCC agents, in contrast to systemic chemo-therapy, enhances the efficiency of anticancer agents, since the hepatic artery is the sole blood source for HCC (25). Therefore, trans-hepatic arterial injection chemotherapy is a promising treatment for advanced HCC. In addition, the implantation of an intra-arterial catheter can also provide continuous drug infusion through the hepatic artery.

In this study, the survival of 10 HCC patients with PVTT treated with trans-hepatic arterial continuous injection chemotherapy was compared to 13 HCC patients with PVTT, who received best supportive care only, to validate the efficacy of continuous trans-hepatic arterial injection chemotherapy by an implanted catheter for the treatment of HCC with PVTT.

Materials and methods

Patients. Twenty-three patients diagnosed with HCC complicated with PVTT were enrolled in this study. They were diagnosed using contrast-enhanced computed tomography (CT), magnetic resonance imaging (MRI) and ultrasound (US) from January 1997 to December 2005 in our hospital. The inclusion criteria included: PVTT present in the first order branches (Vp3) or main trunk (Vp4) of the portal vein; HCC with no indication for resection; and patients with no contra-indication for the implantation of the intra-arterial catheter and the drug delivery system. The laboratory data were not included in the criteria. The subjects were divided into two groups; those who received therapy (n=10), and the control group (n=13). The criteria for classification were determined by the attending physician. The control group did not receive any therapy, after being diagnosed with HCC with PVTT. They received supportive care only. Patient disease was staged according to the TNM staging system (26), Cancer of the Liver Italian Program (CLIP) (27) and Japan Integrated Staging (JIS) (27).

Treatment. Treatment cycles were repeated every 4 weeks until there was no progressive disease. All treated patients received hepatic arterial infusion with a low dose of CDDP (20-30 mg/day, Nihon Kayaku, Tokyo, Japan) and 5-FU (250-500 mg/day, Kyowa Hakko, Tokyo, Japan) administered over an ~6-h period on days 1-5 of the first and second week. One patient was treated with radiation therapy (total 50 Gray) for PVTT together with chemotherapy in the first treatment cycle.

Response assessment. CT was repeated at the end of each therapeutic cycle to assess the response to the treatment. The response was classified according to the ECOG criteria (28): complete response (CR) when all measurable lesions disappeared including signs, symptoms and biochemical changes related to the tumor, lasting for >4 weeks, and no appearance of any new lesions; partial response (PR) when the sum of the products of the greatest perpendicular dimension of each lesion decreased by >50%, with no appearance of new lesions; stable disease (SD) when the reduction was <50% or there was a <25% increase and no appearance of new lesions; and progressive disease (PD) when the increase was >25% or the appearance of new lesions was observed. Patients who achieved CR, PR and SD were considered to have achieved successful disease control.

Time-to-progression (TTP) was calculated from the time of study entry to disease progression. The median survival time (MST) was calculated from the time of study entry to death or the last follow-up visit.

Statistical analyses. The difference between the mean values were analyzed using the Student's t-test. The difference in the frequency distribution was analyzed using the Fisher's exact test. Cumulative survival was calculated using the Kaplan-Meier method, and the difference among the groups was analyzed with the log-rank test. Independent factors for survival were assessed with the Cox proportional hazard regression model, including a comparison with historical controls. A value of $P<0.05$ was considered to be statistically significant.

Table I. Baseline clinical characteristics of the patients.

Characteristic	Therapy (n=10)	Control (n=13)	P-value
Gender (male/female)	8/2	11/2	NS
Age (years)[a]	56.1±15.70	67.1±9.7	NS
Backgound (B/C/no B,C)	4/5/1	4/8/1	NS
Stage (Vp3/Vp4)	3/7	4/9	NS
PT (%)[a]	78.2±14.00	73.4±14.90	NS
ALT (IU/l)[a]	44.9±20.60	68.3±32.50	NS
T-Bil (mg/dl)[a]	1.72±1.45	3.70±3.80	NS
Albumin (g/dl)[a]	3.53±0.86	3.36±0.57	NS
AFP (>7 ng/ml %)	70	80	NS
Child-Pugh[a]	7.0±2.10	8.5±2.20	NS
TNM[a]	3.7±0.48	3.8±0.37	NS
CLIP[a]	4.3±0.82	4.6±0.92	NS
JIS[a]	3.5±0.52	3.9±0.83	NS

B, hepatitis B virus; C, hepatitis C virus; PT, prothrombin time; ALT, alanine aminotransferase; T-Bil, total bilirubin; AFP, α-fetoprotein; NS, not significance. Student's t-test: age, PT, ALT, T-Bil, albumin, Child-Pugh, TNM, CLIP and JIS; Chi-square test: sex, background, stage and AFP. [a]mean ± SD.

Results

Patient profile and clinical efficacy. A total of 23 patients were enrolled in the study. The baseline characteristics of patients are listed in Table I. There were no differences in the liver function and HCC stage between the two groups. In the therapy group, all of the patients received at least one cycle, and a median of 2.4 cycles (range 1-6) of the therapy.

TTP and survival. One patient showed a partial response (PR) and two patients showed stable disease (SD) in the treated group, whereas all patients showed progressive disease (PD) in the control group. The median TTP was 130 days (SD, 49.61) in the successful therapy group (PR+SD, 3 cases), whereas it was 30 days (SD, 6.57) in the failure of therapy group (PD, 7 cases). In the two groups, 22 patients died during the follow-up period. The most common reasons for death were cancer (18 cases) and hepatic failure (4 cases). There were no cases of chemotherapy-related liver failure deaths in this study. One patient's survival time was 33 month, and this case is currently a PR case in the treatment group. The cumulative survival among all patients is shown in Fig. 1. The MST was 106 days in the therapy group in comparison to 65 days in the control group. Survival time was significantly different between the two groups ($P=0.01$ according to the log-rank test). The MST was 218 days in the successful treatment patients (PR+SD), whereas it was 106 days in the patients with failed treatment. No statistically significant difference was observed between PR+SD and PD in the therapy group ($P=0.08$).

The factors associated with survival were analyzed in this study. Univariate analyses (Table II) showed the predictors

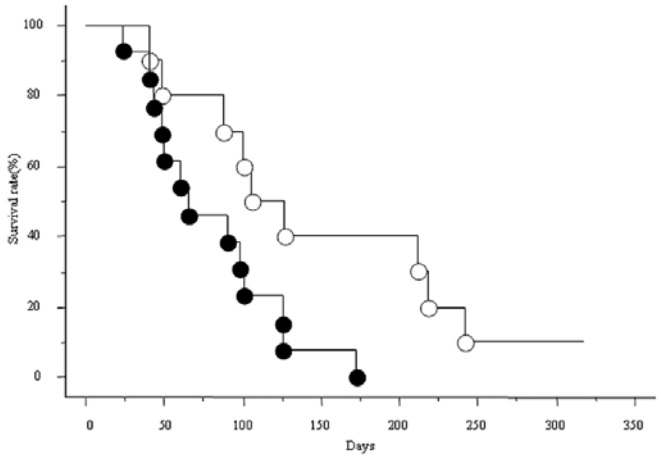

Figure 1. Comparison of the overall survival in the therapy and control groups. The overall survival rate was higher in the therapy group compared to the control group; (P=0.01). ○ therapy group, ● control group.

Table II. Univariate analysis of predictors for survival.

Variable[a]	Risk ratio	95% CI	P-value
Therapy	0.322	0.118-0.174	0.026[b]
Gender (female)	0.774	0.257-2.332	NS
PVTT (Vp3)	0.771	0.300-1.985	NS
PT (<76%)	2.368	0.921-6.087	NS
ALT (<58 IU/l)	0.325	0.116-0.911	0.032[b]
T-Bil (<1.7 mg/dl)	0.414	0.142-1.208	NS
Albumin (<3.6 g/dl)	1.494	0.595-3.752	NS
AFP (<1703 ng/ml)	0.515	0.205-1.291	NS
Child-Pugh (<8 score)	0.355	0.128-0.986	0.046[b]
Effect of therapy (PD)	4.032	0.902-18.034	NS

[a]The median value of each parameter is indicated in parentheses. [b]Statistical significant; NS, not significant. PVTT, portal vein tumor thrombus; PT, prothrombin time; ALT, alanine aminotransferase; T-Bil, total bilirubin; AFP, α-fetoprotein.

for survival to be the therapy (risk ratio 0.322, P=0.026), the alanine aminotransferase levels (risk ratio 0.325, P=0.032) and the Child-Pugh score (risk ratio 0.355, P=0.046). Other factors, listed in Table II, showed no statistical association with the survival rate. Multivariate analyses (Table III), using variables with P<0.2 in Table II, showed the only predictor for survival to be therapy (risk ratio 0.144, P=0.016). The therapy which was administered to the HCC patients was strongly related to the PVTT prognosis.

Complications. Complications included a decreased leukocyte count or platelet count (n=5) (no patients discontinued the therapy or required the administration of granulocyte-colony-stimulating factor) and the presence of nausea and vomiting (n=2). There were no complications resulting from the arterial catheter.

Table III. Multivariate analysis of predictors for survival.

Variables[ab]	Risk ratio	95% CI	P-value
Therapy	0.167	0.036-0.768	0.021[c]
PT (<76%)	1.930	0.270-13.782	NS
ALT (<58 IU/l)	0.472	0.129-1.720	NS
T-Bil (<1.7 mg/dl)	0.847	0.135-5.320	NS
AFP (<1703 ng/ml)	0.269	0.047-1.535	NS
Child-Pugh (<8 score)	1.697	0.345-8.361	NS
Effect of therapy (PD)	3.917	0.651-23.567	NS

[a]The median value of each parameter is indicated in parentheses. [b]Those variables with a value P<0.2 according to a univariate analysis (Table II) were included. [c]Statistical significance; NS, not significant. PT, prothrombin time; ALT, alanine aminotransferase; T-Bil, total bilirubin; AFP, α-fetoprotein.

Discussion

The therapeutic procedures for patients who have HCC with PVTT are limited, and they also remain controversial. A basic protocol for HCC with PVTT has yet to be established. In the current therapy group, 10 patients with PVTT received trans-arterial chemotherapy. They showed an objective response, PR+SD, rate of 30% among patients with PVTT in the therapy group. The improvement in the median survival time was exceptional among those patients, showing a median survival time of 106 days, in contrast to 65 days among the controls.

In general, HCC is resistant to anticancer drugs (29). However, studies have demonstrated the efficacy of combination therapy in HCC patients with PVTT. Okada *et al* reported the results of systemic chemotherapy using several anticancer agents in 71 patients with unresectable HCC, and the response rates ranged from 0 to 20% (30). Of these patients, 22 had PVTT in the main portal vein. The median survival time of the patients with PVTT was 3.9 months. The results of the administration of low-dose CDDP and 5-FU by repeated arterial infusion in 9 patients with HCC and PVTT in the main portal vein were reported by Ando *et al*. The response rate was 44%, and the median survival time was 9.2 months (31). In comparison to this report, the therapy group in the current study demonstrated different responses and survival times. This discrepancy may be due to several factors. First, most of the patients in the current study were recurrent cases (80%), whereas virgin cases were studied in the previous reports. Second, the present study included HCC patients with extrahepatic metastasis (2 cases), whereas no remote metastasis was observed in the above mentioned reports. Third, the total bilirubin level was >1.0 mg/dl in most of the patients (70%) indicating poor liver function and prognosis. In the current report, the effectiveness of trans-arterial chemotherapy was indicated for HCC with PVTT in more advanced HCC stages and in cirrhosis than in the previously mentioned reports.

In this study, a univariate analysis demonstrated that three factors, therapy (risk ratio 0.322, P=0.026), alanine amino-

transferase (risk ratio 0.325, P=0.032) and the Child-Pugh score (risk ratio 0.355, P=0.046) influenced the prognosis. A multivariate analysis revealed that only the therapy was an independent prognosis factor of survival. Several investigators have reported that one of the independent prognostic factors in patients with HCC with PVTT is the therapeutic effect (complete response or partial response) (33,34). The present study demonstrated that most of the patients with combined therapy showed either stable disease or progressive disease, and that the survival was different between the therapy group and the control group. In addition, no significant difference was detected in the survival time between the PR+SD and PD patients in the therapy group. This may have been caused by advanced liver dysfunction and no cases of CR where the therapeutic effect was not a prognostic factor. Accordingly, this may indicate that patients with advanced HCC should be treated with intra-hepatic arterial chemotherapy. The effectiveness of therapy must be re-evaluated following a larger study of patients with advanced HCC with PVTT.

Combined treatment with 5-FU and IFN-α for HCC was first reported by Patt *et al* in 1993, and the response rate was 22% (32). The effects of combined intra-arterial 5-FU and subcutaneous IFN-α therapy for 8 patients with HCC and PVTT in the major portal vein were studied by Sakon *et al* in 2002, and the response rate was 63% (24). Radiation therapy in addition to chemotherapy was also reported to be more effective in HCC (35). Recently, sorafenib, an oral multi-kinase inhibitor has been shown to be an effective anti-HCC agent (36). Hereafter, combinations of newly developed agents and modalities must be evaluated for the treatment of advanced HCC with PVTT.

In conclusion, this study showed the importance of trans-arterial chemotherapy even for advanced dysfunctional cirrhotic HCC patients with PVTT. In the future, a basic protocol for HCC patients with PVTT must be established.

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