

Article

Hepatic Arterial Infusion Chemotherapy with Cisplatin Versus Sorafenib for Intrahepatic Advanced Hepatocellular Carcinoma: A Propensity Score-Matched Analysis

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Simple Summary: Thus far, clinical studies have shown that immunotherapy (atezolizumab–bevacizumab) has shown better and favorable overall survival than sorafenib for advanced hepatocellular carcinoma (HCC). However, the treatment outcomes of hepatic arterial infusion chemotherapy (HAIC) with cisplatin in comparison with sorafenib for intrahepatic advanced HCC remain unclear. We therefore aimed to determine the prognostic factors for HAIC with cisplatin. Our results showed that HAIC with cisplatin could significantly prolong the overall survival for intrahepatic advanced HCC and had a longer prognostic effect than sorafenib, regardless of the hepatic reserve. Therefore, our results suggest that HAIC should be used in intrahepatic advanced HCC.

Abstract: Given that the outcome of hepatic arterial infusion chemotherapy (HAIC) with cisplatin for intrahepatic advanced hepatocellular carcinoma (HCC) is unclear, we aimed to compare prognostic factors for overall survival (OS) following HAIC with cisplatin versus sorafenib for intrahepatic advanced HCC using propensity score-matched analysis. We enrolled 348 patients with intrahepatic advanced HCC who received HAIC with cisplatin (n = 97) or sorafenib (n = 251) between June 2006 and March 2020. No significant difference was observed in OS between HAIC with cisplatin and sorafenib cohorts (median survival time [MST]: 13.9 vs. 12.7 months; p = 0.0989). To reduce confounding effects, 176 patients were selected using propensity score-matched analysis (n = 88 for each treatment). HAIC with cisplatin significantly prolonged OS compared with sorafenib (MST: 16.2 vs. 12.2 months; p = 0.0060). Following stratification according to the Child–Pugh classification, for both patients with class A (MST: 24.0 vs. 15.6 months; p = 0.0097) and class B (MST: 8.5 vs. 6.9 months; p = 0.0391), HAIC with cisplatin rather than sorafenib significantly prolonged OS. Our findings suggest that HAIC with cisplatin demonstrates longer prognostic effects than sorafenib in intrahepatic advanced HCC, regardless of the hepatic reserve.

Keywords: hepatocellular carcinoma; hepatic arterial infusion chemotherapy; cisplatin; sorafenib; multikinase inhibitors; risk factors; propensity score-matched analysis

1. Introduction

Liver cancer was the sixth most commonly diagnosed cancer and the fourth leading cause of cancer-related deaths worldwide in 2018, with an estimated 841,000 new cases and 782,000 deaths [1-4]. Liver cancer includes hepatocellular carcinoma (HCC) that accounts for 75%–85% of all liver cancer cases [1,2]. Early stage HCC may be curable radically via hepatic resection, radiofrequency ablation, or liver transplantation; however, patients with advanced HCC have a poor prognosis [5,6].

Hepatic arterial infusion chemotherapy (HAIC) is a treatment option for advanced HCC [7]. Theoretically, HAIC can increase the concentrations of the anticancer drug in the liver and consequently reduce the occurrence of systemic adverse events caused by the anticancer drug [8]. Recently, there has been accumulating evidence regarding the efficacy of HAIC for treating advanced HCC [9-11].

The use of molecular-targeted agents (MTAs) is another treatment option for advanced HCC [7]. MTAs such as sorafenib were approved as first-line treatment for advanced HCC based on the results of two studies, namely the Sorafenib Hepatocellular carcinoma Assessment Randomized Protocol (SHARP) study [12] and the Asia-Pacific study [13]; these studies reported superior survival outcomes with sorafenib over those with placebo. In addition, immunotherapy, which is based on the combination of atezolizumab and bevacizumab, resulted in better outcomes than sorafenib when used as the first-line treatment for advanced HCC [14].

In a randomized phase II trial, treatment with sorafenib plus HAIC with cisplatin yielded favorable overall survival (OS) compared with treatment with sorafenib alone in patients with advanced HCC [15]. However, treatment outcomes of HAIC with cisplatin versus those of sorafenib for advanced HCC remain unclear. Therefore, in this study, we aimed to determine the prognostic effects of HAIC with cisplatin and the associated OS duration compared with those of sorafenib for advanced HCC. In view of this, to reduce confounding effects, we performed propensity score-matched analysis.

2. Materials and Methods

2.1. Ethical Approval

The study was approved by the Ethics Committee of Kurume University (No. 10009) and Saga Central Hospital (No. 21002) and was conducted according to the guidelines of the 1975 Declaration of Helsinki.

2.2. Diagnosis

HCC was either confirmed histologically or diagnosed using noninvasive criteria according to the European Association for the Study of Liver [16]. Intrahepatic lesions and vascular invasion were diagnosed using a combination of imaging techniques such as contrast-enhanced computed tomography, magnetic resonance imaging, ultrasonography, and digital subtraction angiography. Additionally, serum levels of alpha-fetoprotein (AFP) and des-gamma-carboxy prothrombin (DCP) were measured for up to 1 month before treatment. The presence of intra-abdominal metastases was detected on abdominal computed tomography, magnetic resonance imaging, and ultrasonography, which were performed to evaluate intrahepatic lesions. Liver function was evaluated using both the Child–Pugh classification and albumin–bilirubin (ALBI) score [17]. Tumor stage was determined according to the Barcelona Clinic Liver Cancer (BCLC) staging classification [18,19].

2.3. Patients Receiving HAIC with Cisplatin

Since the approval of cisplatin (DDP-H, IA-Call, Nippon Kayaku, Tokyo, Japan) use for advanced HCC in Japan, we treated 98 patients for advanced HCC with HAIC and

cisplatin in Saga Central Hospital between July 2006 and March 2020. One patient with extrahepatic metastasis was excluded; therefore, we enrolled 97 consecutive patients who were diagnosed with intrahepatic advanced HCC and received HAIC with cisplatin.

After conventional visceral angiography, HAIC was administered by introducing an angiographic catheter into the proper, right, or left hepatic artery or the branched feeding artery using Seldinger's technique and not using any implanted port system for HAIC. Cisplatin was dissolved in saline solution and heated to 50°C, and it was then injected at a dose of 65 mg/m² over 20–40 min without lipiodol and gelatin sponge. Until the appearance of tumor progression and/or unacceptable toxicity, the treatment was repeated every 2–3 months for a maximum of 26 cycles. All patients had antiemetic prophylaxis with a 5-HT₃ antagonist (granisetron 1 mg) and received adequate hydration and diuretics for protection against cisplatin-induced renal dysfunction.

2.4. Patients Receiving Sorafenib

Eligibility criteria for this study were similar to those for the SHARP study [12]. Since the approval of sorafenib use for advanced HCC in Japan, we treated 553 patients for advanced HCC with sorafenib in 19 participating institutions of the Kurume Liver Cancer Study Group of Japan between May 2010 and March 2020. Among those patients, 302 patients with extrahepatic metastasis were excluded; therefore, we enrolled 251 consecutive patients who were diagnosed with intrahepatic advanced HCC and received sorafenib.

2.5. Treatment Outcome

The treatment outcome of this study was OS, which was defined as the time from the initiation of HAIC with cisplatin or sorafenib to the date of death or the patient's last follow-up.

2.6. Statistical Analysis

Baseline patient characteristics were analyzed using descriptive statistical methods: age, albumin level, total bilirubin level, ALBI score, prothrombin time, AFP, and DCP were calculated using the t-test, and sex, etiology, Child–Pugh class, macrovascular invasion, and BCLC stage were calculated using the chi-square test. Survival curves were constructed using the Kaplan–Meier analysis with the log-rank test. A p-value <0.05 was considered to indicate statistical significance. JMP software (SAS Institute, Inc., Cary, NC, USA), version 15, was used for all statistical analyses.

3. Results

3.1. Patient Characteristics

Table 1 shows the characteristics of 348 consecutive patients who were diagnosed with intrahepatic advanced HCC and received either HAIC with cisplatin (n = 97) or sorafenib (n = 251). Results are expressed as the mean ± standard deviation (SD) and the median (range) or n (%). A higher proportion of patients tested positive for the hepatitis C virus (p = 0.0050) and had Child–Pugh class B (p = 0.0012) in the HAIC with cisplatin cohort, whereas a higher proportion of patients had macrovascular invasion (p = 0.0122) and BCLC stage C (p = 0.0242) in the sorafenib cohort. The ALBI score (p = 0.0008) was higher in the HAIC with cisplatin cohort, whereas albumin levels (p = 0.0010) and prothrombin time (p < 0.0001) were higher in the sorafenib cohort. Age; sex; and total bilirubin, AFP, and DCP levels were equivalent between the HAIC with cisplatin and sorafenib cohorts.

Table 1. Patient characteristics (n = 348).

Variable	HAIC (n = 97)	Sorafenib (n = 251)	p-value
Age (years)	73.8 ± 9.3 75.7 (47.8–88.6)	72.5 ± 9.4 73.1 (35.7–94.4)	0.2255
Sex (male/female)	66 (68%)/31 (32%)	196 (78%)/55 (22%)	0.0514
Etiology (HBV/HCV/HBV+HCV/both negative)	6 (6%)/80 (83%)/0 (0%)/11 (11%)	37 (15%)/158 (63%)/3 (1%)/53 (21%)	0.0050
Child–Pugh class (A/B)	62 (64%)/35 (36%)	202 (80%)/49 (20%)	0.0012
Macrovascular invasion (yes/no)	13 (13%)/84 (87%)	65 (26%)/186 (74%)	0.0122
BCLC stage (A/B/C)	9 (9%)/71 (73%)/17 (18%)	8 (3%)/178 (71%)/65 (26%)	0.0242
Albumin (g/dL)	3.4 ± 0.5 3.5 (2.2–4.4)	3.6 ± 0.5 3.6 (2.0–4.8)	0.0010
Total bilirubin level (mg/dL)	1.0 ± 0.5 0.9 (0.3–2.7)	0.9 ± 0.5 0.9 (0.2–3.4)	0.2772
ALBI score	-2.09 ± 0.49 -2.11 (-3.02–0.83)	-2.28 ± 0.45 -2.31 (-3.28–0.95)	0.0008
Prothrombin time (%)	75.6 ± 11.3 74.5 (44.6–105.5)	84.9 ± 17.0 85.0 (16.1–130.0)	<0.0001
AFP (ng/mL)	4,379 ± 23,305 110 (2–222,500)	7,084 ± 48,566 93 (1–720,500)	0.5997
DCP (mAU/mL)	8,138 ± 37,087 264 (6–344,000)	9,700 ± 30,968 518 (8–335,810)	0.6911

Abbreviations; HAIC = hepatic arterial infusion chemotherapy, HBV = hepatitis B virus, HCV = hepatitis C virus, BCLC = Barcelona Clinic Liver Cancer, ALBI = albumin–bilirubin, AFP = alpha-fetoprotein, DCP = Des-gamma-carboxy prothrombin.

Results are expressed as mean ± standard deviation and median (range) or n (%).

3.2. Survival Outcomes

Figure 1 shows the results of the Kaplan–Meier analysis of OS with the log-rank test between the HAIC with cisplatin and sorafenib cohorts. The median survival time (MST) was 13.9 months in the HAIC with cisplatin cohort (blue line, n = 97) and 12.7 months in the sorafenib cohort (red line, n = 251) (p = 0.0989). The OS did not differ significantly between the HAIC with cisplatin and sorafenib cohorts.

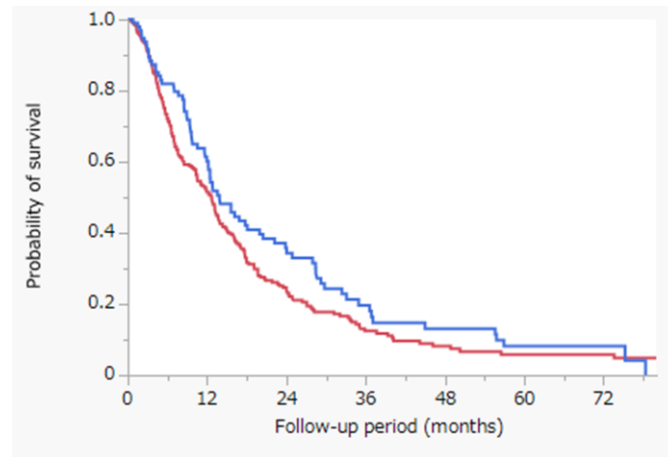


Figure 1. Kaplan–Meier analysis of OS with the log-rank test between the HAIC with cisplatin and sorafenib cohorts.

Blue line, HAIC with cisplatin cohort (n = 97), MST = 13.9 months; red line, sorafenib cohort (n = 251), MST = 12.7 months; p = 0.0989. Abbreviations: OS = overall survival, HAIC = hepatic arterial infusion chemotherapy, MST = median survival time.

3.3. Propensity Score-matched Analysis

To reduce confounding effects, we performed propensity score-matched analysis to match patients treated with HAIC with cisplatin (n = 97) with those treated with sorafenib (n = 251) [20,21]. The following 12 variables related to the prognosis of advanced HCC were considered at the start of the follow-up: age, sex, etiology, Child–Pugh class, macrovascular invasion, BCLC stage, albumin level, total bilirubin level, ALBI score, prothrombin time, AFP, and DCP. The propensity scores (mean \pm SD) of the patients treated with HAIC with cisplatin and sorafenib were 0.8259 ± 5.4288 and -4.4842 ± 8.3682 , respectively. We used these propensity scores to conduct one-to-one nearest neighbor matching within a caliper of 0.20, as previous studies have shown this SD percentage of the logit of the propensity score to be generally suitable as a caliper for propensity score-matched analysis [22]. Based on the results of propensity score-matched analysis, 176 patients were selected (HAIC with cisplatin, n = 88; sorafenib, n = 88). Following propensity score-matched analysis, the propensity scores (mean \pm SD) of the patients treated with HAIC with cisplatin and sorafenib were -0.3910 ± 0.8537 and -0.5052 ± 0.7904 , respectively.

3.4. Characteristics of Patients Diagnosed with HCC Following Propensity Score-matched Analysis

Table 2 shows the characteristics of 176 patients who were diagnosed with intrahepatic advanced HCC and received HAIC with cisplatin (n = 88) or sorafenib (n = 88) following propensity score-matched analysis. No significant differences were observed for any variables between the HAIC with cisplatin and sorafenib cohorts using propensity score-matched analysis.

Table 2. Patient characteristics following propensity score-matched analysis (n = 176).

Variable	HAIC (n = 88)	Sorafenib (n = 88)	p-value
Age (years)	73.8 ± 9.5 75.2 (47.8–88.6)	73.9 ± 9.5 73.6 (35.7–91.6)	0.9654
Sex (male/female)	59 (67%)/29 (33%)	60 (68%)/28 (32%)	0.8720
Etiology (HBV/HCV/HBV+HCV/both negative)	6 (7%)/72 (82%)/0 (0%)/10 (11%)	6 (7%)/73 (83%)/0 (0%)/9 (10%)	0.9707
Child–Pugh class (A/B)	58 (66%)/30 (34%)	62 (70%)/26 (30%)	0.5174
Macrovascular invasion (yes/no)	10 (11%)/78 (89%)	12 (14%)/76 (86%)	0.6485
BCLC stage (A/B/C)	8 (9%)/70 (80%)/10 (11%)	4 (4%)/72 (82%)/12 (14%)	0.4622
Albumin level (g/dL)	3.4 ± 0.5 3.5 (2.2–4.4)	3.5 ± 0.5 3.5 (2.0–4.4)	0.4460
Total bilirubin (mg/dL)	1.0 ± 0.5 0.9 (0.3–2.7)	1.0 ± 0.4 0.9 (0.3–2.9)	0.5631
ALBI score	-2.12 ± 0.49 -2.15 (-3.02–-0.83)	-2.18 ± 0.47 -2.25 (-3.25–-0.95)	0.3859
Prothrombin time (%)	76.0 ± 10.5 74.8 (44.6–100.7)	76.4 ± 12.4 77.8 (39.0–108.0)	0.8179
AFP (ng/mL)	4,286 ± 24,311 90 (2–222,500)	6,557 ± 27,112 105 (3–183,385)	0.5592
DCP (mAU/mL)	8,026 ± 38,630 275 (6–344,000)	7,177 ± 19,756 503 (11–112,000)	0.8545

Abbreviations; HAIC = hepatic arterial infusion chemotherapy, HBV = hepatitis B virus, HCV = hepatitis C virus, BCLC = Barcelona Clinic Liver Cancer, ALBI = albumin–bilirubin, AFP = alpha-fetoprotein, DCP = Des-gamma-carboxy prothrombin.

Results are expressed as mean ± standard deviation and median (range) or n (%).

3.5. Survival Outcomes Following Propensity Score-matched Analysis

Figure 2 shows the results of the Kaplan–Meier analysis of OS with the log-rank test between the HAIC with cisplatin and sorafenib cohorts following propensity score-matched analysis. The MST was 16.2 months in the HAIC with cisplatin cohort (blue line, n = 88) and 12.2 months in the sorafenib cohort (red line, n = 88) (p = 0.0060). The HAIC with cisplatin cohort demonstrated significantly better outcomes with regard to OS than the sorafenib cohort.

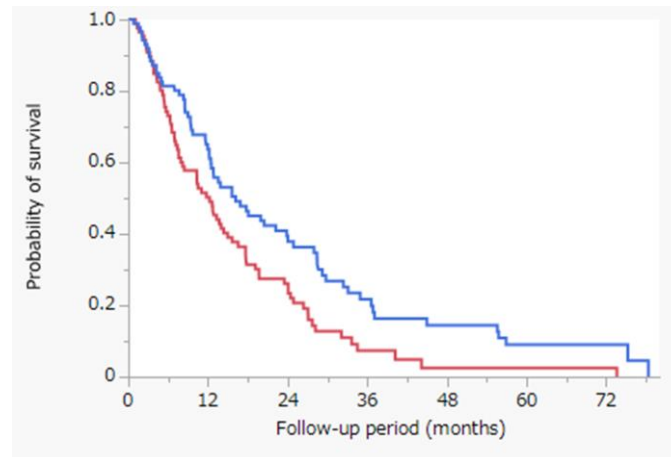


Figure 2. Kaplan–Meier analysis of OS with the log-rank test between the HAIC with cisplatin and sorafenib cohorts following propensity score-matched analysis.

Blue line, HAIC with cisplatin cohort (n = 88), MST = 16.2 months; Red line, sorafenib cohort (n = 88), MST = 12.2 months; p = 0.0060. Abbreviations: OS = overall survival, HAIC = hepatic arterial infusion chemotherapy, MST = median survival time.

3.6. Survival Outcomes per Child–Pugh Class Following Propensity Score-matched Analysis

Figure 3 shows the results of the Kaplan–Meier analysis of OS with the log-rank test between the HAIC with cisplatin and sorafenib cohorts per Child–Pugh class following propensity score-matched analysis. For patients with Child–Pugh class A, the MST was 24.0 months in the HAIC with cisplatin cohort (red line, n = 58) and 15.6 months in the sorafenib cohort (green line, n = 62) (p = 0.0097). For patients with Child–Pugh class B, the MST was 8.5 months in the HAIC with cisplatin cohort (blue line n = 30) and 6.9 months in the sorafenib cohort (brown line, n = 26) (p = 0.0391). The HAIC with cisplatin cohort exhibited significantly better outcomes with regard to OS than the sorafenib cohort.

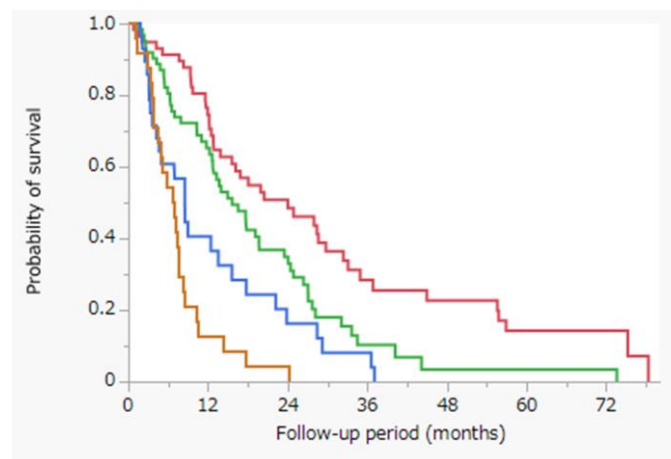


Figure 3. Kaplan–Meier analysis of the OS with the log-rank test between the HAIC with cisplatin and sorafenib cohorts per Child–Pugh class following propensity score-matched analysis.

Red line, HAIC with cisplatin cohort having Child–Pugh class A (n = 58), MST = 24.0 months; Green line, sorafenib cohort having Child–Pugh class A (n = 62), MST = 15.6 months; p = 0.0097. Blue line, HAIC with cisplatin cohort having Child–Pugh class B (n = 30), MST = 8.5 months; Brown line, sorafenib cohort having Child–Pugh class B (n = 26), MST = 6.9 months; p = 0.0391. Abbreviations: OS = overall survival, HAIC = hepatic arterial infusion chemotherapy, MST = median survival time.

3.7. Univariate and Multivariate Analyses of OS in the HAIC with Cisplatin Cohort

Table 3 shows the results of univariate and multivariate analyses of OS in the HAIC with cisplatin cohort. Univariate analyses of OS revealed five variables as prognostic factors: Child–Pugh class ($p < 0.0001$), macrovascular invasion ($p < 0.0001$), BCLC stage ($p < 0.0001$), ALBI score ($p = 0.0195$), and AFP ($p = 0.0117$). Multivariate analyses of OS identified two variables as independent prognostic factors: Child–Pugh class ($p = 0.0108$) and AFP ($p = 0.0155$).

Table 3. Results of univariate and multivariate analyses of OS in the HAIC with cisplatin cohort ($n = 97$).

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (≥ 75.7 years)	0.827 (0.523–1.307)	0.4165		
Sex (male)	0.964 (0.593–1.566)	0.8815		
Etiology (HCV)	1.129 (0.607–2.099)	0.7006		
Child–Pugh class (B)	2.729 (1.687–4.416)	<0.0001	2.532 (1.239–5.173)	0.0108
Macrovascular invasion (Yes)	4.233 (2.189–8.185)	<0.0001	1.866 (0.565–6.158)	0.3061
BCLC stage (C)	3.922 (2.135–7.203)	<0.0001	2.128 (0.728–6.218)	0.1673
ALBI score (≥ -2.11)	1.725 (1.092–2.726)	0.0195	0.900 (0.457–1.772)	0.7596
AFP (≥ 110 ng/mL)	1.814 (1.141–2.883)	0.0117	1.816 (1.120–2.944)	0.0155
DCP (≥ 264 mAU/mL)	1.560 (0.976–2.493)	0.0632		

Abbreviations: OS = overall survival, HAIC = hepatic arterial infusion chemotherapy, HR = hazard ratio, CI = confidence interval, HCV = hepatitis C virus, BCLC = Barcelona Clinic Liver Cancer, ALBI = albumin–bilirubin, AFP = alpha-fetoprotein, DCP = des-gamma-carboxy prothrombin.

4. Discussion

In this study, we assessed the OS of patients with intrahepatic advanced HCC between the HAIC with cisplatin and sorafenib cohorts. The results showed that the OS did not differ significantly between the HAIC with cisplatin and sorafenib cohorts for intrahepatic advanced HCC among the enrolled patients (Figure 1). However, in the HAIC with cisplatin cohort, tumor factors were significantly better, whereas in the sorafenib cohort, the hepatic reserve factor was significantly better (Table 1). To reduce confounding effects, we performed propensity score-matched analysis to match patients treated with HAIC with cisplatin with those treated with sorafenib (Table 2). HAIC with cisplatin resulted in significantly better outcomes with regard to OS than sorafenib following propensity score-matched analysis (Figure 2). Our results suggest that HAIC should be used rather than sorafenib for intrahepatic advanced HCC without extrahepatic metastasis.

There are several treatment strategies for advanced HCC, such as transarterial chemoembolization (TACE), HAIC, and systemic therapy. There has been consensus for managing advanced HCC with extrahepatic metastasis, i.e., systemic therapy (MTAs or

immunotherapy, such as the combination of atezolizumab and bevacizumab) should be used [14]. In contrast, for managing intrahepatic advanced HCC without extrahepatic metastasis, the optimal choice remains controversial.

Fundamentally, the indication for administering sorafenib for managing advanced HCC is only Child–Pugh class A [12]. Therefore, we stratified patients according to their Child–Pugh class following propensity score-matched analysis. Following stratification according to Child–Pugh class, for both class A and B patients, HAIC with cisplatin showed significantly better outcomes with regard to OS than sorafenib (Figure 3). Our results suggest that HAIC should be used for treating intrahepatic advanced HCC without extrahepatic metastasis regardless of the hepatic reserve. Particularly, for patients with Child–Pugh class B, sorafenib is not indicated for this condition; therefore, there is no treatment option except for HAIC in patients with Child-Pugh class B.

Moreover, using univariate and multivariate analyses, we assessed prognostic factors for intrahepatic advanced HCC managed with HAIC with cisplatin in all enrolled patients. Multivariate analyses of OS revealed two variables as independent prognostic factors: Child–Pugh class and AFP (Table 3). It is well known that the hepatic reserve factor and tumor factor contribute to OS of patients with HCC, which is consistent with the finding observed in the present study. [23-25]

For managing intrahepatic advanced HCC, TACE or HAIC has been widely used for obtaining a higher antitumor effect as they evenly distribute the anticancer drug through the hepatic artery [26]. However, TACE involves inserting a microcatheter selectively into the tumor feeding artery; this requires high-level skills and adequate treatment time. In HAIC with the reservoir system, to place an implantable port system, it is necessary to place a catheter in the appropriate position and embolize the blood vessels with a coil so that the anticancer drug is delivered only to HCC; this also requires high-level skills and adequate treatment time [27]. In this study, we administered HAIC with cisplatin only by introducing the angiographic catheter into the proper, right, or left hepatic artery or the branched feeding artery using Seldinger's technique and then injecting the anticancer drug. The HAIC with cisplatin method is more convenient than TACE or HAIC with the reservoir system. In this study, only some patients were able to continue HAIC for up to 26 cycles. One reason for this was the occurrence of few adverse events, which made it impossible to continue HAIC. However, despite this finding, our results suggest that HAIC has advantages of being simple to use and resulting in only few adverse events [28].

Two randomized controlled trials (RCTs) have verified the additional effect of HAIC over sorafenib for managing advanced HCC [29,30]. One study described that the addition of HAIC to sorafenib did not significantly improve OS of patients with advanced HCC [29], whereas another study described that sorafenib plus HAIC improved OS compared with sorafenib alone in patients with HCC and portal vein invasion [30]. However, several non-RCTs have revealed that HAIC improved OS compared with sorafenib in patients with advanced HCC [31-33]. Therefore, RCTs comparing HAIC and sorafenib in patients with advanced HCC should be conducted.

Our current study had some limitations. First, regarding the HAIC with cisplatin cohort, our study had a single-center retrospective design with a relatively small sample size ($n = 97$) for intrahepatic advanced HCC. Second, the treatment (HAIC with cisplatin or sorafenib) was selected at the discretion of the chief physician, and patients were not randomized after receiving approval for sorafenib use. This resulted in a selection bias for advanced HCC patients. Third, the therapeutic effects and adverse events in all cases could not be evaluated. Fourth, no further investigations have been conducted after the secondary treatment. Therefore, a multicenter prospective study with a larger patient population should be conducted in the future.

5. Conclusions

HAIC demonstrated significantly better outcomes with regard to OS than sorafenib following propensity score-matched analysis. Our results suggest that HAIC should be used rather than sorafenib in intrahepatic advanced HCC cases without extrahepatic metastasis regardless of the hepatic reserve.

Author Contributions: Conceptualization, data curation, formal analysis, writing—original draft, writing—review & editing, Y.Z., M.Nakano.; data curation, K.F., Y.Y., K.T., T.N., K.K., M.F., T.Sakae., S.Y., M.Nakazaki., R.K., S.O., H.I., S.S., T.Shirono., Y.N., N.K.; supervision, H.K., T.T. All authors have read and agreed to the published version of the manuscript.

Funding: Not applicable

Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of KURUME UNIVERSITY (No. 10009 and approved on 20 May 2010) and SAGA CENTRAL HOSPITAL (No. 21002 and approved on 21 June 2021).

Informed Consent Statement: Informed consent was obtained from all patients regarding treatment. However, the consent regarding the study was waived because of the retrospective study design.

Data Availability Statement: The data that support the findings of this study are available from the corresponding author, M.Nakano, on reasonable request.

Acknowledgments: The authors thank the staff of the Kurume Liver Cancer Study Group of Japan; Asakura Medical Association Hospital, Chikugo City Hospital, Iwamoto Clinic, Kurume Central Hospital, Kurume General Hospital, Kurume University Hospital, Kurume University Medical Center, Kyushu Medical Center, Nagata Hospital, Ōmuta City Hospital, Saga Central Hospital, Saiseikai Futsukaichi Hospital, Saiseikai Ōmuta Hospital, Social Insurance Tagawa Hospital, St. Mary's Hospital, Tobata Kyoritsu Hospital, Yame General Hospital, Yanagawa Hospital, and Yokokura Hospital, for their valuable support, and we also thank Editage (www.editage.jp) for English language editing.

Conflicts of Interest: The authors declare no conflict of interest.

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