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

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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.

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Key words: Hepatocellular carcinoma; Hepatic arterial infusion chemotherapy; 5-fluorouracil; Transarterial chemoembolization
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. 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. 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, 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 ofanticancer 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. 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, and also a retrospective cohort study of this combined hepatic arterial infusion chemotherapy (HAIC). 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, 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. 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.

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...
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 divided, and the remaining 9 patients (47.4%) showed PD.

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.

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(67)/3(13)| 15(79)/4(21)| NS (P = 0.488) |
| Etiology of LC   | HCV         | 13 (87)     | NS (P = 0.320) |
|                  | HBV         | 2 (9)       | NS (P = 0.515) |
|                  | HCV + HBV   | 0 (0)       | NS (P = 0.515) |
|                  | Alcohol     | 4 (17)      | NS (P = 0.515) |
|                  | NonB-nonC   | 4 (17)      | NS (P = 0.515) |
| Albumin (g/dL)   | 3.6 ± 0.6   | 3.5 ± 0.6   | NS (P = 0.503) |
| Total bilirubin (mg/dL) | 11 ± 0.7 | NS (P = 0.397) |
| PT (INR)         | 1.19 ± 0.13 | 1.17 ± 0.10 | NS (P = 0.607) |
| AST (U/L)        | 64 ± 33     | 79.5 ± 5.1  | 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 (× 10^4/μL)  | 14.3 ± 6.5  | 12.1 ± 5.8  | NS (P = 0.262) |
| AFP (median, ng/mL) | 7550 | NS (P = 0.434) |
| DCP (median, mAU/mL) | 12314 | 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) | ≤ 5/6/7/10 > 10 | 5 (22)/7 (30) | 5 (26)/8 (42) | 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 1/II/III/IV | 0 (0)/0 (0)/0 (0) | 0 (0)/0 (0)/0 (0) | NS (P = 0.180) |
| Duration of treatment received prior to HAIC (mo) | 16.3 ± 20.7 | 16.2 ± 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-α, Pegylated interferon-α2b | 11 (48) | 8 (42) |

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

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 [2]. 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) [20].

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.

via the injection reservoir. Each chemotherapy cycle lasted 2-4 wk. 5-FU (300 mg/m² 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 [2]. 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) [20].

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Kirikoshi H et al. HAIC for HCC resistant to TACE

Both the response rate [CR and PR patients/all patients \( \times 100\% \)] and the tumor suppression rate [CR, PR, and SD patients/all patients \( \times 100\% \)] 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, \( P = 0.203 \)).

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, \( P = 0.040 \)).

**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\%, 15.8\% and 0\%, respectively, \( P = 0.095 \)).

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, \( P = 0.192 \)).

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

| Factors                              | 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 (×10^3/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 IV/A                  | 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     | 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 IV/A (OR: 13.800, P = 0.016), and CR, PR to HAIC (OR: 0.024, P = 0.0001) as significant independent predictors influencing 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 [10], 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 [18] 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%, respectively, P < 0.001). However, repeat sessions of TACE were often required which can potentially result in deterioration of the liver function [28]. 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 [24,25]. Ando et al [25] 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-q2b 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 [29]. 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[39] 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 sub-analysis 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[30,31].

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 administering 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, 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.

REFERENCES
1 El-Serag HB, Mason AC. Rising incidence of hepatocellular carcinoma in the United States. N Engl J Med 1999; 340: 745-750
2 Taylor-Robinson SD, Foster GR, Arora S, Hargreaves S, Thomas HC. Increase in primary liver cancer in the UK, 1979-94. Lancet 1997; 350: 1142-1143
3 El-Serag HB, Rudolph KL. Hepatocellular carcinoma: epidemiology and molecular carcinogenesis. Gastroenterology 2007; 132: 2557-2576
4 Blum HE. Hepatocellular carcinoma: therapy and prevention. World J Gastroenterol 2005; 11: 7391-7400
5 Okuda K, Fujimoto I, Hanai A, Urano Y. Changing incidence of hepatocellular carcinoma in Japan. Cancer Res 1987; 47: 4967-4972
6 Bruix J. Treatment of hepatocellular carcinoma. Hepatology 1997; 25: 259-262
7 Mor E, Tur-Kaspa R, Sheiner P, Schwartz M. Treatment of hepatocellular carcinoma associated with cirrhosis in the era of liver transplantation. Ann Intern Med 1998; 129: 643-653
8 Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. Lancet 2003; 362: 1907-1917
9 Bruix J, Sala M, Llovet JM. Chemoembolization for hepatocellular carcinoma. Gastroenterology 2004; 127: S179-S188
10 Llovet JM, Bastuñante J, Castells A, Vilara R, Ayuso Mdel C, Sala M, Bro C, Rodés J, Bruix J. Natural history of untreated nonsurgical hepatocellular carcinoma: rationale for the design and evaluation of therapeutic trials. Hepatology 1999; 29: 62-67
11 Omata M, Tateishi R, Yoshida H, Shiina S. Treatment of hepatocellular carcinoma by percutaneous tumor ablation methods: Ethanol injection therapy and radiofrequency ablation. Gastroenterology 2004; 127: S159-S166
12 Lencioni RA, Allgaier HP, Cioni D, Olschewski M, Deibert P, Crocetti L, Frings H, Laubenberger J, Zubcr I, Blum HE, Bartolozzi C. Small hepatocellular carcinoma in cirrhosis: randomized comparison of radio-frequency thermal ablation versus percutaneous ethanol injection. Radiology 2003; 228: 235-240
13 Kirikoshi H, Saito S, Yoneda M, Fujita K, Kawatari H, Uchiyama T, Higurashi T, Goto A, Takahashi H, Abe Y, Inamori M, Kobayashi N, Kubota K, Sakaguchi T, Ueno N, Nakajima A. Outcome of transarterial chemoembolization monotherapy, and in combination with percutaneous ethanol injection, or radiofrequency ablation therapy for hepatocellular carcinoma. Hepatol Res 2009; 39: 553-562
14 Takayasu K, Arii S, Ikai I, Omata M, Okita K, Ichida T, Matsuyama Y, Nakanuma Y, Kojiro M, Makuchii M, Yamaoka Y. Prospective cohort study of transarterial chemoembolization for unresectable hepatocellular carcinoma in 8510 patients. Gastroenterology 2006; 131: 461-469
15 Clinical Practice Guidelines for Hepatocellular Carcinoma - The Japan Society of Hepatology 2009 update. Hepatol Res 2010; 40 Suppl 1: 1-144
16 Sakon M, Nagano H, Dono K, Nakamori S, Umeshita K, Yamada A, Kawata S, Imay L, Iijima S, Monden M. Combined intraarterial 5-fluorouracil and subcutaneous interferon-alpha therapy for advanced hepatocellular carcinoma with tumor thrombi in the major portal branches. Cancer 2002; 94: 435-442
Kirikoshi H et al. HAIC for HCC resistant to TACE

17 Ota H, Nagano H, Sakon M, Eguchi H, Kondo M, Yamamoto T, Nakamura M, Dadmindersen B, Wada H, Marubashi S, Miyamoto A, Dono K, Umemita K, Nakamori S, Wakahara K, Monden M. Treatment of hepatocellular carcinoma with major portal vein thrombosis by combined therapy with subcutaneous interferon-alpha and intra-arterial 5-fluorouracil; role of type 1 interferon receptor expression. Br J Cancer 2005; 93: 557-564

18 Obi S, Yoshida H, Toune R, Unuma T, Kanda M, Sato S, Tateishi R, Teratani T, Shiina S, Omata M. Combination therapy of intraarterial 5-fluorouracil and systemic interferon-alpha for advanced hepatocellular carcinoma with portal venous invasion. Cancer 2006; 106: 1990-1997

19 Nagano H, Miyamoto A, Wada H, Ota H, Marubashi S, Takeda Y, Dono K, Umemita K, Sakon M, Monden M. Interferon-alpha and 5-fluorouracil combination therapy after palliative hepatic resection in patients with advanced hepatocellular carcinoma, portal venous tumor thrombus in the major trunk, and multiple nodules. Cancer 2007; 110: 2493-2501

20 Nagano H, Sakon M, Eguchi H, Kondo M, Yamamoto T, Ota H, Nakamura M, Wada H, Dändinsuren B, Marubashi S, Miyamoto A, Takeda Y, Dono K, Umemita K, Nakamori S, Monden M. Hepatic resection followed by IFN-alpha and 5-FU for advanced hepatocellular carcinoma with tumor thrombus in the major portal branch. Hepatogastroenterology 2007; 54: 172-179

21 Ando E, Tanaka M, Yamashita F, Kuromatsu Y, Yutani S, Fukumori K, Sumie S, Yano Y, Okuda K, Sata M. Hepatic arterial infusion chemotherapy for advanced hepatocellular carcinoma with portal vein tumor thrombosis: analysis of 48 cases. Cancer 2002; 95: 588-595

22 Kasai K, Kuodera H, Ushio A, Sawata K, Takikawa Y, Suzuki K. Evaluation of newly developed combination therapy of intra-arterial 5-fluorouracil and systemic pegylated interferon alpha-2b for advanced hepatocellular carcinoma with portal venous invasion: preliminary results. Hepatol Res 2009; 39: 117-125

23 Mawatari H, Kirikoshi H, Yoneda M, Higurashi T, Fujita K, Saito S, Inamori M, Takahashi H, Abe Y, Kubota K, Nakajima A. Effective treatment for advanced hepatocellular carcinoma with portal venous invasion using a combination therapy of intra-arterial 5-fluorouracil and subcutaneous pegylated interferon-alpha-2b. Hepatogastroenterology 2008; 55: 1776-1777

24 Kirikoshi H, Saito S, Mawatari H, Yoneda M, Fujita K, Nosaka Y, Suzuki K, Takahashi H, Abe Y, Inamori M, Kobayashi N, Kubota K, Ueno N, Nakajima A. Combined 5-fluorouracil and pegylated interferon α-2b therapy for advanced hepatocellular carcinoma. Hepato gastroenterol 2010; In press

25 Oken MM, Creech RH, Torrence DC, Horton J, Davis TE, McFadden ET, Carbone P. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5: 649-655

26 Liver Cancer Study Group of Japan. General rules for the clinical and pathological study of primary liver cancer. 2nd ed. Tokyo: Kanehara, 2003

27 Therasse P, Arbucks SG, Eischenauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbemeke M, van Oosterom AT, Christian MC, Gwyther SG. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000; 92: 209-216

28 National Cancer Institute-Common Toxicity Criteria. Available from: URL: http://ctep.cancer.gov/reporting/cancer.gov/reporting/ctc.html

29 Ahrrar K, Gupta S. Hepatic artery embolization for hepatocellular carcinoma: technique, patient selection, and outcomes. Surg Oncol Clin N Am 2003; 12: 105-126

30 Lu W, Li YH, Yu ZJ, He XF, Chen Y, Zhao JB, Zhu ZY. A comparative study of damage to liver function after TACE with use of low-dose versus conventional-dose of anticancer drugs in hepatocellular carcinoma. Hepatogastroenterology 2007; 54: 1499-1502

31 Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, de Oliveira AC, Santoro A, Raoul JL, Forner A, Schwartz M, Porta C, Zeeuzem S, Bolondi L, Greten TF, Galle PR, Seitz JF, Borbath I, Haussinger D, Giannaris T, Shang M, Moscovici M, Voliotis D, Bruix J. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008; 359: 379-390

32 Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, Luo R, Feng J, Ye S, Yang TS, Xu J, Sun Y, Liang H, Liu J, Wang J, Tak FY, Han P, Burock K, Zhou J, Voloti M, Guan Z. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol 2009; 10: 25-34

33 Galle P, Blanc J, Van Laethem J-L, Marrero J, Beaunagoud M, Moscovici M, Shan M, Nadel A, Voloti M, Bruix J, Llovet JM. Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma and prior anti-tumor therapy: a subanalysis from the SHARP trial. J Hepatol 2008; 48: 537-542

34 Kudo M. Hepatocellular carcinoma 2009 and beyond: from the surveillance to molecular targeted therapy. Oncology 2008; 75 Suppl 1: 1-12

35 Kudo M, Ushikiya K. Positioning of a molecular-targeted agent, sorafenib, in the treatment algorithm for hepatocellular carcinoma and implication of many complete remission cases in Japan. Oncology 2010; 78 Suppl 1: 154-166

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April 28, 2012 | Volume 18 | Issue 16 |