P.O.Box 2345, Beijing 100023,China
Fax: +86-10-85381893
E-mail: wjg@wjgnet.com www.wjgnet.com

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• LIVER CANCER •

Hepatic arterial infusion chemotherapy for hepatocellular carcinoma with tumor thrombosis of the portal vein

Yung-Chih Lai, Cheng-Yen Shih, Chin-Ming Jeng, Sien-Sing Yang, Jui-Ting Hu, Yung-Chuan Sung, Han-Ting Liu, Shaw-Min Hou, Chi-Hwa Wu, Tzen-Kwan Chen

Yung-Chih Lai, Cheng-Yen Shih, Sien-Sing Yang, Jui-Ting Hu, Yung-Chuan Sung, Han-Ting Liu, Chi-Hwa Wu, Tzen-Kwan Chen, Department of Internal Medicine, Cathay General Hospital, Taipei, Taiwan, China
Chin-Ming Jeng, Department of Radiology, Cathay General Hospital, Taipei, Taiwan, China
Shaw-Min Hou, Department of Surgery, Cathay General Hospital, Taipei, Taiwan, China
Correspondence to: Dr. Yung-Chih Lai, Department of Internal Medicine, Cathay General Hospital, 280, Jen-Ai Road, Section 4, Taipei 106, Taiwan, China. yungchihlai@hotmail.com
Telephone: +86-2-27082121 Ext.3120 **Fax:** +86-2-27074949
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Abstract

AIM: Hepatocellular carcinoma (HCC) with portal vein tumor thrombosis (PVTT) is associated with poor prognosis. The aim of this prospective study was to evaluate the efficacy of hepatic arterial infusion chemotherapy (HAIC) for patients with this disease.

METHODS: Eighteen HCC patients with PVTT were treated with HAIC via a subcutaneously implanted injection port. A course of chemotherapy consisted of daily cisplatin (10 mg for one hour) followed by 5-fluorouracil (250 mg for five hours) for five continuous days within a given week. The patients were scheduled to receive four consecutive courses of HAIC. Responders were defined in whom either a complete or partial response was achieved, while non-responders were defined based on stable or progressive disease status. The prognostic factors associated with survival after treatment were analyzed.

RESULTS: Six patients exhibited partial response to this form of HAIC (response rate = 33 %). The 3, 6, 9, 12 and 18-month cumulative survival rates for the 18 patients were 83 %, 72 %, 50 %, 28 %, and 7 %, respectively. Median survival times for the six responders and 12 non-responders were 15.0 (range, 11-18) and 7.5 (range, 1-13) months, respectively. It was demonstrated by both univariate and multivariate analyses that the therapeutic response and hepatic reserve function were significant prognostic factors.

CONCLUSION: HAIC using low-dose cisplatin and 5-fluorouracil may be a useful alternative for the treatment of patients with advanced HCC complicated with PVTT. There may also be survival-related benefits associated with HAIC.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide, especially in Asia and South Africa[1]. The incidence of HCC has increased over the past decade, and it has become the leading cause of death among patients with cirrhosis[2]. Despite the marked progress in diagnostic techniques and therapeutic procedures, the prognosis for HCC patients remains discouraging. Surgical resection or liver transplantation for these individuals is frequently not feasible due to poor hepatic reserve function, advanced HCC stage, and/or lack of suitable donor livers[3,4]. In past studies, the median survival period for unresectable HCC cases has been only a few months. The survival rate for patients with advanced HCC with portal vein tumor thrombosis (PVTT) was even worse[5-8]. It has been reported that patients with diffuse HCC complicated with PVTT survived only 1-2 months if effective treatment could not be delivered[9]. Transcatheter arterial embolization (TAE), microwave coagulation therapy (MCT), radiofrequency ablation (RFA), and percutaneous ethanol injection (PEI) were all of limited value for such patients[10,11]. Systemic chemotherapy has also been trialed in cases of this type, but without any appreciable survival benefit[12].

Recent advances in implantable drug delivery systems have made it possible to administer repeated arterial infusion of chemotherapy agents[13,14]. Hepatic arterial infusion chemotherapy (HAIC) has the advantages of increased local drug concentrations and a reduction in systemic side effects, making it appropriate, therefore, as a palliative treatment for patients with advanced, unresectable HCC complicated with PVTT. Several authors in this field have reported the efficacy of HAIC[15], with favorable results achieved by a regimen consisting of cisplatin and 5-fluorouracil (5-FU)[16-18]. Based on these considerations, the aim of our prospective study was to evaluate the efficacy of low-dose cisplatin and 5-FU chemotherapy for cases of advanced HCC with PVTT, and analyze the clinical results.

MATERIALS AND METHODS

Patients

From June 1, 2000 to May 31, 2003, twenty patients with unresectable HCC complicated with PVTT received HAIC at the Department of Internal Medicine, Cathay General Hospital. The treatment consisted of low-dose cisplatin and 5-FU delivered via a subcutaneously implanted injection port. Given the severity of HCC or coexisting liver cirrhosis, these patients were not suitable for either surgical resection[4] or nonsurgical treatments such as MCT[19], RFA[20], PEI[21], or TAE[22]. Of the initial 20 subjects, two withdrew due to technical difficulties associated with the indwelling catheter. These were related to the excessive size of the tumor, which hindered insertion of the catheter in one case; and stenosis of the hepatic artery in the other. In total, 18 patients were enrolled in the current study. Informed consent was obtained from all the subjects before the start of the investigation. The diagnosis of HCC was made by histopathology and/or imaging study. Of the 18 diagnoses, six were proven by histopathology and 12 were confirmed clinically using imaging studies, including ultrasonography

(US), computed tomography (CT), angiography, and magnetic resonance imaging, and/or based on a high plasma level of α-fetoprotein (AFP). There were no distant metastases at the time of commencement of the interventional therapy. Patients with any evidence of cardiac disease (congestive heart failure or history of myocardial infarction within the previous three months), severe vascular disease or uncontrolled concomitant infection were excluded. The exlusion criteria also included hepatic encephalopathy, hepatorenal syndrome, gastrointestinal bleeding, refractory ascites, serum bilirubin >5 mg/dl, serum creatinine >1.8 mg/dl, WBC count <3 000/mm^3, and platelet count <30 000/mm^3. The presence of PVTT was confirmed in all the cases by demonstration of one of the following: an intraluminal mass in the portal vein or portal branch from US or enhanced CT scan[23]; the "thread-and streaks" sign or arterioportal shunts on hepatic angiography[24]; or filling defects in the portal vein or in the portal branch as noted in an indirect portogram obtained from a venous phase angiogram of the superior mesenteric artery.

The clinical characteristics for the 18 HAIC-treated HCC patients with PVTT are shown in Table 1. The average age of the 16 male and two female patients was 56.9 (range, 43-75) years. Thirteen individuals were infected with hepatitis B virus (HBV) and five with hepatitis C virus (HCV). The Child-Pugh' s staging classification was used to estimate the degree of hepatic reserve function[25]. Ten patients had a past history of HCC treatment using surgery and/or TAE. The PVTT grading and tumor-extent rating were evaluated using the criteria of the Liver Cancer Study Group of Japan[26]. The PVTT grading was based on the location of the tumor thrombus in the portal vein as follows: Vp1, tumor thrombus in a third or more of the peripheral branch of the portal vein; Vp2, tumor thrombus in a second branch of the portal vein; and, Vp3, tumor thrombus in the first branch or trunk of the portal vein. Tumor-extent rating was estimated from imaging study. The rating system was based on the tumor-extent percentage (E): E1, less than 20 % of the whole liver; E2, 20-40 % of the whole liver; E3, 40-60 % of the whole liver; and, E4, greater than 60 % of the whole liver.

Catheter-implantation technique

The hepatic artery was catheterized using a femoral approach. The tip of the catheter was placed in the proper hepatic artery after HCC localization. The other end of the catheter was connected to the injection port which was implanted in a subcutaneous pocket in the right lower abdominal quadrant[16]. The gastroduodenal artery was occluded using steel coils to prevent injury to the gastrointestinal tract from exposure to the chemotherapy agents[15,16]. Heparin solution was infused regularly via the injection port to keep the catheter from occluding.

Chemotherapeutic regimen

After the set up of drug delivery system, the patients began to receive repeated arterial infusions of chemotherapy agents via the injection port. One course of chemotherapy consisted of cisplatin (10 mg per day) followed by 5-FU (250 mg per day) for five continuous days, with the patients resting on days 6 and 7. Both the cisplatin and 5-FU were administered by a mechanical infusion pump set at a rate of 10 mg for 1 hour and 250 mg for 5 hours, respectively[16]. Basically, the patients were expected to undergo four consecutive courses of chemotherapy, and then they were deemed to have completed HAIC. HAIC was considered incomplete for patients whose chemotherapy was suspended before the completion of the four consecutive courses because of adverse reactions or complications. Maintenance therapy based on the above regimen (cisplatin 10 mg and 5-FU 250 mg for one day) was continued every two weeks after the completion of the initial four courses of the HAIC, with duration depending on tumor response, hepatic function, adverse reactions, and complications.

Assessment of therapeutic response

Abdominal US and CT were performed regularly (every 2-3 and 4-6 months, respectively) to measure the size of the tumor. Local response to treatment was classified according to World Health Organization criteria[27]. Complete response (CR) was defined as the complete disappearance of all known disease, and no new lesions, as determined from two observations no less than four weeks apart. Partial response (PR) was deemed to have occurred where there was a greater than 50 % reduction in total tumor load for all measurable lesions, as determined by two observations no less than four weeks apart. Stable disease (ST) did not qualify for CR/PR or progressive disease (PD) status, with the latter defined as a greater than 25 % increase in the size of one or more measurable lesions or the appearance of new lesions.

Statistical analysis

The Kaplan and Meier method was used to plot the estimated survival curves from the first day of treatment to the last day of follow-up. The results of the univariate analysis were compared to those from the log-rank test to identify predictors of survival. The results of the multivariate analysis were then investigated using Cox' s proportional hazards model. A *P* value less than 0.05 was considered to be statistically significant.

RESULTS

Therapeutic response and patient survival

The salient clinical characteristics for the patients are presented in Table 1. Fifteen patients completed HAIC, while three did not complete the initial four courses series because of deteriorating liver function, sepsis, and gastric ulcer bleeding, respectively. Overall the CR, PR, ST, and PD in response to chemotherapy were zero (0 %), six (33 %), seven (39 %), and five (28 %) in the 18 patients respectively. The response rate (CR and PR/all patients) was 33 %.

Table 1 Clinical characteristics of the 18 patients with hepatocellular carcinoma

Characteristics	*n*
Gender (male / female)	16 / 2
Age (younger than 60 yrs / 60 yrs and older)	9 / 9
HBV / HCV	13 / 5
Child-Pugh's stage (A / B / C)	7 / 7 / 4
Previous treatment (yes / no)	10 / 8
Serum AFP (<1 000 ng.ml^{-1} / ⩾1 000 ng.ml^{-1})	6 / 12
Tumor location (unilobe / bilobe)	10 / 8
Tumor type (nodular / massive / diffuse)	7 / 6 / 5
Maximum tumor size (<5 cm / ⩾5 cm)	13 / 5
Tumor extent (E1 / E2 / E3 / E4)[a]	1 / 6 / 7 / 4
Grade of portal vein invasion (Vp1 / Vp2 / Vp3)[bc]	0 / 5 / 13
Completion of protocol (yes / no)	15 / 3
Therapeutic response (CR / PR / ST / PD)	0 / 6 / 7 / 5

HBV: hepatitis B virus; HCV: hepatitis C virus; AFP: α-fetoprotein; Vp: portal vein tumor thrombosis; CR: complete response; PR: partial response; ST: stable disease; PD: progressive disease. [a]Tumor extent. Tumor replacement of liver parenchyma: E1, <20 %; E2, 20-40 %; E3, 40-60 %; E4,>60 %. [bc]Portal vein invasion. Vp1: in a third or more of the peripheral branch; Vp2: in the second branch; Vp3: in the first branch or trunk.

The cumulative survival for the 18 patients is shown in Figure 1. The 3, 6, 9, 12, 15 and 18-month cumulative survival rates for all the 18 patients were 83 %. 72 %, 50 %, 28 %, 14 %, and 7 %, respectively. While for the six responders (CR and PR), the 3, 6, 9, 12, 15 and 18-month cumulative survival rates were 100 %, 100 %, 100 %, 67 %, 44 %, and 22 %, respectively. The median survival time for the 18 HAIC-treated patients was 9.5 (range, 1-18) months.

The median survival times for the six responders (CR and PR) and the 12 non-responders (ST and PD) were 15.0 (range, 11-18) and 7.5 (range, 1-13) months, respectively. Based on hepatic reserve function, the median survival times for Child-Pugh' s stages A, B, and C were 13.0 (range, 11-18), 8.0 (range, 2-15), and 3.5 (range, 1-9) months, respectively.

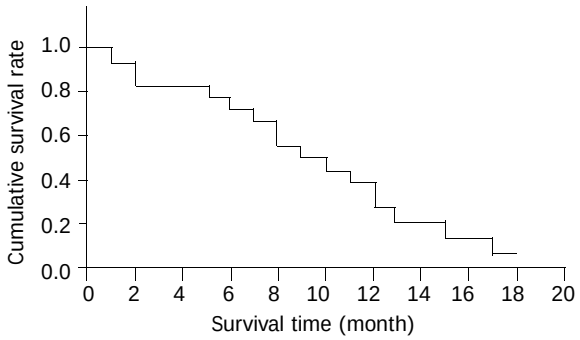

Figure 1 Cumulative survival for 18 hepatocellular carcinoma patients with portal vein tumor thrombosis undergoing hepatic arterial infusion chemotherapy. The 3, 6, 9, 12, 15 and 18-month cumulative survival rates for the 18 patients were 83 %, 72 %, 50 %, 28 %, 14 %, and 7 %, respectively.

Prognostic factors related to survival

Two of the 13 factors was demonstrated to have prognostic significance using univariate analysis: Child-Pugh' s stage (P=0.001) and therapeutic response (P<0.001; Table 2). Multivariate analysis also confirmed these two variables as independent predictors of survival (P=0.005 and 0.001, respectively). None of the other factors were significantly related to patient survival.

Serial computed tomography (CT) revealed progressive improvement in a 55-year-old male patient with HCC complicated with PVTT who presented with a good partial response to HAIC (Figure 2). The huge tumor was decreased markedly from 14×10×9 cm initially to 5×5×3 cm after four months of HAIC.

Table 2 Factors associated with cumulative survival of patients by univariate analysis (log-rank test)

	P value*
Gender (male / female)	0.950
Age (younger than 60 yrs / 60 yrs and older)	0.948
HBV / HCV	0.825
Child-Pugh's stage (A / B / C)	0.001
Previous treatment (yes / no)	0.753
Serum AFP (<1 000 ng.ml^{-1} / ⩾1 000 ng.ml^{-1})	0.994
Tumor location (unilobe / bilobe)	0.938
Tumor type (nodular / massive / diffuse)	0.541
Maximum tumor size (<5 cm / ⩾5 cm)	0.761
Tumor extent (E1 / E2 / E3 / E4)[ac]	0.429
Grade of portal vein invasion (Vp1 / Vp2 / Vp3)[bd]	0.309
Completion of protocol (yes / no)	0.155
Therapeutic response (CR / PR / ST / PD)	<0.001

HBV: hepatitis B virus; HCV: hepatitis C virus; AFP: α-fetoprotein; Vp: portal vein tumor thrombosis; CR: complete response; PR: partial response; ST: stable disease; PD: progressive disease. [ac]Tumor extent. Tumor replacement of liver parenchyma: E1,<20 %; E2, 20-40 %; E3, 40-60 %; E4,>60 %. [bd]Portal vein invasion. Vp1: in a third or more of the peripheral branch; Vp2: in the second branch; Vp3: in the first branch or trunk.

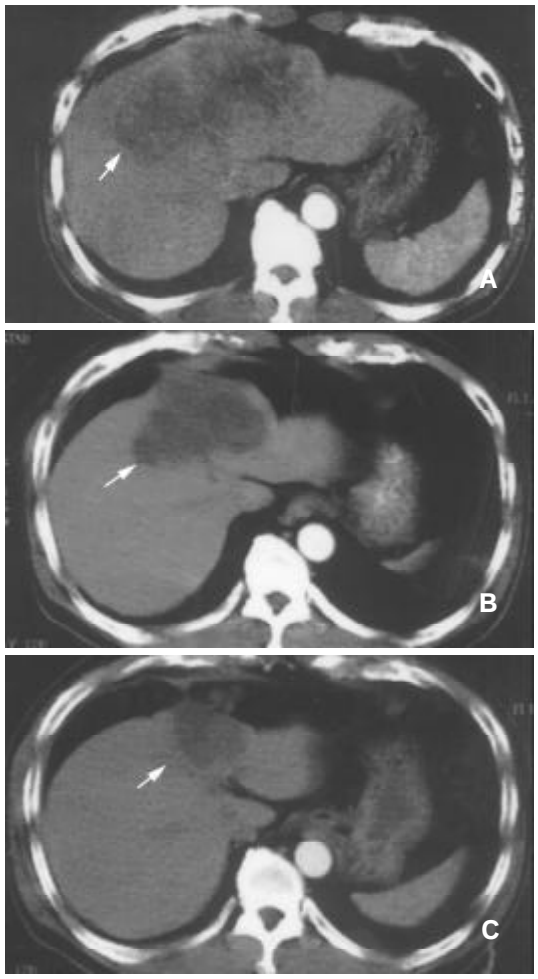

Figure 2 Image study using abdominal computed tomography (hepatic artery phase) of an HCC patient with good partial response to hepatic arterial infusion chemotherapy (HAIC) shows a marked decrease in tumor size from 14×10×9 cm (A: before HAIC) to 9×8×7 cm (B: 1.5 months after initiation of HAIC) and 5×5×3 cm (C: 4 months after initiation of HAIC).

Side effects and complications

The most common adverse reactions to HAIC were nausea and loss of appetite (five cases, 28 %). Two patients (11 %) experienced leukopenia and thrombocytopenia, with one of them unable to continue the chemotherapy due to severe leukopenia. Peptic ulcer was a complication in one case and renal damage in another. Deterioration of liver function occurred in two individuals, causing one of them to quit therapy. Most of these side effects were managed using medical treatment and were not considered serious.

Complications associated with the indwelling catheter were obstruction (n=2), infection (n=2), dislocation of the catheter tip (n=1), and hematoma around the injection port (n=1). All these technical problems were overcome by medical treatment, infusion of heparin solution, or implantation of a new catheter.

Causes of death

Two patients survived the follow-up period. The remaining 16 patients expired, ten (63 %) due to cancer-related causes.

Of these, seven were as a result of tumor extension and three due to tumor rupture. Three individuals (19 %) died of gastrointestinal bleeding; of the rest, three (19 %) died of sepsis related to pneumonia (*n*=2) or urinary tract infection (*n*=1).

DISCUSSION

A standard optimal therapy for advanced unresectable HCC is still lacking[28] . HCC has a high predilection for portal vein invasion, which has been shown to be a poor prognostic factor[5-8]. Although surgery may be considered for some HCC patients with PVTT[6], most are not suitable for this invasive treatment because of dissemination of the tumor throughout the liver, or the coexistence of cirrhotic change. The presence of tumoral portal invasion precludes most potential curative interventions such as TAE, PEI, MCT, and RFA[7]. Further, liver transplantation is not indicated for such patients. Additionally, systemic chemotherapy, hormonal therapy, and IFN therapy are all reported to be of limited value[1,11].

Most of the blood supply to HCC is derived from the hepatic artery, whereas the portal vein supplies the normal liver parenchyma. It is reasonable to assume, therefore, that intra-arterial administration of cytotoxic agents may facilitate delivery of a higher therapeutic concentration to the tumor tissue[29]. Both cisplatin and 5-FU have an anti-tumor effect[30]. In addition, cisplatin plays a synergistic role as a modulator of 5-FU, inhibiting the transport of neutral amino acids, including L-methionine, into tumor cells, and resulting in enhancement of its antitumor effects[31]. Additionally, the combination of cisplatin and 5-FU allows low-dose administration with an associated reduction in adverse reactions. Hepatic extraction of chemotherapeutic agents can result in minimal systemic concentrations of these agents and, thus, minimize systemic toxicity[32] .

In comparison to analogous research, more patients were enrolled in the study of Ando *et al*., (2002), with an HAIC response rate and median survival duration of 48 % and 10.2 (range, 1.7-76.9) months, respectively for their 48 patients with PVTT[18] . By comparison, our response rate and median survival time was 33.3 % and 9.5 (range, 1-18) months, respectively. Moreover, the median survival time for our six responders and 12 non-responders were 15.0 (range, 11-18) and 7.5 (range, 1-13) months, respectively. In the above larger study, the median survival times for the 23 responders and 25 non-responders were 31.6 (range, 9.3-76.9) and 5.4 (range, 1.9-29.0) months, respectively[18]. The longest follow-up for a survivor in their study was 76.9 months, whereas it was only 18 months in our investigation. This variation in the follow-up period may account for the difference in the results outlined above. More cases are needed to continue this study and deliver a more comprehensive and accurate result. Even in our non-responder group, however, the median survival time was 7.5 months, which is still longer than analogous reports[5,7]. The reason that some tumors responded to HAIC, and others not, was not determined in the current study, however. This critical piece of information awaits further investigations, including immunological and/or molecular biological study of tumor cells, to reveal the underlying causes.

In an evaluation of HCC prognosis conducted by the Liver Cancer Study Group of Japan, the severity of any associated cirrhosis, and the size and number of lesions were independent predictive factors[33]. In our study, however, only hepatic reserve function and the patient' s therapeutic response were associated with survival. This difference may result from variations in the patient-enrollment criteria. Our subjects were confined to cases of unresectable HCC with PVTT. In such advanced-stage patients, the influence of lesion size and number on survival is no longer significant. Cirrhosis-related complications (e.g. hepatic failure, variceal bleeding, and spontaneous bacterial peritonitis) were known to play key roles in HCC mortality[34]. The patients with more-favorable Child-Pugh' s classifications have fewer complications and may thus have better and more-favorable outcomes.

Kupffer cells and polymorphonuclear cell function are depressed in liver cirrhosis. The serum also shows a reduction in factors such as fibronectin, opsonins and chemo-attractants, including members of the complement system[35,36]. The hepatic cellular-immune responses, which involve natural killer cells, cytotoxic T lymphocytes and macrophages (Kupffer cells), and their cytotoxic reactions against tumor cells are important as a defense mechanism against hepatocarcinogenesis[37]. In cases of poor residual liver function, the complex molecular and cellular mechanisms, which prevent tumor formation and further development and spread of established tumors, are impaired[38]. Therefore, the prognosis for advanced HCC occurring in such patients is inevitably bleak and dismal.

Chemotherapeutic toxicity was infrequent in our study. Myelosuppression was noted in two cases, and deterioration of liver function also diagnosed in two individuals. The most common adverse reaction, nausea or loss of appetite, was related to the gastrointestinal tract.

Although the survival of HCC patients with PVTT can be improved using HAIC, the results remain unsatisfactory. Further research and investigation is still necessary. Combined therapy, consisting of an intra-arterial infusion of a cytotoxic agent and systemic administration of interferon-α was reportedly useful as a palliative treatment for HCC patients with major vascular involvement[1]. Additional therapy following HAIC, including surgery, MCT, PEI, and extra chemotherapy, might be another option for the prolongation of survival in advanced HCC patients[18,39]. Moreover, the identification of tumors which are more sensitive to cytotoxic agents, and the reason for this are also important areas for future research.

In conclusion, the use of HAIC improves the survival of HCC patients with PVTT. Further, most of the side effects are transient and well tolerated. Hepatic reserve function and therapeutic response are the most important survival-related prognostic factors. Based on our findings, therefore, it seems reasonable to suggest that HAIC is a safe and effective alternative for the treatment of advanced HCC.

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