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ORIGINAL ARTICLE

Influence of the etiology of liver cirrhosis on the response to combined intra-arterial chemotherapy in patients with advanced hepatocellular carcinoma

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Abstract
Purpose We have previously reported that intra-arterial chemotherapy prolongs the survival of patients with advanced HCC (aHCC); however, whether the response to intra-arterial chemotherapy depends on the etiology of underlying liver cirrhosis (LC) is still unknown.
Aim The aim of this study was to assess any influences of the etiology of LC on the response to combined intra-arterial chemotherapy for aHCC.
Methods A total of 53 adult Japanese LC patients (46 men and 7 women) with aHCC were treated with combined intra-arterial chemotherapy between 2002 and 2007 at our hospital. All of the patients had a Japan Integrated Staging (JIS) score of 3 or 4. Their tumors were inoperable according to computed tomography findings. Combined intra-arterial chemotherapy was administered via the proper hepatic artery every 5 days for 4 weeks and the chemotherapy regimen was continued for as long as possible.
Results There were 15 patients with HBV infection (B-LC group), 29 patients with HCV infection (C-LC group), and nine patients with alcoholic cirrhosis (A-LC group). The percentage of patients with a complete or partial response after 4 weeks of chemotherapy was 0% in the B-LC group versus 31.0% in the C-LC group and 44.4% in the A-LC group. The survival of the A-LC and C-LC groups was significantly longer than that of the B-LC group with the median survival time being 688, 368, and 211 days, respectively.
Conclusions Combined intra-arterial chemotherapy might be more effective for aHCC in patients with A-LC or C-LC than in patients with B-LC.

Keywords 5-FU · CDDP · Advanced HCC · Liver cirrhosis · Intra-arterial chemotherapy · Etiology

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Introduction

There are a considerable number of patients with advanced hepatocellular carcinoma (aHCC) for whom intra-arterial combination chemotherapy is one of the few remaining options. Continuous local intra-arterial infusion of 5-fluorouracil (5-FU) and cisplatin (CDDP) via an infuser pump and implanted reservoir has been shown to prolong the survival of patients with aHCC [1–3]. We have also reported that intra-arterial treatment with a combination of low-dose 5-FU, CDDP, and leucovorin (LV) prolongs the survival of patients with aHCC [4]. 5-FU has been reported to have two mechanisms of antitumor activity: (1) inhibition of deoxyribonucleic acid (DNA) synthesis through inactivation of thymidylate synthase (TS) by formation of a complex between methylenetetrahydrofolate (CH_2FH_4) and 5-fluoro-2′-deoxyuridine 5′-monophosphate (FdUMP), which is synthesized from 5-FU, (2) interference with ribonucleic acid (RNA) metabolism by the uptake of phosphated 5-fluorouridine 5′-triphosphate into RNA [5]. It was also reported that a bolus dose of 5-FU is more effective for causing RNA dysfunction, while continuous infusion causes more DNA damage [6]. Another study has shown that 5-FU is almost undetectable in the peripheral blood when 5-FU and low-dose CDDP are continuously infused via a central vein or via the hepatic artery in patients with adavanced or metastatic HCC [7]. Furthermore, we have reported that continuous

intra-arterial infusion for 24 h is more effective compared with 6-h infusion in patients with liver cirrhosis (LC) and aHCC due to HCV, although 24-h infusion was associated with stronger hematologic toxicity [8]. However, whether the response to combined intra-arterial chemotherapy varies with the etiology of LC underlying aHCC is still unclear.

For the staging of hepatocellular carcinoma (HCC), the Cancer of the Liver Italian Program (CLIP) score [9] is considered very useful [10–12]. However, it has been reported that patient stratification and prediction of the prognosis of HCC are better with the Japan Integrated Staging (JIS) score [13] than with the CLIP score [14].

The aim of this study was to assess any influences of the etiology of LC on the efficacy of combined intra-arterial chemotherapy with 5-FU, CDDP, and LV for aHCC after using the JIS score to stratify patients.

Methods

Patients

A total of 53 adult Japanese LC patients admitted to the Omori Hospital of Toho University Medical Center were diagnosed as having aHCC between 2002 and 2007, and then received hepatic arterial infusion therapy using an implanted drug delivery system. The diagnosis of HCC was made either by histology or using a combination of radiology [double-contrast spiral computed tomography (CT) scan] and serum alpha fetoprotein (AFP) level of >500 μg/L. These patients were not eligible for surgical resection or for interventions such as percutaneous ethanol injection, transcatheter arterial emobolization, microwave coagulation therapy, or radiofrequency ablation because they had multiple tumors in both lobes of the liver. All of the patients had a JIS score of 3 or 4 and were administered 5-FU, CDDP, and LV via the hepatic artery.

Chemotherapy regimen

Continuous infusion of LV (12 mg/h) CDDP (10 mg/h) and 5-FU [250 mg/(m^2 22 h] was performed via the proper hepatic artery at 5-day intervals for 4 weeks. After that, the same regimen was repeated for as long as possible. The doses of the chemotherapy agents were selected according to a previous report [15].

Delivery system

In each patient, a catheter was inserted via the femoral artery and was attached to a subcutaneously implanted reservoir to allow the performance of intra-arterial chemotherapy [16]. In principle, the gastroduodenal artery and the right gastric artery were occluded with steel coils to prevent gastroduodenal injury by the anticancer agents. Written informed consent was obtained from all of the patients.

Evaluation of efficacy

The primary endpoint of the study was to assess the response rate according to the World Health Organization (WHO) criteria. The secondary endpoints were the evaluation of progression-free survival and toxicity of chemotherapy at the dosages given.

On CT scans obtained after 4 weeks of treatment, the size of each HCC was measured as the product of the two longest perpendicular diameters of the largest tumor. A complete response (CR) was defined as a 100% reduction of the diameters. A partial response (PR) was defined as reduction of the product of the two diameters by more than 50%. In addition, an increase of more than 25% was defined as progressive disease (PD), and smaller changes between these two limits were defined as stable disease (SD). Survival was measured as the interval between the date of starting of treatment and death.

Statistical analysis

Survival was evaluated by the Kaplan–Meier method, and the significance of differences in survival was determined by the log-rank test. Wilcoxon's signed rank sum test was used to compare patient characteristics within the same group. A probability value of less than 0.05 was considered to indicate statistical significance.

Results

A total of 46 male and seven female patients aged from 32 to 83 years (mean ± SD, 66.1 ± 9 years) were enrolled in this study. There were 15 patients with HBV infection (B-LC group), 29 patients with HCV infection (C-LC group), and nine patients with alcoholic cirrhosis (A-LC group). The Child–Pugh class was A for six out of 15 patients in the B-LC group and B for nine patients, while the respective numbers were 14 and 15 patients in the C-LC group and four and five patients in the A-LC group. There were no patients with stage III disease, seven patients with stage IVA disease, and eight patients with stage IVB disease in the B-LC group, while the respective number were 4, 18, and 7 patients in the C-LC group, and two, five and two patients in the A-LC group. There was one patient with tumor thrombi involving major portal vein branches (Vp4) in the C-LC group and two patients in the A-LC group. Three patients from the C-LC group and one patient from the B-LC group had tumor thrombi involving the first portal

vein branches (Vp3). There was also one patient with tumor invasion into the vena cava inferior (vv4) in the C-LC group. One patient had tumor invasion of the right hepatic vein (vv2) in the C-LC group, as did two patients in the B-LC group and one patient in the A-LC group (Table 1).

Response stratified by the etiology of cirrhosis

None of the 15 patients in the B-LC group (0%), nine of the 29 patients (one dropout) in the C-LC group (31.0%), and four of the nine patients in the A-LC group (44.4%) achieved PR. In contrast, ten of the 15 patients in the B-LC group (66.7%) showed PD, as did eight of the 29 patients in the C-LC group (27.6%) and one of the nine patients in the A-LC group (11.1%). Five of the 15 patients in the B-LC group (33.3%) had SD, as did 11 of the 29 patients in the C-LC group (37.9%) and four of the nine patients in the A-LC group (44.4%) (Table 2).

Survival stratified by the etiology of cirrhosis

The 1-year survival rate of the B-LC group was 33.3%, while it was 44.8 and 55.6% in the C-LC group and the A-LC group, respectively. The 2-year survival rate of the B-LC group was 0%, while it was 3.4 and 33.3% in the C-LC group and the A-LC group, respectively (Table 3).

Table 1 Clinical characteristics of the 53 patients with advanced HCC and cirrhosis

Mean age	66.1 ± 9 years
Gender	Male 46, female 7
Etiology of cirrhosis	HBV, 15; HCV, 29; alcohol, 9
Child–Pugh classification	HBV A, 6; B, 9
	HCV A, 14; B, 15
	Alcohol A, 4; B, 5
Stage of tumor	HBV III, 0; IVA, 7; IVB, 8 (Vp4, 0; Vp3, 1; vv4, 0; vv2, 2)
	HCV III, 4; IVA, 18; IVB, 7 (Vp4, 1; Vp3, 3; vv4, 1; vv2, 1)
	Alcohol III, 2; IVA, 5; IVB, 2 (Vp4, 2; Vp3, 0; vv4, 0; vv2, 1)

Table 2 Objective responses of patients with liver cirrhosis related with the etiology

	CR	PR	SD	PD	Response rate (%)
HBV $n = 15$	0	0	5	10	0.0
HCV $n = 29$ (1 dropout)	0	9	11	8	31.0
Alcohol $n = 9$	0	4	4	1	44.4

Data show the number of patients

CR comlete response, *PR* partial response, *SD* stable disease, *PD* progressive disease

Table 3 Survival in relation to the etiology

Survival rate (%)	Etiology		
	HBV	HCV	Alcohol
1 year	33.3	44.8	55.6
2 years	0	3.4	33.3

The survival time of the A-LC and C-LC groups was significantly longer than that of the B-LC group, with the median survival time being 688, 368, and 211 days, respectively ($P < 0.05$ by Kaplan–Meier analysis with the log-rank test) (Fig. 1).

Changes of tumor markers in stratified by the etiology of cirrhosis

We examined the changes of serum tumor marker levels after treatment in each group. In the A-LC group, the vitamin K absence II (PIVKA-II) level was significantly lower after chemotherapy compared with before chemotherapy ($P < 0.05$, Wilcoxon test), while there was no significant difference of the AFP level or the L3-lectin binding AFP (AFP-L3) fraction level after treatment (Fig. 2). In the C-LC group and the B-LC group, there were no significant differences of serum tumor markers levels between before and after treatment (not shown).

Discussion

The present study showed that combined intra-arterial chemotherapy might be more effective for aHCC patients with A-LC or C-LC compared to patients with B-LC. The

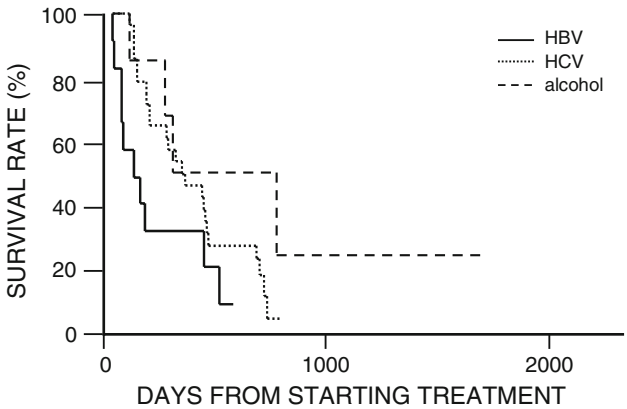

Fig. 1 Survival curves, plotted by the Kaplan–Meier method. The survival of patients who had a JIS score of 3 or 4 and alcoholic LC or LC due to HCV was significantly better than that of patients with the LC due to HBV, and the median survival time of each group was 688, 368 and 211 days, respectively ($P < 0.05$, by the Kaplan–Meier method and log-rank test)

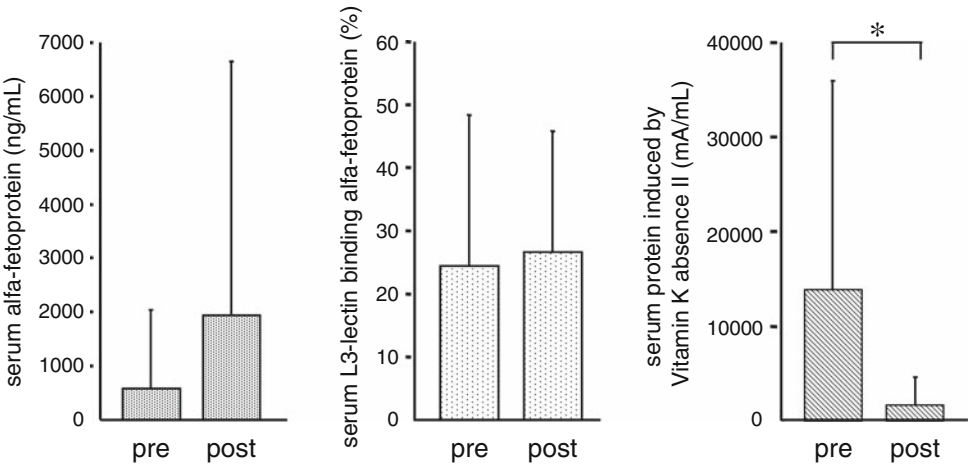

Fig. 2 Changes of serum tumor marker levels with treatment. The serum level of PIVKA-II was decreased after treatment in the alcoholic LC group ($P < 0.05$, Wilcoxon's signed rank sum test). There were no significant differences of tumor marker levels between before and after treatment in the LC patients with HBV or HCV infection

majority of patients who have aHCC do not survive for more than 6 months after diagnosis [17], and other reports have indicated an average survival period of 4 months from the onset of symptoms or 2 months from admission [18]. We previously reported that continuous intra-arterial infusion therapy over 24 h was more effective than 6-h infusion in patients with LC and aHCC due to HCV, although 24-h infusion was associated with stronger hematologic toxicity [8]. However, the response of aHCC to combined intra-arterial chemotherapy has not been assessed in relation to the etiology of LC. Therefore, we investigated the influence of the etiology of LC on the efficacy of combined intra-arterial chemotherapy for aHCC in patients who had a JIS score of 3 or 4. In the present study, none of the 15 patients in the B-LC group (0%), nine of the 29 patients in the C-LC group (31.0%), and four of the nine patients in the A-LC group (44.4%) achieved PR. The survival time of the A-LC and C-LC groups was significantly longer than that of the B-LC group, with the median survival time being 688, 368 and 211 days, respectively, so combined intra-arterial chemotherapy might be more effective for aHCC patients with A-LC or C-LC compared to patients with B-LC. However, we have experience of a few B-LC patients with aHCC who had a JIS score of 2 and achieved CR or PR. Therefore, further study is needed to assess the impact of intra-arterial chemotherapy in B-LC patients with aHCC.

Both 5-FU and CDDP have direct antitumor activity [19]. In addition, CDDP has a synergistic role as a modulator of 5-FU by inhibiting the transport of neutral amino acids (including L-methionine) into tumor cells, resulting in the enhancement of antitumor activity of 5-FU [20]. It has been reported that the gene expression profile of HCC differs between the tumors of patients with underlying HBV or HCV infection [21, 22]. Various proteins have been suggested to have a role in hepatitis B surface antigen-postive HCC or hepatitis C surface antigen-positive HCCs, and the different protein profiles indicate that the mechanism of hepatocarcinogenesis may differ between HBV and HCV infection [23]. Such differences may help to explain why intra-arterial chemotherapy was more effective for aHCC in the A-LC group or the C-LC group than in the B-LC group, along with differences in tumor sensitivity to chemotherapy. Moreover, we previously reported on the influence of host immunity in patients with aHCC, suggesting that Th1 (IFN-gamma + and IL4-T cells) dominance is lost due to an increase of Th2 (IFN-gamma- and IL4 + T cells) activity in HCC patients and that carcinogenesis might be more likely to occur in patients with chronic HCV infection and an increase of Th2 cells [24]. CD8 + tumor-infiltrating lymphocytes (TILs) play an important role in host defences against tumor progression. Some studies have indicated that there is a positive correlation between an increase of CD8 + TILs and the occurrence of tumor cell apoptosis [25, 26]. Ikeguchi et al. [27] reported that there was significant infiltration of CD8 + T cells into the fibrous tissue and sinusoidal capillaries of the non-cancerous liver, as well as around the tumor, although the average number of CD8 + T cells within the tumor was significantly lower than that in the non-cancerous liver tissue and the extent of CD8 + T cell infiltration into non-cancerous hepatic lobules was not correlated with the severity of liver fibrosis. CD4 + CD25 + regulatory T cells (Treg) have an important role in maintaining self-tolerance and regulating the immune response under both physiological and pathological conditions [28]. It has been reported that Treg are increased in the peripheral blood and/or tumor tissue of HCC patients and that this increase of Treg suppresses CD4 + helper T cell responses and appears to promote the progression of HCC [29–31]. We previously reported that the Th1/Th2 balance might be an useful indicator for the effect of combined intra-arterial chemotherapy in LC patients with aHCC. We also reported that the percentage of Th2 cells is significantly higher in PD patients with loss of Th1 dominance due to an increase or malfunction of Treg cells and that these changes may have induce a decrease of CD8 + TILs and a decrease of infiltrating

CD8 + T cells around the tumor [32]. Furthermore, we have found that the percentage of Th1 cells in the PR + SD group or the PD group showed no significant different from that in the control group (stage 1 disease according to the fibrosis score of Desment) before and after chemotherapy. However, the percentage of Th2 cells was significantly higher in the PD group both before and after chemotherapy compared with the control group, although there was no significant difference of Th2 cells between the PR + SD group and the control group either before or after chemotherapy [33]. Such differences may also help to explain why intra-arterial chemotherapy might be more effective for aHCC in the A-LC group and the C-LC group than in the B-LC group.

It was reported that a serum AFP levels 1,000 ng/ml was an independent unfavorable factor for survival after resection of HCC in patients with HCV infection [34]. The serum level of AFP-L3 was also reported to be an useful prognostic indicator in patients with HCC [35, 36], as was the level of PIVKA-II [1]. In the A-LC group, the serum level of PIVKA-II decreased after treatment, although other tumor markers did not respond to chemotherapy. Thus the serum level of PIVKA-II might be useful for assessing the response to chemotherapy in the ALC group, although it is not useful for predicting the response to combined intra-arterial chemotherapy.

In conclusion, aHCC patients with underlying A-LC and C-LC who had a JIS score of 3 or 4 may have better outcome using combined intra-arterial chemotherapy compared to aHCC patients with underling B-LC. Further study is needed to assess any influences of the etiology of LC on the response to combined intra-arterial chemotherapy.

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