Efficacy of sequential sorafenib plus hepatic arterial infusion chemotherapy in patients with Barcelona Clinic Liver Cancer stage B and C hepatocellular carcinoma: a retrospective single-institution study

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Aim of the study: To evaluate the efficacy of sequential combination therapy using sorafenib and hepatic arterial infusion chemotherapy (HAIC) in patients with Barcelona Clinic Liver Cancer stage B/C hepatocellular carcinoma (HCC).

Material and methods: We recruited 98 BCLC stage B/C HCC patients at our institute, who received either sorafenib monotherapy or planned sequential sorafenib-HAIC combination therapy. A total of 26 patients (combination group) received sorafenib for one or two months, followed by HAIC with a single dose of cisplatin-lipiodol suspension and a continuous infusion of 5-fluorouracil. Sorafenib-HAIC cycles were repeated every 2–3 months. The remaining 72 patients (control group) were treated with sorafenib alone. Clinical characteristics and treatment outcomes were compared between the groups. Inverse probability weighting (IPW) using propensity scores was applied to adjust for the between-group differences in baseline characteristics.

Results: The combination group had a significantly lower frequency of extrahepatic metastasis and BCLC stage C disease compared with the control group but had more intrahepatic lesions. The crude median overall survival (OS) was 17.1 months in the combination group compared with 9.7 months in the control group (p = 0.01). The objective response rate was 23.1% in the combination group vs. 6.9% in the control group (p = 0.06). Multivariate analysis identified receipt of sorafenib-HAIC combination (HR: 0.521, 95% CI: 0.297–0.915, p = 0.02) and α-fetoprotein (≥ 400 ng/ml) at baseline as independent factors associated with OS. After adjustment with IPW the combination group still had significantly better OS than the control group (p = 0.04).

Conclusions: The sequential sorafenib-HAIC combination can be an effective and promising treatment option for selected patients with BCLC stage B/C HCC.

Key words: hepatocellular carcinoma, sorafenib, hepatic arterial infusion chemotherapy.

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Introduction

Hepatocellular carcinoma (HCC) is one of the major causes of cancer death worldwide [1]. Despite recent progress in the surveillance and management of HCC, potentially curative treatments such as surgical resection, liver transplantation, or radiofrequency ablation are still only suitable for a limited number of patients due to impaired hepatic reserve, advanced disease stage, or frequent metachronous recurrence [2, 3]. Patients with advanced HCC are only candidates for palliative therapy, and they have a dismal prognosis with a median survival time of less than one year [4, 5].

Sorafenib is an oral multikinase inhibitor that blocks tumour cell proliferation and angiogenesis, and it represents the current standard therapy for improving the overall survival (OS) of patients with advanced HCC [4, 5]. Sorafenib is strictly indicated for HCC patients in Barcelona Clinic Liver Cancer (BCLC) stage C or patients with progressive disease after locoregional therapy provided that they have preserved liver function [6]. In two international, randomised, controlled trials reported in 2008–2009, about half of the patients receiving sorafenib achieved disease control [4, 5]. However, the benefit of sorafenib monotherapy in actual clinical practice has been more modest with low response rates, relatively frequent adverse effects, and high costs [4, 5, 7, 8].

As an alternative or complementary therapy to sorafenib, hepatic arterial infusion chemotherapy (HAIC) is a regional cytotoxic chemotherapy for advanced or unresectable HCC. HAIC directly delivers chemotherapy agents to the feeding vessels of liver tumours, thereby increasing the local drug concentration and minimising systemic toxicity [9]. However, the position of HAIC in the treatment of HCC has not yet been established due to the lack of well-conducted randomised trials, although a number of studies have found benefits of HAIC in relation to response and survival [9–15].

HCC generally consists of a complex and heterogeneous tumour cell population [16, 17]. Furthermore, patients with advanced HCC show diverse clinical presentations associated with multifocal tumour spread, large vessel invasion, and/or extrahepatic metastasis. Multimodal treatment strategies may therefore be required to improve disease control and survival, even though management guidelines for HCC recommend monotherapy as a treatment option. In a recent randomised phase II trial, sorafenib plus HAIC with cisplatin yielded favourable OS when compared with sorafenib alone in patients with advanced HCC [18]. By contrast, addition of HAIC with cis-

platin and 5-fluorouracil to sorafenib failed to significantly improve OS according to phase III trial results [19]. The reasons underlying the discrepancy between these clinical trials remain unclear but warrant further studies, given the potential of combination therapy to extend the survival of advanced HCC patients.

While the above-mentioned studies [18, 19] incorporated continuous sorafenib administration protocol concurrently with HAIC, sequential combination of HAIC with interrupted dosing of sorafenib would be an alternative treatment to reduce toxicity and costs without significant loss in efficacy. In the appropriate clinical setting, we have administered planned sequential therapy with sorafenib and HAIC to eligible patients with BCLC stage B or stage C HCC. We analysed retrospectively patients who had received sequential combination therapy and compared these individuals with patients who received sorafenib monotherapy, to observe differences in the therapeutic effects and survival between these groups.

Material and methods

Patients

We analysed retrospectively data from 141 HCC patients who received sorafenib at our institute between September 2009 and March 2017. Twenty-nine patients were excluded because the duration of sorafenib treatment was less than four weeks (n = 28) or because of Child-Pugh class C liver function (n = 1). Patients were also excluded if they had received HAIC as subsequent therapy after failure of sorafenib monotherapy (n = 14), leaving 98 patients for final analysis. Among them, 64 patients (65.3%) were BCLC stage C and 34 patients (34.7%) were stage B. Of the 98 patients, 26 received planned sequential sorafenib-HAIC combination and were allocated to the combination group. Combination therapy was chosen at the discretion of the treating physician but generally based on the following characteristics: presence of multiple intrahepatic tumours; absence of rapidly progressive, extensive multiorgan or numerous extrahepatic metastases; lack of renal insufficiency that contraindicated cisplatin; Child-Pugh class A or B ≤ 7; Eastern Cooperative Oncology Group performance status (ECOG-PS) ≤ 1; and technical feasibility of HAIC, which depends on the following factors occasionally making catheter placement difficult, e.g. celiac axis stenosis or occlusion, tortuous small hepatic arteries, postsurgical changes or variations in vascular anatomy, and reflux of chemotherapy agents into the gastrointestinal tract and out of the liver. The remaining 72 patients who received sorafenib monotherapy were allocated to the control group. Baseline clinical characteristics and treatment outcomes were compared retrospectively between the groups. Written, informed consent was obtained from each patient. This study was approved by the Institutional Review Board of Meiwa Hospital (permission number: 29–34) and was performed in accordance with the ethical guidelines of the World Medical Association Declaration of Helsinki.

Treatment

Eighty-five patients (86.7%) started sorafenib at a reduced dosage of 400 mg/day according to their age, body weight, and co-morbidities, at the physician's discretion. If the starting dose was tolerated, it was increased stepwise to 600 or 800 mg/day. In the combination group, sorafenib was administered for 1–2 months based on tolerability, after which HAIC was performed sequentially. Briefly, on day 1 of HAIC, 50 mg of cisplatin in 5–10 ml of lipiodol was inject-

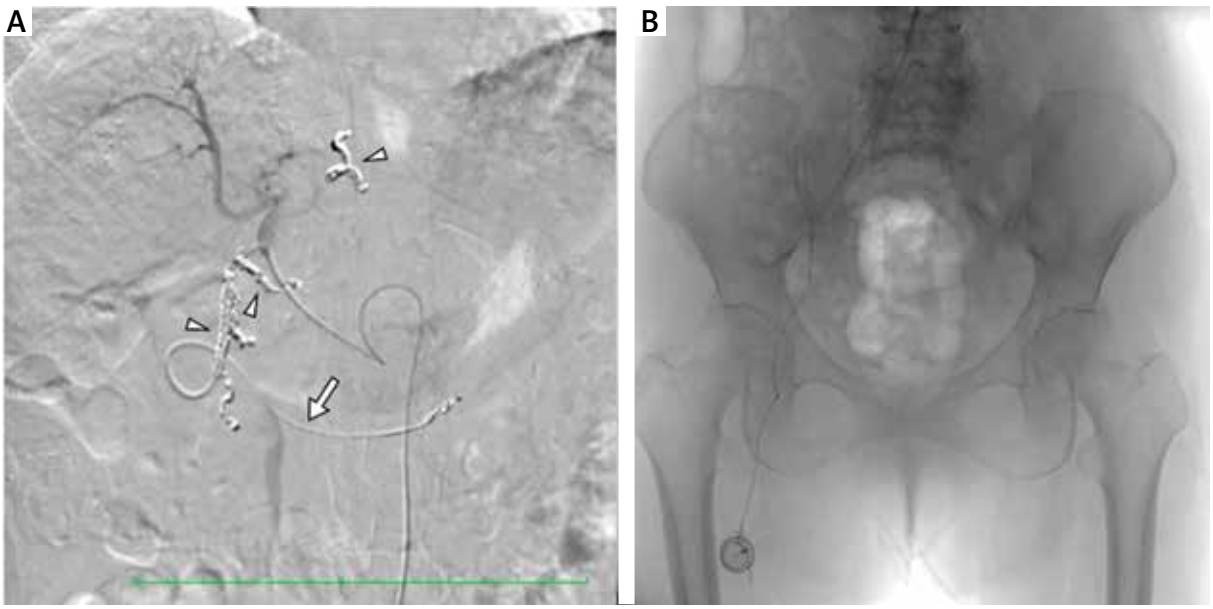


Fig. 1. Placement of a port-catheter system for hepatic arterial infusion chemotherapy. **A)** The tip of the intra-arterial catheter with a side hole was inserted into the gastroduodenal artery (GDA) (arrow), and the side hole was located at the common hepatic artery. The GDA and other arteries supplying the gastroduodenal region were embolised using metallic coils (arrowheads) to prevent gastroduodenal mucosal damage by chemotherapy agents. **B)** The other end of the catheter was connected to the injection port, which was implanted in a subcutaneous pocket at the proximal anterior thigh

ed through a subcutaneously implanted port system (Fig. 1) with adequate systemic hydration. Then 5-fluorouracil (5-FU) (250 mg/day) was continuously infused using a syringe pump for 10 days (on days 1–5 and 8–12) with two days off treatment. This sequential sorafenib-HAIC regimen was repeated every 2–3 months (Fig. 2). The interval between sorafenib treatment and HAIC was not specified but did not exceed two weeks. We reduced the dose of cisplatin by 25–50% in patients with pre-existing or new-onset renal insufficiency, but the dose of 5-FU was fixed in principle. Dose reduction or interruption of sorafenib in response to toxicity was performed in all subjects according to the general recommendations. If the tumour became refractory or there was intolerance to combination therapy or sorafenib monotherapy, patients were considered for subsequent therapy providing that survival or quality of life benefit was expected. Tumour response and disease progression were evaluated by using the modified Response Evaluation Criteria in Solid Tumours criteria [20], and adverse effects were graded according to Common Terminology Criteria for Adverse Events (version 4.03).

Statistical analysis

The Mann-Whitney U test was used to compare paired independent continuous variables, while categorical variables were compared by the chi-square test or Fisher's exact test. OS was calculated from the date of initiating sorafenib therapy until the patient died of any cause or until the finish of follow-up. Kaplan-Meier curves were drawn, and the log-rank test was performed to compare OS between the two treatment groups. Univariate and stepwise multivariate Cox proportional hazard models were employed to detect factors with an influence on OS. To reduce selection bias and better assess the effect of the different treatment modalities, the two groups were balanced by performing inverse probability weighing (IPW) with propensity scores. All statistical analyses were performed with R Statistical Software (Foundation for Statistical Computing, Vienna, Austria), and $p < 0.05$ was considered significant.

Results

The baseline characteristics of the patients are summarised in Table 1. There were no significant differences between the two groups with respect to variables such as age, gender, Child-Pugh score, aetiology, previous treatment for HCC, maximum tumour size, macrovascular invasion, and serum α-fetoprotein (AFP) level. The combination group was significantly less likely to have extrahepatic metastasis and BCLC stage C disease, but was more likely to have numerous intrahepatic tumours (≥ 10) than patients in the control group. Moreover, a good ECOG-PS was significantly more frequent in the combination group than in the control group. After IPW adjustment, baseline characteristics were balanced and the two groups showed no significant differences.

Response and adverse effects

In the combination group, the median number of sorafenib plus HAIC treatment cycles was three (range: 1–9 cycles). The median duration of sorafenib treatment was 5.9 months (range: 1.7–27.3 months) in the combination group and 4.7 months (range: 1.0–32.8 months) in the control group ($p = 0.07$). The best responses to each treatment are summarised in Table 2. In the combination group, 1 (3.8%), 5 (19.2%), and 12 (46.2%) patients showed a complete response, a partial response, and stable disease, respectively. The overall response rate tended to be higher in the combination group compared with the control group (23.1 vs. 6.9%, $p = 0.06$), although the difference was not significant. The disease control rate was significantly better in the combination group compared with the control group (69.2 vs. 44.4%, $p = 0.04$). The incidence of severe treatment-related adverse effects (grades 3–4) was similar in the two groups.

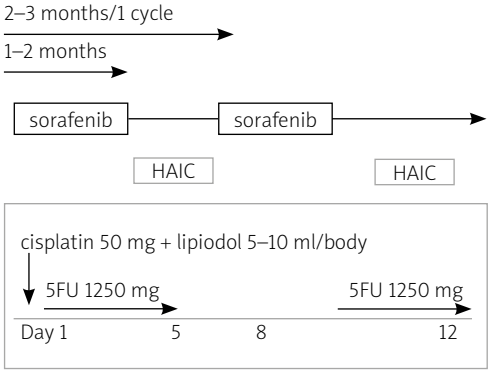


Fig. 2. The combination therapy protocol

Overall survival and prognostic factors

The median follow-up period after initiation of sorafenib was 9.7 (1.2–58.8) months. The crude median OS was 17.1 months (95% confidence interval [CI]: 14.3–25.6 months) in the combination group compared with 9.7 months (95% CI: 7.0–15.1 months) in the control group, with one-year survival rates of 74.2% (95% CI: 51.2–87.6%) and 44.2% (95% CI: 31.7–56.0%), respectively ($p = 0.01$) (Fig. 3A). Univariate analysis revealed that OS was significantly associated with the ECOG-PS, BCLC stage, baseline AFP level (≥ 400 ng/ml), and combination therapy, while neither macrovascular invasion nor extrahepatic metastasis showed significant association with OS. According to multivariate regression analysis, combination therapy (hazard ratio [HR]: 0.521, 95% CI: 0.297–0.915, $p = 0.02$) and the AFP level (≥ 400 ng/ml) (HR: 2.221, 95% CI: 1.338–3.685, $p = 0.002$) were significant determinants of OS (Table 3). After adjustment by IPW, the combination group still showed significantly better OS than the control group ($p = 0.04$) (Fig. 3B).

Discussion

In the previous two largest studies, the SHARP trial [4] and the Asia-Pacific trial [5], the objective partial response rate to sorafenib monotherapy was only 2–3.3%, and no complete responses were obtained. Furthermore, sorafenib only extended the median OS by three months. Because of such limited efficacy, many studies have fo-

Table 1. Baseline patient characteristics

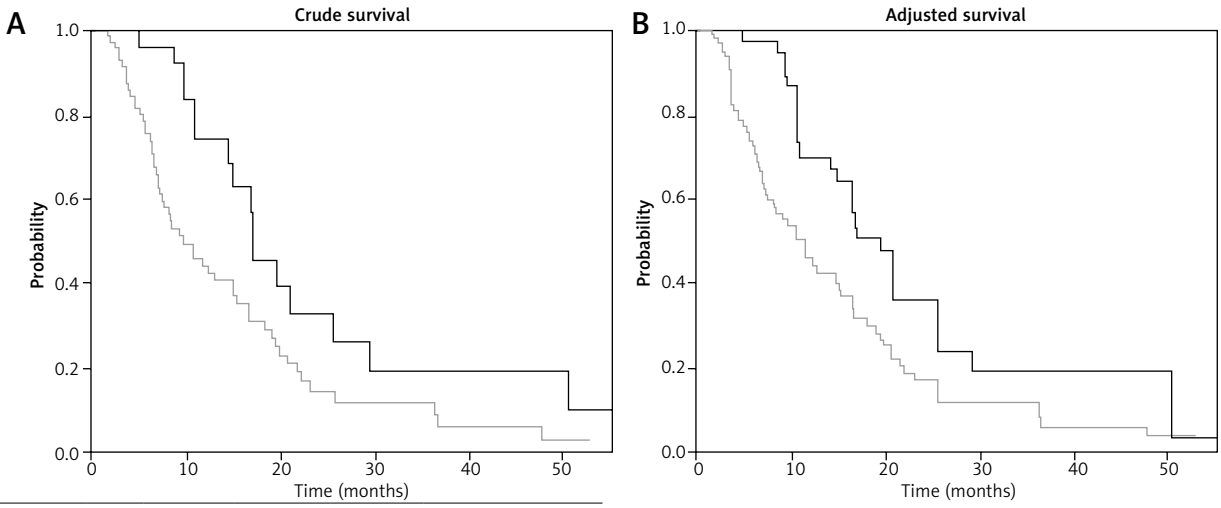
	All patients (*N* = 98)			Adjusted by IPW		
	Combination (*n* = 26)	**Control (*n* = 72)**	***p*-value**	**Combination**	**Control**	***p*-value**
Age, mean (SD)	72.4 (8.9)	69.0 (9.9)	0.21	69.9 (10.5)	70.5 (9.0)	0.91
Male gender, *n* (%)	20 (76.9)	61 (84.7)	0.38	(75.0)	(76.0)	0.94
ECOG-PS 1, *n* (%)	1 (3.8)	17 (23.6)	0.04	(8.9)	(17.4)	0.47
Child-Pugh score, *n* (%) 5/6/7	15/8/3	40/18/14	0.70	(59.4)/(23.2)/(17.5)	(50.2)/(33.6)/(16.2)	0.70
Aetiology, *n* (%) HBV/HCV/NBNC	4/11/11	14/35/23	0.69	(25.6)/(36.9)/(37.5)	(15.4)/(54.1)/(30.5)	0.42
Previous treatment for HCC, *n* (%)	25 (96.2)	68 (94.4)	1.0	(97.4)	(94.9)	0.53
No. of intrahepatic tumours, *n* (%) 0/1–3/4–9/≥ 10	0/2/4/20	7/20/19/26	0.004	(0.0)/(11.2)/(35.5)/(53.3)	(6.8)/(20.7)/(23.1)/(49.4)	0.36
Maximum tumour size, mm (mean [SD])	29.8 (18.9)	36.8 (24.5)	0.21	30.5 (20.9)	34.7 (22.6)	0.68
Macrovascular invasion, *n* (%)	6 (23.1)	25 (34.7)	0.33	(26.2)	(28.8)	0.84
Extrahepatic metastasis, *n* (%)	2 (7.7)	31 (43.1)	0.001	(12.0)	(31.3)	0.15
BCLC stage C, *n* (%)	8 (30.8)	56 (77.8)	< 0.001	(38.1)	(56.8)	0.21
AFP ≥ 400 ng/ml, *n* (%)	5 (19.2)	23 (31.9)	0.31	(19.9)	(25.8)	0.42

IPW – inverse probability weighing; ECOG-PS – Eastern Cooperative Oncology Group performance status; BCLC stage – Barcelona Clinic Liver Cancer stage; AFP – α-fetoprotein

Table 2. Treatment response, subsequent therapy, and major adverse effects

	Combination (*n* = 26)	**Control (*n* = 72)**	***p*-value**
Treatment cycle, *n*	3 (1–9)	–	–
Duration of sorafenib treatment, months	5.9 (1.7–27.3)	4.7 (1.0–32.8)	0.07
Response to treatment			
Complete response, *n* (%)	1 (3.8)	0 (0)	0.27
Partial response, *n* (%)	5 (19.2)	5 (6.9)	0.12
Stable disease, *n* (%)	12 (46.2)	27 (37.5)	0.49
Progressive disease, *n* (%)	8 (30.8)	32 (44.4)	0.25
Not evaluated, *n* (%)	0 (0)	8 (11.1)	0.11
Response rate, %	23.1	6.9	0.06
Disease control rate, %	69.2	44.4	0.04
Subsequent therapy, *n* (%)			
TACE			
Conventional with lipiodol	5 (19.2)	14 (19.4)	1.00
With drug-eluting beads	1 (3.8)	1 (1.4)	0.46
Local ablation	4 (15.4)	10 (13.9)	1.00
Radiotherapy	0 (0)	8 (11.1)	0.11
Palliative resection	2 (7.7)	2 (2.8)	0.29
Regorafenib	1 (3.8)	1 (1.4)	0.46
Other systemic chemotherapy	1 (3.8)	5 (6.9)	1.00
Adverse effects (grades 3–4), *n* (%)			
Anaemia	0 (0)	1 (1.4)	1.00
Neutropaenia	1 (3.8)	0 (0)	0.27
Thrombocytopaenia	2 (7.7)	5 (6.9)	1.00
Creatinine increased	1 (3.8)	0 (0)	0.27
Diarrhoea	1 (3.8)	6 (8.3)	0.67
Fatigue	0 (0)	4 (5.6)	0.57
Hand-foot syndrome	2 (7.7)	12 (16.7)	0.34

TACE – transarterial chemoembolisation



Number at risk						
Combination	26	19	6	3	3	2
Control	72	28	11	5	2	1

Fig. 3. Crude **(A)** and adjusted **(B)** overall survival curves for the combination and control groups

Table 3. Univariate and multivariate analysis of factors associated with overall survival

	Univariate			Multivariate		
	Hazard ratio	**95% CI**	***p*-value**	**Hazard ratio**	**95% CI**	***p*-value**
Age	0.991	0.969–1.014	0.46			
Gender male (vs. female)	1.033	0.526–2.028	0.93			
ECOG-PS 1 (vs. PS 0)	2.067	1.172–3.648	0.01	1.310	0.697–2.462	0.40
Child-Pugh B (vs. A)	1.019	0.533–1.949	0.95			
HCV (vs. HBV)	1.492	0.768–2.897	0.24			
NonBNonC (vs. HBV)	1.300	0.651–2.597	0.46			
Macrovascular invasion	1.622	0.994–2.646	0.05			
Extrahepatic metastasis	1.432	0.874–2.348	0.15			
BCLC stage C (vs. stage B)	1.757	1.068–2.891	0.03	1.573	0.915–2.705	0.10
AFP ≥ 400 ng/ml (vs. < 400 ng/ml)	2.332	1.407–3.862	0.001	2.221	1.338–3.685	0.002
Combination therapy	0.494	0.282–0.866	0.01	0.521	0.297–0.915	0.02

95% CI – 95% confidence interval; ECOG-PS – Eastern Cooperative Oncology Group performance status; BCLC stage – Barcelona Clinic Liver Cancer stage; AFP – α-fetoprotein

cused on combining sorafenib with other treatments, including transarterial chemoembolisation (TACE) [21], systemic chemotherapy [22, 23], and other molecular targeting agents [24]. However, no combination therapy has yet been shown to have a clear survival benefit.

HAIC has been widely used in Asian countries to treat advanced HCC, with favourable response rates ranging from 14.3% to 86.3% [9–15]. The Japanese guidelines for management of HCC recommend HAIC for the same patients as those indicated for sorafenib [25]. Among numerous HAIC regimens, cisplatin alone [10, 11], 5-FU plus cisplatin [12–14], and 5-FU plus interferon [15] are used most frequently in Japan. 5-FU and cisplatin combination have been shown to produce a synergistic antitumour effect [14, 26]. Cisplatin has both time-dependent and concentration-dependent features; however, 5-FU exerts a time-dependent antitumour effect with continuous infusion [26]. In 2010, Nagamatsu *et al*. reported on the efficacy of HAIC using cisplatin suspended in lipiodol and 5-FU in 51 HCC patients with portal vein tumour thrombus [14], achieving a very high response rate of 86.3% and long median OS of 33 months. Based on these promising results, we modified their HAIC regimen for our combination group.

A recent study investigating sorafenib combined with HAIC suggested that combining systemic therapy and regional cytotoxic chemotherapy could enhance antitumour activity. In a prospective multicentre phase II trial, a total of 108 patients with advanced HCC were randomised to treatment with sorafenib monotherapy or sorafenib plus HAIC with cisplatin. The response rate was 21.7% with sorafenib plus HAIC vs. 7.3% with sorafenib monotherapy ($p = 0.09$), and the median OS was significantly longer with sorafenib plus HAIC compared to sorafenib monotherapy (10.6 vs. 8.8 months, $p = 0.031$) [18]. In another multicentre, open-

label, randomised, phase III trial of sorafenib plus HAIC (low-dose cisplatin and 5-FU) vs. sorafenib monotherapy performed in 206 patients with advanced HCC, sorafenib plus HAIC failed to significantly improve survival (median OS was 11.8 months in both groups), but it improved OS for the subgroup of patients with portal vein involvement [19]. The response rate of 17.5% in the sorafenib arm observed in this phase III trial was higher than the observed response rates in the sorafenib arm in other studies, and OS was significantly better in patients who responded to sorafenib monotherapy than in non-responders. It is speculated that the difference in the efficacy of combining HAIC with sorafenib could be attributed to patient population differences, specifically related to sorafenib sensitivity.

It is noteworthy that we combined sorafenib with HAIC sequentially every 2–3 months, while HAIC was administered concomitantly with sorafenib every 4–6 weeks in the previous trials [18, 19]. Our results suggest that sequential HAIC can enhance antitumour activity even when delivered at relatively long intervals, while sorafenib acts as a disease stabiliser. In preclinical studies, sorafenib was shown to exert a synergistic anticancer effect with cisplatin [27], but antagonism between platinum drugs and sorafenib was also found at the cellular level [28]. Therefore, the optimal regimen for combining sorafenib and HAIC (sequential or concomitant) should be investigated further at the clinical level.

The influence of sorafenib on the prognosis partly depends on the duration of treatment [29, 30], rather than the daily dosage [31, 32]. In the present study, the duration of sorafenib treatment tended to be longer in the combination group than in the control group. In addition, although the difference was not significant, there was a lower rate of severe adverse effects related to sorafenib with combination therapy compared to sorafenib monotherapy. One possible advantage of sequential combination is that interruption of sorafenib administration during HAIC may prolong the total treatment period with this agent by reducing the risk of, or promoting recovery from, adverse effects such as hand-foot syndrome.

The present study had some limitations. First, the sample size was small. Second, this study was performed retrospectively, and selection bias could not be avoided. The IPW adjustment did not eliminate completely the between-group differences, for example with regard to the incidence of extrahepatic metastasis and BCLC stage C disease. However, these differences were not an independent prognostic factor in multivariate analysis; therefore, the difference did not significantly influence OS. Since a phase III trial [19] has already demonstrated limited value of combining sorafenib and HAIC, we should be conservative in interpreting our results. Third, the time to progression was not evaluated because this study was based on data obtained during routine clinical practice, and radiological assessment was performed at the discretion of each physician.

Conclusions

In conclusion, this study suggests that the sequential sorafenib-HAIC combination is a feasible and promising treatment option for selected patients with BCLC stage B/C HCC. Because a considerable proportion of HCC patients are unable to receive curative treatment, it is important to explore multimodal strategies for such patients. Further studies will be required to convincingly establish the efficacy of sequential combination therapy with HAIC and sorafenib.

The authors declare no conflict of interest.

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