SHORT COMMUNICATION

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Effect of hepatic arterial infusion chemotherapy of 5-fluorouracil and cisplatin for advanced hepatocellular carcinoma in the Nationwide Survey of Primary Liver Cancer in Japan

K Nouso*[,1], K Miyahara[2], D Uchida[2], K Kuwaki[2], N Izumi[3,14], M Omata[4], T Ichida[5,14], M Kudo[6,14], Y Ku[7,14], N Kokudo[8,14], M Sakamoto[9,14], O Nakashima[10,14], T Takayama[11,14], O Matsui[12,14], Y Matsuyama[13,14], K Yamamoto[2] and the Liver Cancer Study Group of Japan

*[1]Department of Molecular Hepatology, Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, 2-5-1 Shikata-cho, Kita-ku, Okayama-city, Okayama, 700-8558, Japan; [2]Department of Gastroenterology and Hepatology, Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, 2-5-1 Shikata-cho, Kita-ku, Okayama-city, Okayama, 700-8558, Japan; [3]Department of Gastroenterology, Musashino Red Cross Hospital, Musashino-city, Tokyo, 180-8610, Japan; [4]Yamanashi Prefectural Hospital Organization, Kofu-city, Yamanashi, 400-8506, Japan; [5]Department of Gastroenterology, Juntendo University Shizuoka Hospital, Izunokuni-city, Shizuoka, 410-2295, Japan; [6]Department of Gastroenterology and Hepatology, Kinki University School of Medicine, Sayama-city, Osaka, 589-8511, Japan; [7]Division of Hepato-Biliary-Pancreatic Surgery, Kobe University Graduate School of Medicine, Kobe-city, Hyogo, 650-0017, Japan; [8]Department of Hepato-Biliary-Pancreatic Surgery Division, Department of Surgery, Graduate School of Medicine, University of Tokyo, Bunkyo-ku, Tokyo, 113-0033, Japan; [9]Department of Pathology, Keio University School of Medicine, Shinjuku-ku, Tokyo, 160-8582, Japan; [10]Department of Pathology, Kurume University School of Medicine, Kurume-city, Fukuoka, 830-0011, Japan; [11]Department of Digestive Surgery, Nihon University School of Medicine, Itabashi-ku, Tokyo, 173-8610, Japan; [12]Department of Radiology, Kanazawa University Graduate School of Medical Science, Kanazawa-city, Ishikawa, 920-8641, Japan and [13]Department of Biostatistics, School of Public Health, University of Tokyo, Bunkyo-ku, Tokyo, 113-0033, Japan

Background: The efficacy of hepatic arterial infusion chemotherapy for the treatment of advanced hepatocellular carcinoma (HCC) remains unclear.

Methods: The outcome of 476 patients with HCC who underwent hepatic arterial infusion chemotherapy with 5-fluorouracil and cisplatin (HAIC) were compared with 1466 patients who did not receive active therapy.

Results: A survival benefit of the therapy after adjusting for known risk factors was observed (hazard ratio, 0.48; 95% CI, 0.41–0.56; $P<0.0001$). In propensity score-matched analysis ($n=682$), median survival time was longer for patients who underwent chemotherapy (14.0 months) than for patients who did not receive active treatment (5.2 months, $P<0.0001$).

Conclusion: For advanced HCC, HAIC is considered to be an effective treatment.

*Correspondence: Dr K Nouso; E-mail: nouso@cc.okayama-u.ac.jp
[14]These authors are part of the Liver Cancer Study Group of Japan.

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Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide (Jemal *et al*, 2011). Screening patients with chronic liver diseases increases the chance that HCC can be diagnosed in the early stage (Kudo *et al*, 2011; European Association for Study of Liver; European Organisation for Research and Treatment of Cancer, 2012; Sherman *et al*, 2012). However, many HCCs are detected at an advanced stage.

According to the treatment algorithm of HCC, patients with advanced disease are candidates for chemotherapy (Kudo *et al*, 2011; European Organisation for Research and Treatment of Cancer, 2012; Sherman *et al*, 2012). Currently, sorafenib is the only chemotherapy proven to be effective for advanced HCC (Llovet *et al*, 2008; Cheng *et al*, 2009). Several other therapies have been evaluated, including hepatic arterial infusion of 5-fluorouracil (5-FU) and cisplatin, which was the most common regimen in Japan (Ueshima *et al*, 2010; Kim do *et al*, 2011; Yamashita *et al*, 2011). However, most of these studies were retrospective and nonrandomised; therefore, its efficacy remains unclear.

The Liver Cancer Study Group of Japan uses questionnaires to collect data from patients with HCC every 2 years, with several minor modifications of the contents since 1965 (Ikai *et al*, 2005, 2007). We used the three most recent sets of data to determine the efficacy of arterial infusion therapy with 5-FU and cisplatin for advanced HCC.

MATERIALS AND METHODS

Data sources. From January 2000 to December 2005, a total of 62 315 patients with primary liver cancer were newly registered by the Liver Cancer Study Group of Japan (Ikai *et al*, 2005, 2007). The cohort was followed up biannually and their clinical outcome was examined. Of these 62 315 patients, 57 445 (92.2%) received a diagnosis of HCC, and 31 743 patients with complete data were selected for this study. Among the patients, 1150 patients initially underwent chemotherapy and 1466 patients received no active therapy (no therapy group). In patients who underwent chemotherapy, 476 (41.4%) underwent arterial infusion chemotherapy with 5-FU and cisplatin using a subcutaneous infusion port (HAIC group). All patients in the HAIC group and in the no therapy group were enrolled in this study (Supplementary Figure 1).

Hepatocellular carcinoma was diagnosed primarily by imaging modalities such as computed tomography (1579, 81.3%), magnetic resonance imaging (257, 13.2%), ultrasonography (1167, 60.1%), and/or angiography (360, 18.5%) with the findings of hyperattenuation at the arterial phase and hypoattenuation at the portal phase and/or tumour staining. A histological diagnosis was made in 4.5% ($n=87$) of the patients. Treatment effect was evaluated by a criteria, 'Treatment effect of the target nodule', outlined by the Liver Cancer Study Group of Japan (Liver Cancer Study Group of Japan, 2003).

All data were provided anonymously. This study was approved by the review board of the Liver Cancer Study Group of Japan.

Statistical analysis. Continuous variables were compared by *t*-test, and categorical variables were compared by χ^2 test. Survival was estimated by the Kaplan–Meier method and compared by the log-rank test.

Univariate and multivariate analyses of the primary cohort ($n=1942$) were carried out using the Cox proportional hazard model. Adjusted hazard ratios for HAIC according to subgroups (prognostic tumour factors in multivariate analysis) were also analysed and presented as a forest plot.

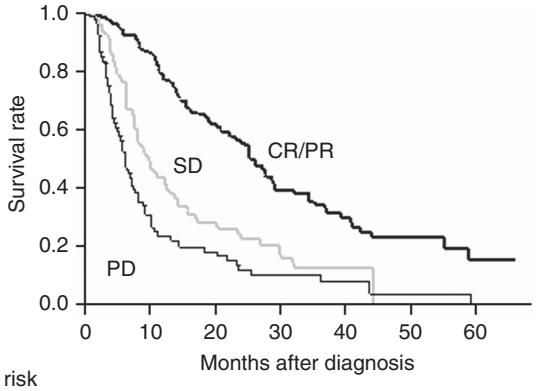
To determine the efficacy of HAIC, propensity score-matching analysis was performed (HAIC, $n=476$; no therapy, $n=1466$). A propensity score for use of HAIC was estimated using a logistic regression model fit with 15 variables: sex, age, hepatitis B surface antigen (HBsAg) positivity, hepatitis C virus (HCV) antibody positivity, alcohol intake, presence of encephalopathy, presence of ascites, total bilirubin, albumin, prothrombin time, maximum tumour size, tumour number, portal vein invasion, extrahepatic metastasis, and α-fetoprotein level. To create a propensity-matched cohort of patients who underwent HAIC or no therapy (1 : 1 match), a nearest-neighbour-matching algorithm with a 'greedy' heuristic was used (Austin and Mamdani, 2006).

The same matching procedure was carried out in patients with Child–Pugh A/B disease and portal vein invasion or more than three tumours, and survival rates for each matched cohort were compared.

RESULTS

Patient characteristics. The HAIC group was significantly younger and had more males than the no therapy group (Supplementary Table 1). Patients in the HAIC group had better liver function but more cases of hepatitis B infection and more advanced tumours than the no therapy group. These differences except follow-up period disappeared after propensity score matching.

Treatment effect of HAIC. In the HAIC group, the response rates were as follows: complete response (CR, $n=19$, 4.0%), partial response (PR, $n=173$, 36.5%), stable disease (SD, $n=112$, 23.6%), progressive disease (PD, $n=129$, 27.2%), and undefined ($n=41$, 8.7%). The 1- and 3-year survival rates according to response were CR/PR (77.7% and 34.6%), SD (44.2% and 13.3%), and PD (23.7% and 10.3%), respectively ($P<0.0001$, Figure 1). All factors including HAIC treatment correlated with prognosis in the univariate analysis (Table 1). Multivariate analysis revealed that HBsAg, more than three tumours, large tumours (>3 cm), distant metastasis, portal vein invasion (VP3 and VP4), and high α-fetoprotein levels (>400 ng ml^{-1}) were associated with poor survival. The VP3 and VP4 indicated tumour invasion to the first-order branches of the portal vein and the invasion to the main trunk of the portal vein, respectively (Liver Cancer Study Group of Japan, 2003). Conversely, Child–Pugh A/B disease (hazard ratio,



Patients at risk

CR/PR	192	136	72	37	20	9	5
SD	112	34	16	9	2	0	0
PD	129	29	12	6	4	2	0

Figure 1. Survival of patients who underwent hepatic arterial infusion of 5-fluorouracil and cisplatin using a subcutaneous infusion port. The 1- and 3-year survival rates and median survival times according to response were as follows: CR/PR (77.7%, 34.6%, 25.8 months), SD (44.2%, 13.3%, 9.5 months), and PD (23.7%, 10.3%, 6.0 months) ($P<0.0001$). Abbreviations: CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease.

Table 1. Risk factors for survival

	Univariate			Multivariate		
Characteristics	**HR**	**95% CI**	***P*-value**	**HR**	**95% CI**	***P*-value**
Age >70 years	0.87	0.77–0.98	0.025	1.02	0.89–1.16	0.708
Male sex	1.19	1.04–1.37	0.007	1.04	0.90–1.21	0.541
HBsAg positive	1.47	1.27–1.69	<0.001	1.20	1.01–1.44	0.037
HCV Ab positive	0.78	0.69–0.88	<0.001	0.93	0.81–1.08	0.379
Alcohol intake >90 g day^{-1}	1.18	1.05–1.34	0.006	1.08	0.94–1.23	0.259
Child–Pugh grade A/B	0.51	0.45–0.58	<0.001	0.51	0.45–0.59	<0.001
Total bilirubin >2 mg dl^{-1}	1.99	1.76–2.24	<0.001			
Albumin >3 g dl^{-1}	0.65	0.57–0.73	<0.001			
Prothrombin time >80%	0.71	0.63–0.80	<0.001			
Ascites	2.54	2.26–2.86	<0.001			
Encephalopathy	1.28	1.09–1.50	0.002			
More than three tumours	1.84	1.64–2.07	<0.001	1.47	1.29–1.67	<0.001
Tumour >3 cm	2.26	1.98–2.58	<0.001	1.76	1.51–2.04	<0.001
Distant metastasis	2.11	1.81–2.45	<0.001	1.43	1.22–1.67	<0.001
Portal vein invasion, VP3 and VP4	3.08	2.72–3.47	<0.001	2.28	1.99–2.62	<0.001
AFP >400 ng ml^{-1}	2.35	2.09–2.65	<0.001	1.46	1.28–1.67	<0.001
HAIC/no therapy	0.71	0.62–0.81	<0.001	0.48	0.41–0.56	<0.001

Abbreviations: AFP = α-fetoprotein; CI = confidence interval; HAIC = hepatic arterial infusion chemotherapy with 5-fluorouracil and cisplatin; HBsAg = hepatitis B virus surface antigen; HCV Ab = hepatitis C virus antibody; HR = hazard ratio; VP3 = tumour invasion to the first-order branches of the portal vein; VP4 = tumour invasion to the main trunk of the portal vein.

0.51; 95% confidence interval (CI), 0.45–0.59; $P<0.0001$) and HAIC (hazard ratio, 0.48; 95% CI, 0.41–0.56; $P<0.0001$) were associated with better survival.

An exploratory subgroup analysis of patients who underwent HAIC therapy evaluated six prognostic variables: presence of HBsAg, tumour number, tumour size, presence of extrahepatic metastasis and vascular invasion, and α-fetoprotein levels. Compared with no therapy, HAIC improved survival, regardless of the values of these six prognostic factors (Supplementary Figure 2).

Survival rates of propensity score-matched cohorts. In the propensity score-matched cohort ($n=682$), 198 patients in the HAIC group and 199 patients in the no therapy group died during the observation period. The cause of death was liver related that included death by liver cancer as well as by liver failure in 184 patients (92.9%) in the HAIC group and 180 patients (90.4%) in the no therapy group ($P=0.47$). Median survival times were 14.0 months (HAIC group) and 5.2 months (no therapy group), and survival was significantly higher in the HAIC group ($P<0.0001$) (Figure 2). Hazard ratio of HAIC in this propensity score-matched cohort was 0.60 (95% CI, 0.49–0.73; $P<0.0001$). The same relationship was observed even when the event was limited to liver-related death ($P<0.0001$). Median survival times were 15.4 months (HAIC group) and 7.3 months (no therapy group).

Because most treatment guidelines for HCC recommend chemotherapy for patients with Child–Pugh A/B disease who have portal vein invasion and/or more than three tumours, we analysed the effect of HAIC in patients who met these criteria in the propensity score-matched cohort. In cases of Child–Pugh A/B disease with more than three tumours (370 propensity score-matched patients), median survival times were 13.9 months (HAIC) and 3.7 months (no therapy), and a survival benefit of HAIC treatment was observed ($P<0.0001$; Supplementary Figure 3). The same relationship was also observed in cases of

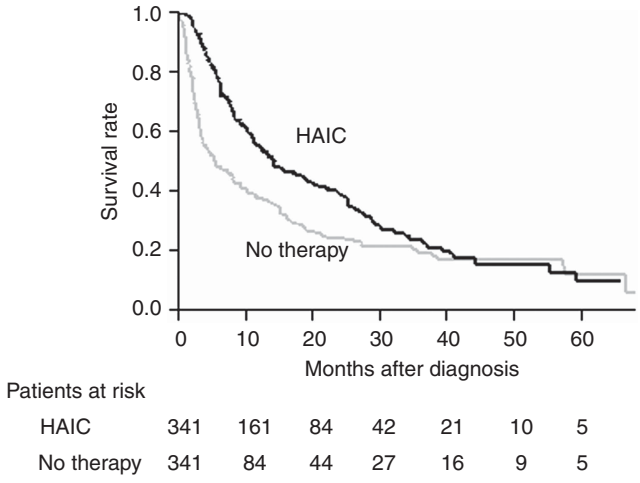


Figure 2. Survival of propensity score-matched patients who underwent hepatic arterial infusion of 5-fluorouracil and cisplatin (HAIC) or no active therapy (no therapy). Median survival times were 14.0 months (HAIC) and 5.2 months (no therapy) ($P<0.0001$).

Child–Pugh A/B disease with portal vein tumour thrombus (378 propensity score-matched patients, $P<0.0001$; Supplementary Figure 4). Median survival times were 7.9 months (HAIC) and 3.1 months (no therapy).

DISCUSSION

Hepatic arterial infusion of cisplatin and 5-FU using a subcutaneous infusion port has been widely used in Japan to treat advanced

HCC because of its relatively high response rate (27.8–57.1%) (Ando *et al*, 2002; Eun *et al*, 2009; Ueshima *et al*, 2010; Kim do *et al*, 2011; Kim *et al*, 2011); however, no randomized control trial has been conducted to demonstrate its effectiveness and survival benefit. Most reports of HAIC were retrospective studies with small numbers of patients. In this study we used data from a large-scale nationwide survey and found that the response rate to HAIC was high (40.5%), survival was prolonged, and response to therapy could be used as a surrogate marker for overall survival. The survival benefit was also observed when only liver-related deaths were treated as 'events'.

Cisplatin interacts with DNA, preferentially binding nucleophilic N7 sites on purine bases (Galluzzi *et al*, 2012). As a consequence, protein–DNA complexes and DNA–DNA inter- and intra-strand adducts are generated, inducing cytotoxicity. Cisplatin also increases the folate concentration in cancer cells, reinforcing the effect of 5-FU through the formation of an inactive ternary complex (Scanlon *et al*, 1986; Kim *et al*, 2002). This synergistic effect of cisplatin and 5-FU is the basis of HAIC therapy.

Our study has some limitations. The information of dose reduction or termination due to drug toxicity is missing. Propensity scores were used to adjust for patient characteristics; however, it is not possible to adjust for all possible confounding factors related to survival, and the exact reasons of no therapy in control group were not known. Another weak point in this study is that performance status was not included as a covariate because two-thirds of the patients enrolled in this study lacked these data. However, the survival benefit of HAIC was observed even when the event was limited to liver-related death and when analysing the most recent database, which included performance status (median observation period 3 months, data not shown). Finally, we did not know the precise regimen used in this study population; however, many studies of HAIC report the administration of low-dose cisplatin (5–20 mg) several times a week, and continuous infusion of 5-FU for a few weeks.

As sorafenib has become the standard treatment for advanced HCC, several randomized controlled trials have been planned to evaluate new drugs using sorafenib as a control (Kudo, 2012). Some of these trials will evaluate HAIC, which will clarify some of the uncertainties of the present study.

In this large-scale retrospective study, we demonstrated the effectiveness of HAIC, although it was difficult to achieve long-term survival because HCCs re-grew even after response to the drugs. Our findings indicate that HAIC could be an alternative therapy for advanced HCC. Further examination of the factors that can predict the therapeutic effect is important for achieving long survival in future.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Supplementary Information accompanies this paper on British Journal of Cancer website (http://www.nature.com/bjc)