World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/1007-9327office
wjg@wjgnet.com
doi:10.3748/wjg.v18.i16.1933

World J Gastroenterol 2012 April 28; 18(16): 1933-1939
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

BRIEF ARTICLE

Is hepatic arterial infusion chemotherapy effective treatment for advanced hepatocellular carcinoma resistant to transarterial chemoembolization?

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Supported by A Grant-in-Aid for research on the Third Term Comprehensive Control Research for Cancer from the Ministry on Health, Labour and Welfare, Japan, to Atsushi Nakajima; a grant from the National Institute of Biomedical Innovation (NBIO) to Atsushi Nakajima; a grant from the Ministry of Education, Culture, Sports, Science and Technology, Japan (KIBAN-B), to Atsushi Nakajima, (KIBAN-C), to Satoru Saito; the grant program, "Collaborative Development of Innovative Seeds," from the Japan Science and Technology Agency (JST)

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Received: September 13, 2011 Revised: November 24, 2011
Accepted: February 27, 2012
Published online: April 28, 2012

Abstract

AIM: To evaluate the effectiveness of hepatic arterial infusion chemotherapy (HAIC) for advanced hepatocellular carcinoma (HCC) resistant to transarterial chemoembolization (TACE).

METHODS: This study was conducted on 42 patients who received HAIC for advanced HCC between 2001 and 2010 at our hospital. 5-fluorouracil (5-FU) was administered continuously for 24 h from day 1 to day 5 every 2-4 wk *via* an injection reservoir. Intra-arterial cisplatin or subcutaneous interferon was administered in combination with the 5-FU. The patients enrolled in this retrospective study were divided into two groups according to whether or not they fulfilled the criteria for resistance to TACE proposed by the Japan Society of Hepatology in 2010 (written in Japanese); one group of patients who did not fulfill the criteria for TACE resistance (group A, n = 23), and another group who fulfilled the criteria for TACE resistance (group B, n = 19). We compared the outcomes in terms of the response and survival rates between the two groups.

RESULTS: Both the response rate and tumor suppression rate following HAIC were significantly superior in group A than in group B (response rate: 48% *vs* 16%, P = 0.028, tumor suppression rate: 87% *vs* 53%, P = 0.014). Furthermore, both the progression-free survival rate and survival time were significantly superior in group A than in group B (3-, 6-, 12-, and 24-mo = 83%, 70%, 29% and 20% *vs* 63%, 42%, 16% and 0%, respectively, P = 0.040, and 9.8 mo *vs* 6.2 mo, P = 0.040). A multivariate analysis (Cox proportional hazards regression model) showed that resistance to TACE was an independent predictor of poor survival (P = 0.007).

CONCLUSION: HAIC administrating 5-FU was not effective against advanced HCC resistant to TACE. Other tools for treatment, i.e., molecular-targeting agents may be considered for these cases.

Key words: Hepatocellular carcinoma; Hepatic arterial infusion chemotherapy; 5-fluorouracil; Transarterial chemoembolization

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Kirikoshi H, Yoneda M, Mawatari H, Fujita K, Imajo K, Kato S, Suzuki K, Kobayashi N, Kubota K, Maeda S, Nakajima A, Saito S. Is hepatic arterial infusion chemotherapy effective treatment for advanced hepatocellular carcinoma resistant to transarterial chemoembolization? *World J Gastroenterol* 2012; 18(16): 1933-1939 Available from: URL: http://www.wjgnet.com/1007-9327/full/v18/i16/1933.htm DOI: http://dx.doi.org/10.3748/wjg.v18.i16.1933

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common malignant diseases around the world, and the number of HCC-related deaths has been increasing worldwide[1-5]. HCC has a poor prognosis due to its rapidly-infiltrating growth characteristic and occurrence in a background of liver cirrhosis (LC). Surgical treatment is only indicated in a small proportion of patients, due to the frequently large tumor size, presence of multiple tumors, and poor hepatic function[6,7]. Regional interventional therapies have led to major breakthroughs in the management of HCC; transarterial chemoembolization (TACE) has been reported as an effective treatment modality for patients with advanced HCC, especially those with multiple nodules[8-15], therefore, it is often repeated several times for the treatment of recurrent HCC. Furthermore, advances in implantable drug delivery systems have made it possible to administer repeated arterial infusions of anticancer agents, and recent studies, including our previous reports, have shown the effectiveness of combined therapy with intra-arterial 5-fluorouracil (5-FU) plus cisplatin or subcutaneous interferon (IFN) therapy in patients with advanced HCC[16-24]. We previously reported a case of unresectable advanced HCC with portal vein tumor thrombosis (PVTT) who was treated successfully by combined intra-arterial 5-FU plus subcutaneous pegylated interferon-α2b (PEG-IFN-α2b) therapy[23], and also a retrospective cohort study of this combined hepatic arterial infusion chemotherapy (HAIC)[24]. However, the precise efficacy of HAIC in patients with advanced HCC resistant to TACE still remains unclear.

In the present cohort study, we evaluated the effectiveness and outcomes, in terms of the overall survival rate, median survival time and response to therapy, of HAIC in patients with unresectable advanced HCC with and without a resistance to TACE.

MATERIALS AND METHODS

Patients and eligibility

The subjects of this study were 42 patients with HCC in whom the diagnosis was made on the basis of the pathological or radiological findings between January 2001 and December 2010 at Yokohama City University Hospital, Kanagawa, Japan. Of the 42 patients, 5 had not received any treatment before enrollment in this study, 27 had been treated by TACE, 8 had undergone hepatic resection, and 2 had been treated by local ablation therapy before enrollment in this study. All the patients satisfied the following criteria: Child-Pugh class A or B, white blood cell > 2000/μL, neutrophil count > 1000/μL, Plt > 50 000/μL, total bilirubin < 3.0 mg/dL, serum creatinine < 1.5 mg/dL, unresectable or unsuitable for local ablation therapy, 4 or more lesions throughout the liver or presence of vessel invasion, Eastern Cooperative Oncology Group Performance Status, 0-2[25], absence of extra-hepatic metastases, and absence of past history of treatment with 5-FU. The PVTT grade and tumor stage were determined according to the criteria of the Liver Cancer Study Group of Japan[26]. All patients gave written informed consent for participation in this study, and the study was conducted with the approval of the Ethics Committee of Yokohama City University Graduate School of Medicine. The patients enrolled in this retrospective study were divided into two groups according to whether or not they fulfilled the criteria for resistance to TACE proposed by the Japan Society of Hepatology in 2010 (written in Japanese) (Table 1); one group of patients who did not fulfill the criteria (group A, $n = 23$), and another group of patients who fulfilled the criteria for TACE resistance (group B, $n = 19$). We compared the outcomes in terms of the response and survival rates between the two groups. A comparison of the patient characteristics between the two groups before the start of HAIC is shown in Table 2. The duration of treatment from the first detection of HCC to the time of the HAIC (i.e., to enrollment in this study) was significantly longer in group B than in group A (36.2 mo *vs* 16.3 mo, $P = 0.004$). The liver function parameters did not differ significantly between the two groups.

Table 1 Criteria for transarterial chemoembolization resistance

The evaluation was performed on the day of TACE and 1 mo after the TACE; the following were observed at least two times
Staining with the injected agent (lipiodol-anticancer agent emulsion) was considered insufficient with evaluation CT [the occupation rate was less than 50% of lesion(s)]
Appearance of multiple new recurrent lesions on the evaluation CT
Appearance of vessel invasion after TACE
Appearance of distal metastasis after TACE
Persistent elevation of tumor marker(s) regardless of TACE

TACE: Transarterial chemoembolization; CT: Computed tomography.

Arterial catheterization

The arterial catheter was inserted into the right or left femoral artery by the Seldinger method. A heparin-coated catheter (Clinical Supply, Gifu, Japan) was inserted into the femoral artery and its tip was advanced to the

Table 2 Comparison of the patient characteristics in the two groups prior to hepatic arterial infusion chemotherapy *n* (%)

	Group A	Group B	*P* value
Patients	23	19	
Age (yr)	66.6 ± 6.9	65.5 ± 7.3	NS ($P = 0.635$)
Gender			
Male/female	20 (87)/3 (13)	15 (79)/4 (21)	NS ($P = 0.488$)
Etiology of LC			
HCV	13 (57)	11 (58)	NS ($P = 0.070$)
HBV	2 (9)	6 (32)	
HCV + HBV	0 (0)	1 (5)	
Alcohol	4 (17)	0 (0)	
NonB-nonC	4 (17)	1 (5)	
Albumin (g/dL)	3.6 ± 0.6	3.5 ± 0.6	NS ($P = 0.503$)
Total bilirubin (mg/dL)	1.1 ± 0.7	1.3 ± 0.5	NS ($P = 0.397$)
PT (INR)	1.19 ± 0.13	1.17 ± 0.10	NS ($P = 0.607$)
AST (U/L)	64 ± 33	79 ± 51	NS ($P = 0.256$)
ALT (U/L)	47 ± 30	53 ± 38	NS ($P = 0.569$)
GGT (U/L)	155 ± 169	76 ± 76	NS ($P = 0.067$)
WBC (/μL)	4600 ± 1400	4400 ± 900	NS ($P = 0.431$)
Hb (g/dL)	13.1 ± 2.0	12.8 ± 1.0	NS ($P = 0.521$)
Plt ($\times 10^4$/μL)	14.3 ± 6.5	12.1 ± 5.8	NS ($P = 0.262$)
AFP (median, ng/mL)	7550	3116	NS ($P = 0.434$)
DCP (median, mAU/mL)	12314	3363	NS ($P = 0.159$)
Child-Pugh A/B	12 (52)/11 (48)	6 (32)/13 (68)	NS ($P = 0.219$)
Child-Pugh score	6.8 ± 1.7	7.1 ± 1.4	NS ($P = 0.582$)
Number of tumor (s) ≤ 5/6-10/> 10	5 (22)/7 (30)/11 (48)	5 (26)/8 (42)/6 (32)	NS ($P = 0.515$)
Size of the largest tumor (cm)	7.3 ± 5.2	3.8 ± 1.3	$P = 0.008$
Vessel invasion presence/absence	12 (52)/11 (48)	7 (37)/12 (63)	NS ($P = 0.320$)
Clinical stage Ⅰ/Ⅱ/Ⅲ/ⅣA	0 (0)/0 (0)/11 (48)/12 (52)	0 (0)/0 (0)/13 (68)/6 (32)	NS ($P = 0.180$)
Duration of treatment received prior to HAIC (mo)	16.3 ± 20.7	36.2 ± 21.5	$P = 0.004$
Previous number of TACE session (s)	0.9 ± 0.6	4.5 ± 1.8	$P < 0.0001$
HAIC regimens			
5-FU, cisplatin	8 (35)	7 (37)	NS ($P = 0.923$)
5-FU, natural IFN-α	4 (17)	4 (21)	
5-FU, PEG-IFN-α2b	11 (48)	8 (42)	

HCV: Hepatitis C virus; HBV: Hepatitis B virus; LC: Liver cirrhosis; PT: Prothrombin time; INR: International ratio; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GGT: γ glutamyl transferase; AFP: α-fetoprotein; WBC: White blood cell; DCP: Des-γ-carboxyprothrombin; HAIC: Hepatic arterial infusion chemotherapy; TACE: Transarterial chemoembolization; 5-FU: 5-fluorouracil; IFN: Interferon; PEG-IFN-α2b: Pegylated interferon-α2b.

common hepatic artery or proper hepatic artery. The other end of the catheter was connected to the injection reservoir, already implanted into a subcutaneous pocket created in the right or left lower quadrant of the abdomen. The gastroduodenal and right gastric arteries were occluded with coils to prevent potential gastroduodenal injury by the anticancer agents.

Treatment protocol

Patients received arterial infusions of the anticancer agents *via* the injection reservoir. Each chemotherapy cycle lasted 2-4 wk. 5-FU (300 mg/m^2 per day, Kyowa Hakko, Tokyo, Japan) was administered continuously for 24 h *via* the infusion pump on days 1 to 5 of each of the two weeks. PEG-IFN-α2b (PEG-INTRON, MSD KK, Tokyo, Japan) on Day 1 of every week or natural IFN-α (OIF, Otsuka Pharmaceuticals, Tokyo, Japan) on Days 1, 3, 5 of every week was administered by the subcutaneous route. The administered dose of PEG-IFN-α2b was adjusted by the weight of each patient (50 μg-100 μg), and the dose of natural IFN-α was fixed at 5.0 × 10^6 unit. In another HAIC regimen, cisplatin (10 mg/body per day, Nihon-Kayaku Pharmaceuticals, Tokyo, Japan) was combined with 5-FU (250 mg/body per day) administered continuously for 24 h *via* the infusion pump on days 1 to 5 of each of the four weeks. Each of the HAIC therapy regimens was repeated for a total of at least 2 cycles until the response changed to progressive disease (PD) or a severe adverse reaction appeared.

Evaluation

The duration of the progression-free survival was measured from the date of start of HAIC to the date on which the response was judged to have changed to PD. The response to the HAIC was evaluated by contrast-enhanced computed tomography (CT) after every 2 cycles of treatment. The response criteria of the Response Evaluation Criteria in Solid Tumors were used[27]. The duration of the response was measured from the date of start of treatment to the date of documented progression. Adverse reactions were assessed every week during therapy based on the United States National Cancer Institute Common Toxicity Criteria (NCI-CTC; version 3.0)[28].

Statistical analysis

The statistical analysis was performed using the StatView software, version 5.0 (SAS, Cary, NC). Group comparisons were performed by the chi-square test for independence or by Fisher's exact test for comparison of more than two independent groups. The overall survival rate of each group was evaluated by the Kaplan-Meier method and the logrank test from the start of HAIC until the patient's death, and the progression-free survival rate was evaluated until the effect of the HAIC changed to PD. *P* values of < 0.05 were considered to denote significance in all the statistical tests. The closing date of the study was May 31, 2011.

RESULTS

Response to the HAIC

In group A, 2 patients (8.7%) showed complete response (CR), 9 patients (39.1%) showed partial response (PR), 9 patients (39.1%) showed stable disease (SD), and the remaining 3 patients (13.1%) showed PD. On the other hand, in group B, none of the patients (0%) showed CR, 3 patients (15.8%) showed PR, 7 patients (36.8%) showed SD, and the remaining 9 patients (47.4%) showed PD.

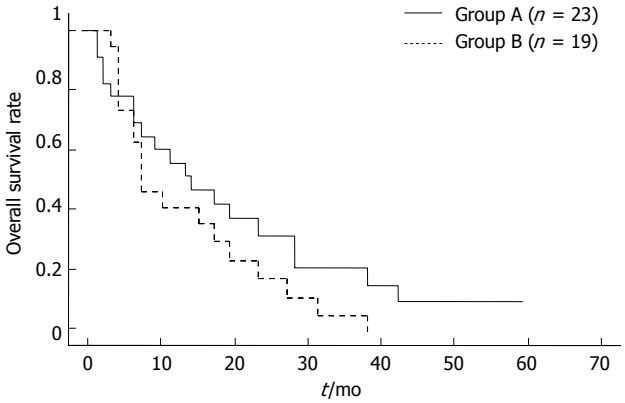

Figure 1 The overall survival rate tended to be superior in group A (a solid line) than in group B (a dotted line) (3-, 6-, 12-, 24-, and 36 mo = 82.6%, 78.3%, 56.5%, 32.8% and 21.9% *vs* 94.7%, 73.7%, 42.1%, 18.4%, and 6.1%, respectively, *P* = 0.203).

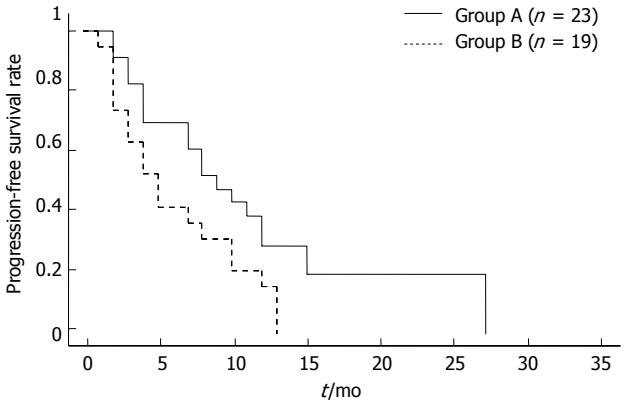

Figure 2 The progression-free survival rate was significantly superior in group A (a solid line) than in group B (a dotted line) (3-, 6-, 12-, and 24 mo = 82.6%, 69.6%, 29.3%, and 19.6% *vs* 63.2%, 42.1%, 15.8% and 0%, respectively, *P* = 0.040).

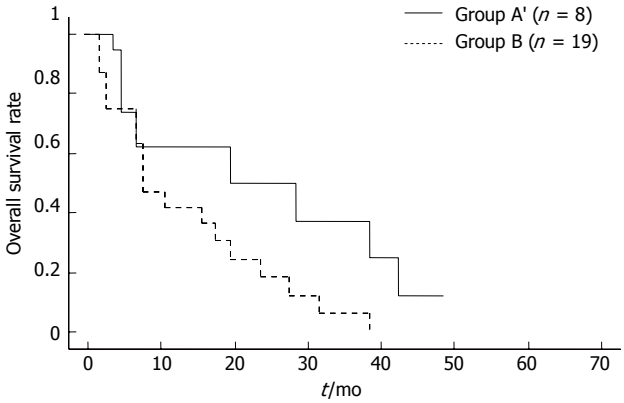

Figure 3 The overall survival rate and survival time tended to be superior in group A' (a solid line) than in group B (a dotted line) (3-, 6-, 12-, 24-, and 36 mo = 75.0%, 75.0%, 62.5%, 50.0% and 37.5% *vs* 94.7%, 73.7%, 42.1%, 18.4%, and 6.1%, respectively, *P* = 0.095).

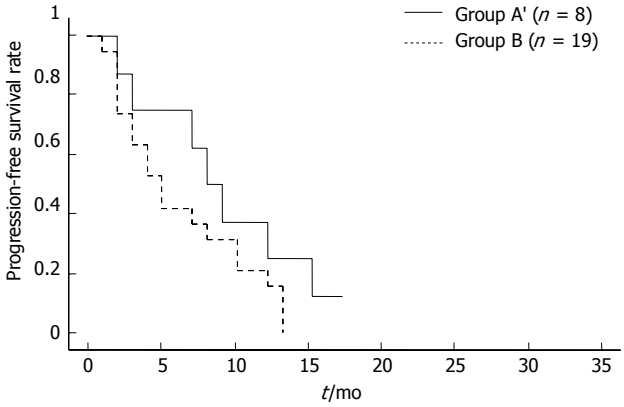

Figure 4 The progression-free survival rate and time tended to be superior in group A' (a solid line) than in group B (a dotted line) (3-, 6-, 12-, and 24 mo = 75.0%, 75.0%, 25.0%, and 0% *vs* 63.2%, 42.1%, 15.8% and 0%, respectively, *P* = 0.192).

Both the response rate [CR and PR patients/all patients × 100(%)] and the tumor suppression rate [CR, PR, and SD patients/all patients × 100(%)] following HAIC were significantly superior in group A than in group B (response rate: 47.8% *vs* 15.8%, $P = 0.028$, tumor suppression rate: 86.9% *vs* 52.6%, $P = 0.014$).

Survival

The overall survival rate and survival time tended to be superior in group A than in group B (3-, 6-, 12-, 24-, and 36 mo = 82.6%, 78.3%, 56.5%, 32.8% and 21.9% *vs* 94.7%, 73.7%, 42.1%, 18.4%, and 6.1%, respectively, $P = 0.203$ (Figure 1), and 18.8 mo *vs* 14.0 mo, $P = 0.267$). Furthermore, the progression-free survival rate and time were significantly superior in group A than in group B (3-, 6-, 12-, and 24 mo = 82.6%, 69.6%, 29.3%, and 19.6% *vs* 63.2%, 42.1%, 15.8% and 0%, respectively, $P = 0.040$ (Figure 2), and 9.8 mo *vs* 6.2 mo, $P = 0.040$).

Subgroup analysis

In group A, both the patients who received TACE once or twice ($n = 8$) and who did not receive TACE ($n = 15$) were included. Therefore, to evaluate the effectiveness of HAIC after TACE, we performed subgroup analysis compared the patients who received TACE in group A (group A', $n = 8$) to group B. In group A', 1 patient (12.5%) showed CR, 3 patients (37.5%) showed PR, 3 patients (37.5%) showed SD, and the remaining 1 patient (12.5%) showed PD. Both the response rate and the tumor suppression rate following HAIC tended to be superior in group A' than in group B (response rate: 50.0% *vs* 15.8%, $P = 0.064$, tumor suppression rate: 87.5% *vs* 52.6%, $P = 0.087$).

The overall survival rate and survival time tended to be superior in group A' than in group B (3-, 6-, 12-, 24-, and 36 mo = 75.0%, 75.0%, 62.5%, 50.0% and 37.5% *vs* 94.7%, 73.7%, 42.1%, 18.4%, and 6.1%, respectively, $P = 0.095$ (Figure 3), and 24.0 mo *vs* 14.0 mo, $P = 0.086$). Furthermore, the progression-free survival rate and time also tended to be superior in group A' than in group B (3-, 6-, 12-, and 24 mo = 75.0%, 75.0%, 25.0%, and 0% *vs* 63.2%, 42.1%, 15.8% and 0%, respectively, $P = 0.192$ (Figure 4), and 9.1 mo *vs* 6.2 mo, $P = 0.143$). These results of comparison between group A' and group B was similar to that between group A and group B.

Table 3 Multivariate analysis (Cox proportional hazards regression model) to identify factors influencing the survival

	Odds ratio	95% CI	*P* value
Age > 66 (yr)	0.284	0.077-1.044	NS (*P* = 0.058)
Gender: female	3.995	0.704-22.662	NS (*P* = 0.118)
Resistance to TACE	8.264	1.770-38.461	*P* = 0.007
AFP > 200 (ng/mL)	0.385	0.121-1.230	NS (*P* = 0.107)
DCP > 200 (mAU/mL)	1.181	0.218-6.390	NS (*P* = 0.847)
Albumin > 3.5 (g/dL)	0.012	0.001-0.181	*P* = 0.001
Total bilirubin > 1.0 (mg/dL)	4.000	1.004-15.933	*P* = 0.049
PT (INR) > 1.20	0.490	0.155-1.551	NS (*P* = 0.225)
ALT > 50 (U/L)	1.229	0.378-3.999	NS (*P* = 0.732)
Plt > 15.0 (× 10^4/μL)	1.251	0.330-4.736	NS (*P* = 0.742)
Number of tumors > 6	0.403	0.090-1.794	NS (*P* = 0.233)
Size of the largest tumor > 5.0 cm	0.913	0.215-3.884	NS (*P* = 0.902)
Clinical stage: ⅣA	13.800	1.638-116.257	*P* = 0.016
Response to HAIC: CR, PR	0.024	0.004-0.160	*P* = 0.0001
Child-Pugh: B	0.251	0.019-3.307	NS (*P* = 0.293)
Hepatic encephalopathy: presence	0.643	0.123-3.347	NS (*P* = 0.599)
Ascites: presence	3.471	0.835-14.419	NS (*P* = 0.087)

TACE: Transarterial chemoembolization; AFP: α-fetoprotein; DCP: Des-γ-carboxyprothrombin; PT: Prothrombin time; INR: International ratio; ALT: Alanine aminotransferase; HAIC: Hepatic arterial infusion chemotherapy; CR: Complete response; PR: Partial response; CI: Confidence interval.

Multivariate analysis to identify factors influencing the survival

A multivariate analysis (Cox proportional hazards regression model) was performed to identify factors that might influence the survival following HAIC, which identified resistance to TACE [odds ratio (OR): 8.264, *P* = 0.007], serum albumin > 3.5 g/dL (OR: 0.012, *P* = 0.001), serum total bilirubin > 1.0 mg/dL (OR: 4.000, *P* = 0.049), clinical stage ⅣA (OR: 13.800, *P* = 0.016), and CR, PR to HAIC (OR: 0.024, *P* = 0.0001) as significant independent predictors influencing of the survival (Table 3).

Adverse reactions

The common systemic adverse reactions were fever, loss of appetite and general fatigue, however, none exceeded Grade 1 to 2 in severity. Furthermore, no case of serious leukopenia or thrombocytopenia was observed, with the severity of these adverse reactions not exceeding Grade 1 to 2 in any of the cases; none of the patients required administration of granulocyte-colony-stimulating factor or blood transfusion. On the other hand, among the 42 patients, there were 3 patients who developed Grade 2 generalized skin rash, 3 patients who developed obstruction of hepatic artery, and 2 patients who developed infection of reservoir. There were no cases of adverse event-related death.

DISCUSSION

According to the treatment algorithm for hepatocellular carcinoma in the Clinical Practice Guidelines for Hepatocellular Carcinoma in Japan[15], TACE and HAIC are recommended when the number of HCCs is four or more, with preserved liver function. In a large prospective cohort study of 8510 patients with a long follow-up period of 8 years, Takayasu *et al*[14] reported that TACE using an anticancer agent-lipiodol emulsion with or without gelatin sponge particles improved the survival of patients with advanced HCC, with overall 1-, 3-, 5-, and 7-year survival rates of 82%, 47%, 26%, and 16%, respectively, and a median survival duration of 34 mo. We also reported the superior effectiveness of TACE using a cisplatin- or epirubicin-lipiodol emulsion as compared with that of palliative treatment in a recent study of patients with advanced HCC[13]; both the overall survival rate and median survival time in patients who received TACE were significantly superior to those in patients who received only palliative treatment (1-, 2-, 5-, and 8-year survival rates of 98%, 90%, 56% and 16% *vs* 47%, 39%, 23% and 0%, respectively; median survival duration, 25 mo *vs* 10 mo). However, repeat sessions of TACE were often required which can potentially result in deterioration of the liver function[29]. Another group reported that selective TACE using conventional doses of anticancer drugs can cause persistent, serious worsening of the liver function[30].

Several recent studies have reported the effectiveness and survival benefit of combined therapy with intra-arterial 5-FU plus cisplatin or systemic various IFN in patients with unresectable advanced HCC[16-24]. Ando *et al*[21] investigated the outcomes of HAIC using a combination 5-FU plus cisplatin for HCC patients with complicating PVTT (*n* = 48), and reported a response rate of 48%, median survival time of 31.6 mo, and 1-, 2-, 3- and 5-year survival rates of 45%, 31%, 25% and 11%, respectively. Obi *et al*[18] reported an objective response rate of 52.6% (61/116 patients) in 116 patients with advanced HCC and Vp 3 or 4 treated with a combination of 5-FU plus natural IFN-α. A recent study conducted by us demonstrated the effectiveness of combined therapy with 5-FU plus subcutaneous PEG-IFN-α2b for unresectable advanced HCC (*n* = 18); the response rate was 33.3%, the median survival time was 17.7 mo, and the 6-, 12-, 24- and 36-mo survival rates were 89%, 71%, 39% and 29%, respectively[24]. However, few reports have investigated the effectiveness of HAIC in patients with advanced HCC resistant to TACE. This study revealed that HAIC yielded an unsatisfactory survival rate and survival time in patients with HCC resistant to TACE, and a multivariate analysis identified resistance to TACE as one of the independent predictors of poor survival in these patients.

Recently, a multikinase inhibitor, sorafenib, was approved as the first molecular targeted agent for advanced HCC, and two global phase Ⅲ trials[31,32] showed survival benefit with this drug administered orally for advanced HCC patients with preserved liver function. The SHARP Study was a randomized double-blind placebo-controlled multicenter study conducted in western countries, which showed that both the overall survival and the time to progression were significantly superior in the sorafenib group (*n* = 299) than in the placebo group (*n* = 303) (10.7 mo *vs* 7.9 mo, and 5.5 mo *vs* 2.8 mo, respectively). Interestingly, 86 patients (29% of sorafenib group) and 90 patients (30%

of placebo group) who had previously received TACE were included in the SHARP Study. Galle *et al*[33] reported that among 176 patients after TACE, the overall survival and the time to progression were superior in the sorafenib group (n = 86) than in the placebo group (n = 90) (11.9 mo *vs* 9.9 mo, and 5.8 mo *vs* 4.0 mo, respectively) in subanalysis of the SHARP Study. These results suggest that sorafenib may be an effective treatment agent for patients with advanced HCC resistant to TACE. Furthermore, the Asia-Pacific Study, performed in eastern Asian countries, also showed, similar to the SHARP study, significant survival prolongation in the sorafenib group as compared with that in the placebo group. Therefore, in Japan, sorafenib has recently been recommended for the treatment of patients with advanced HCC and extra-hepatic metastasis or major vessel invasion with preserved liver function, e.g., Child-Pugh class A[34,35].

In conclusion, although the evaluation needs to be conducted in a larger number of patients and the study was a retrospective cohort study, the results of this study revealed that HAIC administered with 5-FU exerted insufficient effect against advanced HCC resistant to TACE. Molecular-targeting agents may need to be considered in the future for patients with HCC resistant to TACE.

COMMENTS

Background

Hepatocellular carcinoma (HCC) is one of the most common malignant diseases around the world, and interventional therapies such as transarterial chemoembolization (TACE) or hepatic arterial infusion chemotherapy (HAIC) has been performed for patients with advanced HCC, especially those with multiple nodules, therefore, it is often repeated several times for the treatment of recurrent HCC. However, the precise efficacy of HAIC in patients with advanced HCC resistant to TACE still remains unclear.

Research frontiers

Advances in implantable drug delivery systems have made it possible to administer repeated arterial infusions of anticancer agents, and recent studies, including our previous reports, have shown the effectiveness of combined therapy with intra-arterial 5-fluorouracil (5-FU) plus cisplatin or subcutaneous interferon (IFN) therapy in patients with advanced HCC which have multiple intra-hepatic lesions or portal vein tumor thrombosis.

Innovations and breakthroughs

The study was considered the first report which investigated the effectiveness of HAIC administrating 5-FU for advanced HCC resistant to TACE. The patients enrolled in their study were divided into two groups according to whether or not they fulfilled the criteria for resistance to TACE proposed by the Japan Society of Hepatology in 2010 (written in Japanese) (Table 1); one group of patients who did not fulfill the criteria for TACE resistance (group A, n = 23), and another group who fulfilled the criteria for TACE resistance (group B, n = 19). They compared the outcomes in terms of the response and survival rates between the two groups. Both the response rate and tumor suppression rate following HAIC were significantly superior in group A than in group B. Furthermore, both the progression-free survival rate and survival time were significantly superior in group A than in group B. A multivariate analysis (Cox proportional hazards regression model) showed that resistance to TACE was an independent predictor of poor survival.

Applications

The results of this study revealed that HAIC administered with 5-FU exerted insufficient effect against advanced HCC resistant to TACE.

Terminology

HAIC administrating 5-FU was not effective against advanced HCC resistant to TACE, and our study showed the limitation of interventional therapies to prolong the survival for advanced HCC and consideration of new strategy including other tools for treatment, i.e., molecular-targeting agents.

Peer review

In this study, the authors report that patients with HCC resistant to TACE exhibit a poorer response to HAIC. This paper is clearly written and the topic material is important.

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S- Editor Cheng JX **L- Editor** A **E- Editor** Zhang DN