Feasibility and efficacy of hepatic arterial infusion chemotherapy for advanced hepatocellular carcinoma after sorafenib

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Short title: HAIC in HCC after sorafenib therapy

Abstract

Aim: Sorafenib is the standard treatment for advanced hepatocellular carcinoma (HCC). However, although there is no proven therapeutic procedure following the termination of sorafenib, hepatic arterial infusion chemotherapy (HAIC) may be a treatment option in advanced HCC. The aim of this study was to evaluate feasibility and efficacy of HAIC for patients with advanced HCC as subsequent therapy.

Methods: We retrospectively evaluated 27 consecutive patients with advanced HCC who were treated with HAIC following sorafenib between June 2009 and December 2012 at our hospital. Cisplatin (20 mg/m^2/day) was administered via the hepatic artery for 10 min, prior to the continuous administration of 5-FU (330 mg/m^2/day) over 24 h from days 1–5 and 8–12 and the subcutaneous administration of pegylated interferon α-2b (1 μg/kg) on days 1, 8, 15, and 22. A treatment cycle consisted of 28 days of drug administration followed by 14 days of rest.

Results: The toxicity profile showed that hematological toxicities were common, and grade 3/4 neutropenia and thrombocytopenia were observed (51.9% and 48.1%, respectively). Five patients (18.5%) experienced device-related complications. No unexpected adverse reactions and no treatment-related deaths were observed. Partial response was obtained in eight patients (29.6%), and stable disease was noted in nine patients (33.3%). Median progression-free survival and median survival time from initiation of HAIC were 4.0 and 7.6 months, respectively.

Conclusions: Because HAIC was well tolerated and exhibited moderate antitumor activity, it is

a potentially useful treatment procedure in patients with advanced HCC even after failure of sorafenib.

Key Words: hepatic arterial infusion chemotherapy, hepatocellular carcinoma, sorafenib

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the third leading cause of cancer-related mortality worldwide [1]. A variety of new techniques of imaging modalities have enabled the detection of HCC at an early stage [2], and advances in various therapeutic procedures have improved its curability [3,4]. However, the number of patients with HCC who can be treated curatively is limited because of impaired hepatic function and frequent recurrence even after curative therapy. The prognosis of patients with advanced HCC where tumor has spread over the liver or invaded major vessels remains extremely poor [5].

Sorafenib, an oral multikinase inhibitor that blocks tumor cell proliferation and angiogenesis, is the only systemic therapy that has shown survival benefit for patients with advanced HCC [6.7], and it is recognized worldwide as standard first-line therapy in advanced HCC [8.9]. Alternative systemic chemotherapies using cytotoxic agents or novel targeted drugs have been attempted in patients with advanced HCC [10,11]; however, to date none have proven effective, except sorafenib. Moreover, following sorafenib therapy most patients are not suitable candidates for subsequent therapy because of the progressive nature of their disease, poor general condition, and impaired hepatic function.

Compared with systemic chemotherapy, hepatic arterial infusion chemotherapy (HAIC) is based on theoretical advantages such as higher concentrations of drugs delivered directly to tumors [12] and first-pass effect reducing systemic toxicity [13]. Although few reports have recorded

the survival benefits of HAIC, HAIC in combination with interferon (IFN) has been reported to be a useful treatment procedure in patients with advanced HCC [14,15]. Although an optimal protocol of HAIC has not been established, the clinical benefits of HAIC regimen consisting of 5-FU and cisplatin with IFN were reported in a randomized phase II study [15]. However it remains unclear whether HAIC is also safe and effective in patients with advanced HCC who were previously administered sorafenib.

The aim of the present study was to evaluate the feasibility and efficacy of HAIC in patients with advanced HCC after failure of sorafenib therapy. This approach provides useful information in determining treatment strategies for sorafenib-refractory patients with HCC.

Methods

Patients

All of 68 consecutive patients with unresectable advanced HCC who had received sorafenib monotherapy at Kanazawa University Hospital and for whom this therapy was subsequently stopped because of tumor progression or/and unacceptable adverse effects between June 2009 and December 2012 were considered for enrollment. HCC was diagnosed by either histological confirmation or typical radiological findings, which showed hyperattenuation in the early phase and hypoattenuation in the late phase on dynamic computed tomography (CT) [16]. All patients underwent dynamic CT to assess the extent of the cancer, and their hepatic and major organ functions were evaluated by physical examination and laboratory findings. We reviewed patients' medical records and investigated their backgrounds, treatment courses, and outcomes.

Sorafenib

The following were the inclusion criteria for sorafenib at our institution: patients with advanced HCC involving macroscopic vascular invasion, extrahepatic lesions, and/or intrahepatic multiple lesions considered unsuitable for surgical resection, locoregional therapy, or transarterial chemoembolization; all patients with an Eastern Cooperative Oncology Group (ECOG) performance status score of ≤2 and with appropriate function of major organs, such as bone marrow, kidney, and heart; and patients categorized as Child–Pugh A in terms of hepatic function.

HAIC

The inclusion criteria for HAIC at our institution is nearly same as that of sorafenib. Patients with extrahepatic lesions were also considered eligible if these lesions were mild, and intrahepatic lesions were considered as prognostic factors. With regard to hepatic function, patients categorized as Child–Pugh A or B were eligible.

The reservoir system implantation technique was the same as described previously [15]. Catheters were introduced through the right femoral artery, and angiography from the celiac artery was initially performed to localize the HCC and evaluate intra- and extrahepatic vascularization. We then inserted a catheter with a side vent into the gastroduodenal artery, positioning the vent in the common hepatic artery using an image-guided procedure. The gastroduodenal artery, right gastric artery, and other arteries presumed to supply the gastroduodenal region were embolized as far as possible to prevent gastrointestinal mucositis. The other end of the catheter was connected to an injection port that was subcutaneously implanted in the right lower abdomen. Finally, blood flow redistribution was confirmed.

HAIC was initiated approximately 5 days after implantation of the reservoir, and the following protocol was then implemented: 5-FU (330 mg/m^2/day) was continuously administered via the hepatic artery using an infuser pump over 24 h from days 1–5 and 8–12, and cisplatin (20 mg/m^2/day) was also administered via the hepatic artery for 10 min prior to 5-FU administration. Pegylated interferon α-2b (1.0 μg/kg) was subcutaneously administered on days 1, 8, 15, and 22.

A treatment cycle consisted of 28 days of drug administration followed by 14 days' rest. The treatment protocol was approved by the Ethics Committee of Kanazawa University, and informed consent for participation in the study was obtained from each subject. The study conformed to the guidelines of the 1975 Declaration of Helsinki.

Evaluation

Tumor staging was assessed according to the criteria of the Liver Cancer Study Group of Japan [17,18]. The efficacies of HAIC and sorafenib were assessed every 4–6 weeks by dynamic CT, and response to chemotherapy was assessed according to the Response Evaluation Criteria in Solid Tumors ver. 1.1 [19]. Response rate was defined as the sum of complete and partial response rates. Similar to an approach adopted in a recent report, the causes of progression after sorafenib therapy (progression pattern) were classified as follows: intra-hepatic growth (IHG), extra-hepatic growth (EHG), new intra-hepatic lesion (NIH), or new extra-hepatic lesion and/or vascular invasion (NEH) [20]. Adverse effects, including both hematological and nonhematological toxicities, were assessed by the Common Terminology Criteria for Adverse Events ver4.0.

Statistical analysis

Progression-free survival (PFS) was calculated from the first day of HAIC until either the date of radiological progression, the date of death, or the last day of the follow-up period. Overall

survival (OS) was calculated from the first day of HAIC until either the date of death or the last day of the follow-up period. A chi-squared test was used to analyze the predictive factor for the response to HAIC. To compare prognosis according to response to chemotherapy and the progression pattern, cumulative survival was calculated using the Kaplan–Meier method [21] and any differences were evaluated using the log-rank test. *P*-values of <0.05 were considered to be statistically significant, and all tests were two-sided. All statistical analyses were performed using the SPSS statistical software program package (SPSS version 11.0 for Windows).

Results

Patients

Of 68 patients, 41 were not treated with HAIC because of either poor general condition (n = 12), massive extrahepatic lesions (n = 9), inadequate major organ function (n = 8), treatment with HAIC prior to sorafenib therapy (n = 7), or refusal to be treated with HAIC (n = 5). Finally, 27 patients who had been treated with HAIC were analyzed in this study, all of whom had previously received sorafenib monotherapy. The response and tumor control rates for sorafenib therapy were 7.4% and 44.4%, respectively. In 22 patients (81.5%), sorafenib therapy was terminated because of tumor progression and in 5 (18.5%) because of unacceptable adverse effects. The median period of sorafenib therapy was 2.4 months (range, 0.1–18.0).

Patient characteristics at commencement of treatment with HAIC are summarized in Table 1. Because hepatic function was impaired in more than half of the patients in this study, 18 patients (66.7%) were classified as Child–Pugh class B or C. Macroscopic vascular invasion and extrahepatic metastasis were observed in 25.9% and 44.4% of the patients, respectively.

Treatment

A total of 60 courses were administered to 27 patients, with a median number of 2 (range, 0–5). All, but 2, patients completed at least one course of HAIC. The median duration between cessation of sorafenib therapy and commencement of HAIC was 1.2 months (range, 0–9.0). The median observation period from commencement of HAIC was 7.0 months (range, 0.8–48.0).

Treatment with HAIC was terminated in 25 patients due to radiological tumor progression (20 patients), symptomatic tumor progression (1 patient), or change in the treatment procedure (4 patients); however, there were no patients in whom HAIC was terminated because of adverse effects. HAIC was continued in the remaining 2 patients until the last day of the follow-up period.

Safety

All 27 patients were assessed for adverse effects, and the toxicity profile of HAIC is summarized in Table 2. Hematological toxicities were common, particularly grade 3/4 neutropenia and grade 3/4 thrombocytopenia, which were observed in 14 (51.9%) and 12 (48.1%) patients, respectively, even though no serious complication such as sepsis or bleeding were observed and all toxicities were tolerable and reversible. Mild and low-frequency nonhematological toxicities were observed, except in one patient who had grade 3 diarrhea. Although 5 patients (18.5%) had device-related complications (3 catheter obstruction, 1 hepatic artery occlusion, and 1 hepatic arteritis), all issues were satisfactorily resolved by either exchanging the reservoir or conservative therapy. No unexpected adverse reactions were noted, and no treatment-related deaths were observed.

Response to treatment and patient outcomes

Of the 27 patients, one died due to tumor progression and hepatic failure before radiological

assessment could be performed; however, the remaining 26 were assessable for response to treatment. Tumor responses to HAIC are shown in Table 3. Although no patient achieved complete response, 8 patients (29.6%) achieved partial response (PR) and 9 (33.3%) achieved stable disease (SD); therefore, the response rate to HAIC was 29.6%. These results were independent of the Child–Pugh class, the response to previous sorafenib therapy, and the progression pattern (Table 3), and none of the tested factors were found to be a significant predictive factor for response to HAIC (Supplementary Table).

The median PFS of patients from commencement of HAIC was 4.0 months (Figure 1). The median survival time (MST) of all patients was 7.6 months, with a 1-, 2-, and 3-year survival rate of 29.4%, 24.5%, and 16.4%, respectively (Figure 2A). The MST of patients who achieved PR were 36.7 months, which was significantly better than that of patients who achieved SD/progressive disease /not evaluable, i.e., 6.6 months ($p < 0.01$; Figure 2B). Patient prognosis did not differ according to the progression pattern (Supplementary figure).

Discussion

The development of a safe and effective alternative therapy is essential because sorafenib, which represented a breakthrough in the treatment of advanced HCC, had a low response rate and frequent adverse effects, often leading to a cessation of treatment [22,23]. An increasing number of emerging agents, including novel molecular targeted drugs, have been attempted in sorafenib refractory HCC. Nevertheless, their efficacy was found to be limited (response rate, 0%–4.3%; time to progression, 1.6–2.7 months) [24-26].

The first aim of this study was to investigate the feasibility of HAIC in advanced HCC after the failure of sorafenib therapy. In this study, the frequency of hematological toxicity, particularly neutropenia and thrombocytopenia, was high. One of the possible causes of these toxicities was pre-existing pancytopenia derived from liver cirrhosis in most patients, and another was the concurrent administration of IFN added to 5-FU and CDDP [15]. All of the patients recovered immediately after the end of treatment and no additional complications were noted. Moreover, the frequencies of leukocytopenia, neutropenia, and thrombocytopenia observed in this study (74.1%, 77.8%, and 88.9%, respectively) were very similar to those of patients who were not pretreated by sorafenib and underwent HAIC with the same protocol, including 5-FU/CDDP/IFN (75.4%, 77.2%, and 89.5%, respectively) [15], which suggested that prior administration of sorafenib did not have an additional impact on hematological toxicities. With regard to nonhematological toxicities, most of them were less frequent than those in a

previous report [15], and there were no unexpected adverse reactions. These favorable results may be derived from newly available drugs such as a second-generation 5-hydroxytryptamine 3 receptor antagonist and neurokinin-1-receptor antagonist or active supportive therapy. These findings suggested that HAIC was considered tolerable even for those patients who were previously administered sorafenib.

The response rate obtained in the present study (29.6%) appears to be low compared with that of previous reports [14,15]. Although it is difficult to compare the response rates among studies, possible reasons include variation in patients' hepatic function, the criteria used to evaluate responses, the effect of previous administration of sorafenib, and the relatively small number of patients. In addition, the proportion of patients with extrahepatic lesions may have been a meaningful factor because it was higher (44.4%) in this study than that of the previous study (0-14%) [14,15] and the response rate was reported to be lower in patients with HCC having extrahepatic metastases than in those without [27]. We could not identify any significant predictive markers for the response to HAIC in this study, and further investigation is needed to examine the factors affecting the response rate of HAIC, and to select the appropriate population to receive HAIC after sorafenib therapy.

Another interesting finding of the present study was that half of our patients were categorized as Child–Pugh class B, and no correlation was observed between the response to HAIC and Child–Pugh classification. Although certain molecular targeted agents are currently being tested for sorafenib-refractory patients with HCC, the objectives in most of these trials are restricted to

patients with good hepatic function. Other reports have described systemic chemotherapy by combination of gemcitabine and oxaliplatin is potentially safe for patients with Child–Pugh class B [28] and useful in sorafenib-refractory patients with HCC [29]. The results of the present study suggest that HAIC may be also considered as one of treatment procedures for patients with Child–Pugh class B after sorafenib therapy.

The present study has several limitations, including its retrospective nature, the small number of patients, the lack of controls, and single-institution subsets. A prospective trial with a larger number of patients in proper design is needed to confirm our findings.

In conclusion, HAIC has good feasibility and moderate antitumor activity and is a useful treatment option for patients with advanced HCC after failure of sorafenib therapy.

Acknowledgments: none

Conflicts of interest: none to declare

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Figure legends

Figure 1: Kaplan–Meier plot of PFS since commencement of hepatic arterial infusion chemotherapy (HAIC). Median PFS was 4.0 months

Figure 2: Kaplan–Meier plot of overall survival since commencement of HAIC: (A) all patients and (B) according to response to HAIC. The median survival time (MST) of all patients was 7.6 months, and the MST of patients who achieved partial response (PR) were 36.7 months (black line), which was significantly better than that of the patients with stable disease (SD)/progressive disease (PD)/ not evaluable (NE), i.e., 6.6 months (gray line) (p <0.01).

Supplementary Figure: Kaplan–Meier plot of overall survival since commencement of HAIC according to progression pattern. Patient prognosis did not differ among intra-hepatic growth (IHG) group (black line), new intra-hepatic lesion (NIH) group (gray line), and new extra-hepatic lesion and/or vascular invasion (NEH) group (dashed line).

Tables

Table 1. Patient characteristics

	(n=27)
Age, years	
Median, Range	68, 44-84
Gender, n (%)	
Male	23 (85.2)
ECOG PS [a], n (%)	
0	24 (88.9)
1	3 (11.1)
HBs antigen [b], n (%)	
Positive	9 (33.3)
HCV antibody [c], n (%)	
Positive	15 (55.6)
Child-Pugh class at start of HAIC, n (%)	
A	9 (33.3)
B	16 (59.3)
C*	2 (7.4)
Child-Pugh class at start of sorafenib, n (%)	
A	21 (77.8)
B**	6 (22.2)
Ascites, n (%)	
Presence	18 (66.7)
Albumin, g/dL	
Median, Range	3.2, 2.1-3.9
Prothrombin consumption test, %	
Median, Range	82, 37-112
LCSGJ [d] tumor stage, n (%)	
II, III	12 (44.4)
IVA	4 (14.8)
IVB	11 (40.7)
Macroscopic vascular invasion, n (%)	
Yes	7 (25.9)
Extrahepatic spread, n (%)	

Yes	12 (44.4)
AFP [e], ng/mL	
Median, Range	404, <10-175560

a. ECOG PS: Eastern Cooperative Oncology Group performance status

b. HBs antigen: Hepatitis B surface antigen

c. HCV antibody: Hepatitis C virus antibody

d. LCSGJ: Liver Cancer Study Group of Japan

e. AFP: α-fetoprotein

*; Child-Pugh class B at decision making of HAIC

**; Child-Pugh class A at decision making of sorafenib

Table 2. HAIC toxicities

	All grade n (%)	Grade 3 n (%)	Grade 4 n (%)
Hematological toxicities			
Leukocytopenia	20 (74.1)	10 (37.0)	0 (0)
Neutropenia	21 (77.8)	10 (37.0)	4 (14.8)
Anemia	12 (44.4)	1 (3.7)	1 (3.7)
Thrombocytopenia	22 (88.9)	13 (48.1)	0 (0)
Nonhematological toxicities			
Anorexia	7 (25.9)	0 (0)	0 (0)
Fever	5 (18.5)	0 (0)	0 (0)
Dirrhea	4 (14.8)	1 (3.7)	0 (0)
Fatigue	4 (14.8)	0 (0)	0 (0)
Hiccoughs	3 (11.1)	0 (0)	0 (0)
Gastric ulcer	3 (11.1)	0 (0)	0 (0)
Creatinine increased	2 (7.4)	0 (0)	0 (0)
Mucositis oral	2 (7.4)	0 (0)	0 (0)
Nausea	1 (3.7)	0 (0)	0 (0)
Ascites	1 (3.7)	0 (0)	0 (0)
Edema	1 (3.7)	0 (0)	0 (0)
Abdominal pain	1 (3.7)	0 (0)	0 (0)
Hypokalemia	1 (3.7)	0 (0)	0 (0)
Encephalopathy	1 (3.7)	0 (0)	0 (0)
Device-related complications			
Catheter obstruction	3 (11.1)	0 (0)	0 (0)
Hepatic artery occlusion	1 (3.7)	0 (0)	0 (0)
Vasculitis	1 (3.7)	0 (0)	0 (0)

Table 3. Tumor response

Response to HAIC [a]	All n (%)	Child-Pugh class*		Response to sorafenib				Progression pattern**		
		A	B or C	PR	SD	PD	NE	IHG [g]	NIH [h]	NEH [i]
CR [b]	0 (0)	0	0	0	0	0	0	0	0	0
PR [c]	8 (29.6)	1	7	0	4	3	1	3	0	1
SD [d]	9 (33.3)	5	4	1	5	3	0	7	2	0
PD [e]	9 (33.3)	3	6	0	4	4	1	6	2	0
NE [f]	1 (3.7)	0	1	1	0	0	0	1	0	0
Total	27 (100)	9	18	2	13	10	2	17	4	1

a. HAIC: hepatic arterial infusion chemotherapy

b. CR: complete response

c. PR: partial response

d. SD: stable disease

e. PD: progressive disease

f. NE: not evaluable

g. IHG: intra-hepatic growth

h. NIH: new intra-hepatic lesion

i. NEH: new extra-hepatic lesion

*; at decision making of HAIC

**; at termination of sorafenib therapy

Supplementary Table. Predictive marker for response to HAIC

		n	response rate (%)	p*
Age, years	>=68	14	14.3	0.070
	<68	13	46.2	
Gender	Male	23	26.0	0.33
	Female	4	50.0	
ECOG PS [a]	0	24	29.2	0.88
	1	3	33.3	
HBs antigen [b]	Positive	9	22.2	0.55
	Negative	18	33.3	
HCV antibody [c]	Positive	15	33.3	0.64
	Negative	12	25.0	
Intrahepatic lesions, n	>=5	17	29.4	0.97
	<5	10	33.3	
Size of maximum lesion, mm	>=40	14	35.7	0.47
	<40	13	23.1	
Macroscopic vascular invasion	Positive	8	12.5	0.30
	Negative	20	35.0	
Extrahepatic spread	Positive	12	33.3	0.71
	Negative	15	26.7	
LCSGJ [d] tumor stage, n (%)	II, III	12	25.0	0.82
	IVA	4	25.0	
	IVB	11	26.4	
Ascites	Positive	18	33.3	0.55
	Negative	9	22.2	
Albumin, g/dL	>=3.5	9	22.2	0.55
	<3.5	18	33.3	
Child-Pugh class	A	9	11.1	0.14
	B-C	18	38.9	

AFP [e], ng/mL	>=400	14	28.6	0.90
	<400	13	30.8	
Progression pattern	IHG [f]	17	17.6	0.068
	NIH [g]	4	0.0	
	NEH [h]	1	100.0	

a. ECOG PS: Eastern Cooperative Oncology Group performance status

b. HBs antigen: Hepatitis B surface antigen

c. HCV antibody: Hepatitis C virus antibody

d. LCSGJ: Liver Cancer Study Group of Japan

e. AFP: α-fetoprotein

f. IHG: intra-hepatic growth

g. NIH: new intra-hepatic lesion

h. NEH: new extra-hepatic lesion

*; chi-squared test