Revisiting Hepatic Artery Infusion Chemotherapy

Subjects: Oncology
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Hepatic artery infusion chemotherapy (HAIC) is a well-established and common treatment for advanced hepatocellular carcinoma (HCC), particularly in East Asia. However, HAIC is not recognized internationally. Although several trials have demonstrated the safety and efficacy of HAIC, evidence corroborating its overall survival (OS) benefits compared with standard treatments is insufficient. Nevertheless, HAIC may provide prominent benefits in selected patients such as patients with portal vein thrombosis or high intrahepatic tumor burden. Moreover, HAIC has been combined with several therapeutic agents and modalities, including interferon-alpha, multikinase inhibitors, radiation therapy, and immunotherapy, to augment its treatment efficacy. Most of these combinations appeared to increase overall response rates compared with HAIC alone, but results regarding OS are inconclusive. Two prospective randomized controlled trials comparing HAIC plus sorafenib with sorafenib alone have reported conflicting results, necessitating further research. As immunotherapy-based combinations became the mainstream treatments for advanced HCC, HAIC plus immunotherapy-based treatments also showed encouraging preliminary results. The trials of HAIC were heterogeneous in terms of patient selection, chemotherapy regimens and doses, HAIC combination agent selections, and HAIC technical protocols. These heterogeneities may contribute to differences in treatment efficacy, thus increasing the difficulty of interpreting trial results.

hepatocellular carcinoma | intra-arterial chemotherapy | targeted therapy | immunotherapy

1. Introduction

Hepatic artery infusion chemotherapy (HAIC) is a treatment modality for advanced hepatocellular carcinoma (HCC). HAIC entails infusing chemotherapeutic agents directly into hepatic tumors through the percutaneous catheterization of feeding arteries. Because HCC tumors are primarily supplied by the hepatic arteries, HAIC provides a higher intratumoral concentration of chemotherapeutic agents and avoids the first-pass effect, theoretically yielding greater treatment efficacy and less hepatocellular injury [1]. These chemotherapeutic agents subsequently went through the body by circulation and also offered systemic anti-tumor effect but with less concentration advantage. Therefore, HAIC is basically a systemic treatment with more prominent locoregional efficacy. These peculiar features make HAIC distinct from other transarterial therapeutic approaches for HCC, such as transarterial chemoembolization (TACE) and selective internal radiation therapy (SIRT), which yield locoregional efficacy only and failed to provide survival benefit for patients with advanced HCC [2][3][4]. Furthermore, TACE is considered as relative contraindicated in patients with portal vein thrombosis (PVT), since reduced blood supply in

both portal vein system and hepatic arteries may cause substantial hepatocyte injury, especially for Vp3/4 thrombosis (**Figure 1**). In contrast, HAIC can be performed safely in these patients.

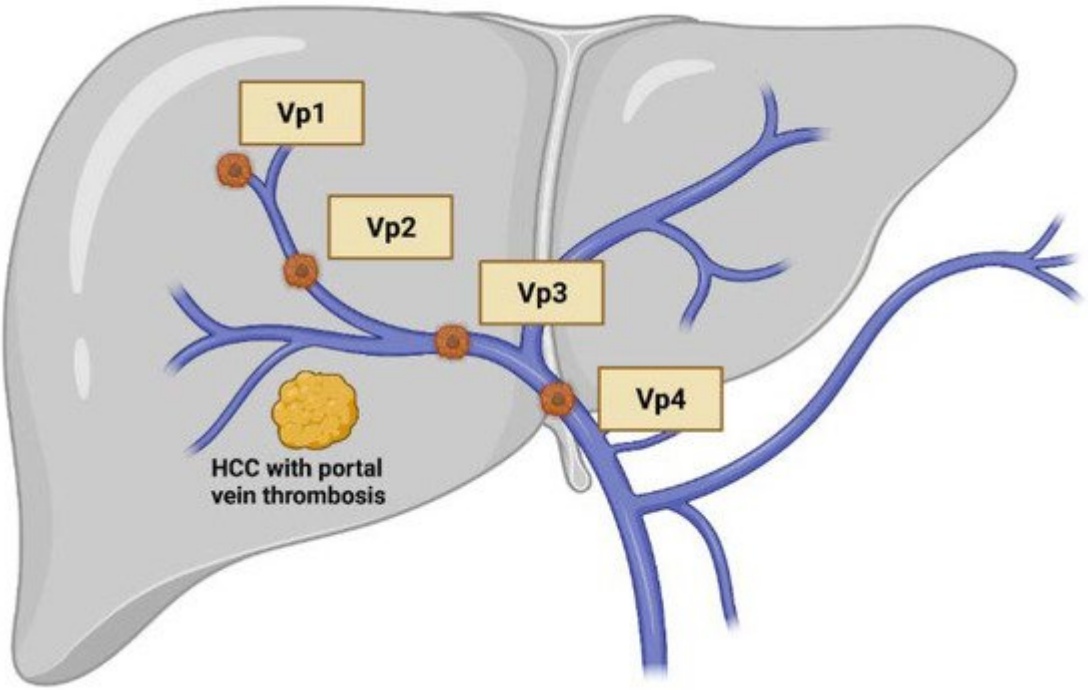

Figure 1. Classification of macrovascular invasion of hepatocellular carcinoma, including portal vein thrombosis and/or tumor invasion. Vp1: the third order branch or portal vein; Vp2: the second order branch of portal vein; Vp3: the first order branch of portal vein; Vp4: the main trunk of portal vein. Created with BioRender.com.

2. HAIC Monotherapy

HAIC has long been reported as a potential therapy for advanced HCC [5]. Before the advent of sorafenib, advanced HCC was often most effectively treated with supportive care, antiangiogenesis agents such as thalidomide [6], or chemotherapy. These treatments conferred limited objective response rates (ORR), ranging from 0% to 21%, and were associated with a risk of high rates of hematological toxicity [6][7][8][9]. By contrast, HAIC conferred higher ORRs, ranging from 5% to 71% (**Table 1**), and lower systemic toxicity [1]. A nationwide registry study in Japan compared HAIC treatment with no active treatment for patients with advanced HCC; the study revealed that HAIC was associated with improved overall survival (OS) compared with the most effective supportive care (median survival, 14.0 vs. 5.0 months; hazard ratio [HR], 0.48; $p < 0.001$) [10]. Other retrospective studies have also reported higher efficacy of HAIC compared with transcatheter arterial chemoembolization (TACE) or systemic chemotherapy for advanced HCC [11][12].

Table 1. Selected studies on HAIC versus sorafenib as the first-line treatment for advanced HCC.

Group	Study Type/Characteristics	Patient Number	Regimen	CP-B (%)	HBV (%)	PVT (%)	EHS (%)	ORR (%)	OS (Months)	*p*-Value (OS)
Song et al. [13]	Retrospective PVT	50	Cisplatin 60 mg/m^2, Day 2 5-FU 500 mg/m^2, Days 1–3 +/− Epirubicin 35 mg/m^2, Day 1 (every 3–4 weeks)	10.0	88.0	100	13.0	24.0	7.1	0.011
		60	Sorafenib	21.7	68.3	100	35.0	13.3	5.5	
Hatooka et al. [14]	Retrospective Refractory to TACE	65	Cisplatin 6 mg/m^2, Days 1–5, 8–12 5-FU 300 mg/m^2, Days 1–5, 8–12 * (every 4 weeks)	0	23.1	35.4 (Vp3–4)	0	12.0	8.0	0.021
		58	Sorafenib	0	22.4	10.3 (Vp3–4)	0	6.0	15.0	
Moriguchi et al. [15]	Retrospective Vp3–4	32	Cisplatin 10 mg/m^2, Day 1; 5-FU 250 mg/m^2, Days 1–5 (weekly for 4 weeks, then only Day 1 per week)	0	37.5	100	21.9	31.3	10.3	0.009
		14	Sorafenib	0	28.6	100	35.7	0	4.0	
Nakano et al. [16]	Retrospective With MVI, without EHS	44	Cisplatin 50 mg/m^2 in 5–10 mL lipiodol, Day 1	0	14.0	100	0	71.0	30.4	<0.001

Group	Study Type/Characteristics	Patient Number	Regimen	CP-B (%)	HBV (%)	PVT (%)	EHS (%)	ORR (%)	OS (Months)	*p*-Value (OS)
			5-FU 1500 mg/m^2 for 5 day for 2 weeks then cisplatin 25–30 mg/m^2 + 5FU 500–1000 mg/m^2 (ever 2 weeks)							
		20	Sorafenib	0	25.0	100	0	10.0	13.2	
Kodama et al. [17]	Retrospective No EHS	150	Cisplatin 6 mg/m^2, Days 1–5, 8–12 5-FU 300 mg/m^2, Days 1–5, 8–12 (every 4 weeks)	0	25.3	73.3	0	32.0	10.0	0.007
		134	Sorafenib	0	16.4	29.1	0	4.0	19.0	
Lyu et al. [18]	Retrospective HAIC for patients who refused sorafenib	180	mFOLFOX 6 (HAIC) (every 3 weeks)	0	86.7	54.4	60	29.4	14.5	<0.001
		232	Sorafenib	0	80.2	55.6	58.6	3.0	7.0	
Kondo et al. [19]	Randomized Phase 2 (CP-A to B7)	35	Cisplatin 65 mg/m^2, Day 1 (every 4–6 weeks)	11.4	8.6	60.0	28.6	14.3	10.0	0.780
		33	Sorafenib	12.1	12.1	66.7	24.2	9.1	15.2	
Ahn et al. [20]	Retrospective VP4	38	Cisplatin 60 mg/m^2, Day 1 5-FU 500	29.0	86.8	100	5.3	5.2	10	0.150

Group	Study Type/Characteristics	Patient Number	Regimen	CP-B (%)	HBV (%)	PVT (%)	EHS (%)	ORR (%)	OS (Months)	*p*-Value (OS)
			mg/m^2, Days 1–3							
		35	Sorafenib	31.0	69.0	100	46	0	6.4	
Ueshima et al. [21]	Retrospective Cohort 1 with MVI, Without EHS	270 [24]	Cisplatin + 5FU or 5-FU or cisplatin (detail of regimens were not reported)	36.9	23.0	100 [25]	0	NR	10.6	0.475
		263 [15][16][18][17][19][14][13]	Sorafenib	16.0	21.3	100	0	NR	9.1	
Zaizen et al. [22]	Retrospective Propensity score-matched	83	Cisplatin 65 mg/m^2, Day 1 (every 8–12 weeks)	36.1	7.2	14 (MVI)	0	NR	15.6	0.016
		83	Sorafenib	28.9	8.4	11(MVI)	0	NR	11.0	
Lyu et al. [23]	Randomized Phase 3	130	mFOLFOX 6 (HAIC) every 3 weeks	NR	NR [26][27][28]	NR	NR	NR	13.9	<0.001
		132	Sorafenib	NR	NR	NR	MR	NR	8.2	

HAIC to patients with macrovascular invasion (MVI), a subgroup with inferior prognosis and required prompt treatment response. Retrospective studies focusing on patients with PVT have revealed that patients receiving HAIC had a longer OS compared with those receiving sorafenib treatment [15][13]. HAIC also provided survival benefits for large HCC as shown in retrospective studies [29][30], and also in a randomized Phase 3 study comparing HAIC and TACE in large (>7 cm) intermediate HCC [31]. Adverse events of HAIC in these studies were relatively low [29][31]. At the 2021 American Society of Clinical Oncology conference, Lyu et al. presented the results of FOHAIC trial comparing first-line HAIC with sorafenib in advanced HCC mainly with MVI and high tumor burden; they reported, for the first time in a prospective Phase 3 study, that HAIC could lead to a longer OS than sorafenib could (median survival, 13.9 vs. 8.2 months, $p < 0.001$) [23]. These study results support the efficacy of HAIC in patients with MVI or with large intrahepatic tumor burden.

aHCC: advanced hepatocellular carcinoma; CP: Child–Pugh classification; EHS: extrahepatic spread; HAIC: hepatic arterial infusion chemotherapy; HBV: hepatitis B virus; IFN-α: interferon alpha; MVI: macrovascular invasion; NR: not reported; ORR: overall response rate; OS: overall survival; PVT: portal vein thrombosis; TACE: transcatheter arterial chemoembolization; VP3: right/left portal vein; VP4: main portal vein; 5-FU: 5-fluorouracil. * 57% patients received 5-FU plus IFNα.

Another area for HAIC monotherapy is in patients with poor liver function reserve, such as those with Child–Pugh (CP) Class B or C cirrhosis [32]. For such patients, systemic treatment choice is still very limited because most therapeutic modalities for advanced HCC were developed for patients with adequate liver function. The CP-B cohort in the CheckMate-040 trial [33] exhibited an attenuated ORR (10%) for nivolumab monotherapy, which was only half that observed for the CP-A cohort. Two retrospective studies have revealed survival benefits of HAIC over sorafenib treatment for CP-A and selected CP-B group [19][21], although such benefits were not consistently observed in other retrospective studies [13][20]. Terashima et al. [34] published a notable retrospective study of

patients receiving sorafenib or HAIC and discovered that more patients receiving HAIC exhibited sustained or improved liver function after four weeks of treatment compared with patients receiving sorafenib (72% vs. 50%, p = 0.006). This result further indicates that HAIC may minimize injury to normal hepatocytes and possibly improves liver function by reducing tumor burden. Correspondingly, Liu et al. [35] reported a patient of advanced HCC with CP-C who received HAIC treatment. The patient had a good partial response and his liver function reserve also improved to CP-A gradually. Therefore, HAIC may be considered as a potential first-line treatment for patients withpoor liver function reserve.

3. HAIC-Based Combination Therapy

The following characteristics of HAIC render it a suitable candidate for combination with other antineoplastic agents for advanced HCC: it is associated with fewer systemic adverse events compared with intravenous chemotherapy, and its cytotoxic mechanism is distinct from those of other HCC therapeutic modalities. Several studies have explored potential HAIC-based combination strategies (**Table 2**).

Table 2. Selected studies on HAIC combinations as first-line treatment for advanced HCC.

Group	Study Design	Patient Number (N)	Regimen	CP-B (%)	HBV (%)	PVT (%)	EHS (%)	ORR (%)	OS (Months)	*p*-Value (OS)
INF-α										
Sakon et al. [36]	Phase 2 single arm VP3–4, no EHS	11	5-FU 450–500 mg/m^2, Days 1–5 INF-α5MU qW1,3,5	54.5	36.4	100	0	72.7	8.0	
Eun et al. [37]	Retrospective single arm	31	HAIC: 5-FU 750 mg/m^2, cisplatin 25 mg/m^2, Days 1–4 INF-α 3MU Days 1–4, then QOD	19.4	83.9	100	NR	19.4	4.0	0.353
		21	HAIC alone: 5-FU 750 mg/m^2, cisplatin 25 mg/m^2, Days 1–4	19.0	85.7	100	NR	42.9	7.0	
Sorafenib										

Group	Study Design	Patient Number (N)	Regimen	CP-B (%)	HBV (%)	PVT (%)	EHS (%)	ORR (%)	OS (Months)	*p*-Value (OS)
Ikeda et al. [38]	Randomized Phase 2 CPS-A, B7	65	Cisplatin 65 mg/m^2, Day 1 Every 4–6 weeks plus sorafenib	12.3	33.8	61.5	29.2	21.7	10.8	0.031
		41	Sorafenib	4.9	22.0	41.5	31.7	7.3	8.7	
Kudo et al. [39]	Phase 3 CPS-A, B7	102	Cisplatin 20 mg/m^2, Day 1, 8 5-FU 330 mg/m^2 Days 1–5, 8–12 (every 4 weeks) Plus sorafenib	11.7	25.5	56.9	26.5	36.0 (mRECIST)	11.8	0.995
		103	Sorafenib	9.7	21.4	62.1	25.2	18.0 (mRECIST)	11.5	
Zhao et al. [40]	Retrospective CPS-A	46	Oxaliplatin 85 mg/m^2, Day 1 (every 3 weeks) Plus sorafenib	0	84.8	89.1 (VP3–4)	19.6	34.8	9.4	<0.01
		58	Sorafenib	0	89.7	84.5	27.6	1.7	4.8	
He et al. [41]	Phase 3 PVT CPS-A	125	mFOLFOX 6, Days 1–3 (every 3 weeks) Plus sorafenib	0	80.0	100	30.4	40.8	13.4	<0.01
		122	Sorafenib	0	81.1	100	34.4	2.5	7.1	
Lenvatinib										
Mai et al. [42]	Retrospective Single arm	24	mFOLFOX 6, Days 1–3 (every 3	16.7	10.3	NR	NR	58.3	12 m OS 75%	

Group	Study Design	Patient Number (N)	Regimen	CP-B (%)	HBV (%)	PVT (%)	EHS (%)	ORR (%)	OS (Months)	*p*-Value (OS)
			weeks) plus lenvatinib							
IO-based										
Gu et al. [43]	Retrospective Single arm	6	mFOLFOX 6, Days 1–3 (every 3 weeks) Apatinib 250 mg QD (since D8) Toripalimab 240 mg D4,	0	NR	100	33.3	100	NR	
He et al. [44]	Retrospective	71	mFOLFOX 6, Days 1–3 Lenvatinib Toripalimab 240 mg per session	0	87.3	77.5	22.5	59.2	NR	<0.001
		86	Lenvatinib	0	90.7	72.1	29.1	9.3	11	
RT										
Han et al. [45]	Prospective Single arm PVT	40	5-FU 500 mg/m^2, Days 1–3 cisplatin 60 mg/m^2, Day 2 plus RT	0	92.5	100	NR	45	13.1	
Katamura et al. [46]	Retrospective PVT	16	5-FU 500 mg/m^2, Days 1–5 plus RT	25.0	25.0	100	37.5	75.0	7.5	0.871
		16	5-FU 500 mg/m^2, Days 1–5	18.8	31.3	100	25.0	25.0	7.9	
Fujino et al. [47]	Retrospective PVT, VP3–4 No EHS	41	cisplatin 20 mg/m^2, Day 1, 8 5-FU 330 mg/m^2	19.5	26.5	100	0	56.1	12.1	0.309

Group	Study Design	Patient Number (N)	Regimen	CP-B (%)	HBV (%)	PVT (%)	EHS (%)	ORR (%)	OS (Months)	*p*-Value (OS)
		[36][50][51]	Days 1–5, 8–12 INF-α: recombinant 3MU or natural 5MU plus RT			[49]		[37]		
		42	HAIC plus INF-α as above	23.8	23.8	100	0	33.3	7.2	
Kodama et al. [48]	Retrospective PVT and CPS-A, B7	68	Cisplatin 20 mg/m^2, day 1, 8 5-FU 330 mg/m^2, Days 1–5, 8–12 (5-FU only in cycle 1–2) plus RT	20.6	29.4	100	19.1	[38] 27.8	9.9	0.02
		40	Sorafenib	12.5	42.5	100	40.0	6.7	5.3	[41]

aHCC: advanced hepatocellular carcinoma; CPS: Child–Pugh score; EHS: extrahepatic spread; HAIC: hepatic arterial infusion chemotherapy; HBV: hepatitis B virus; INF-α: interferon-alpha; MVI: macrovascular invasion; mRECIST: modified response evaluation criteria in solid tumors; NR: not reported; ORR: overall response rate; OS: overall survival; PVT: portal vein thrombosis; qW1,3,5: on Monday, Wednesday, Friday every week; QD: every day; QOD: every other day; TACE: transcatheter arterial chemoembolization; VP3: right/left portal vein; VP4: main portal vein; 5-FU: 5-fluorouracil.

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results showed that patients treated with the combination therapy exhibited more favorable outcomes, including higher ORRs and longer OS periods (median survival, 13.4 vs. 7.1 months; HR 0.35; $p < 0.01$). Although these two studies have reported opposite results regarding the effects of first-line HAIC combination, they differed in several aspects. First, they enrolled different patients: all patients enrolled in the study by He et al. had PVT, whereas only 63.2% of those in the study by Kudo et al. had PVT. Hepatitis B virus–related HCC was less prevalent in the study by Kudo et al. (23.4%) than in the study by He et al. (80%). Second, He et al. administered an oxaliplatin-based regimen, modified FOLFOX6, every 3 weeks, which is also a common intravenous chemotherapy regimen for advanced HCC in China; by contrast, the regimen in the SILIUS trial was cisplatin plus 5-fluorouracil (5-FU) every 4 weeks. Because of inherent differences between oxaliplatin and cisplatin, the use of these two platinum-based chemotherapeutic modalities may result in different synergistic effects with sorafenib [52]. Third, He et al. used repeated intra-arterial catheterization, which allows for the adjustment of the microcatheter tip position and the re-embolization of newly developed gastroduodenal collateral arteries. These differences may contribute to the different OS results in these two trials. In summary, HAIC combined with sorafenib could provide favorable ORR and may provide OS benefits. Further research should be conducted to explore the optimal chemotherapeutic agents, protocol procedures, and target patient populations.

Data regarding the combination of HAIC with lenvatinib are limited. A retrospective study of 24 patients treated with HAIC plus standard-dose lenvatinib reported an encouraging ORR of 58% and a disease control rate of 79% [42]. Additional prospective studies of the combination of HAIC and lenvatinib are ongoing.

3.3. HAIC Plus Radiation Therapy

HAIC combined with radiation therapy (RT) has also been extensively investigated, particularly in subgroups of patients with PVT. Han et al. [45] conducted a small-scale single-arm pilot study of three-dimensional conformal RT followed by HAIC for HCC; they observed an ORR of 45% with manageable adverse events. Investigators from Hiroshima University, Japan, have published a series of retrospective studies comparing HAIC plus RT with HAIC alone, focusing on patients with PVT. Their results revealed impressive ORRs in the HAIC-RT combination arm, but no significant survival benefits were observed [46][47]. Furthermore, Kodama et al. [48] retrospectively reviewed the effects of HAIC plus RT compared with treatment with sorafenib in patients with major PVT (Vp3/4) by using case–control matching analysis. The HAIC-RT combination group demonstrated more favorable clinical outcomes, including OS (median survival, 9.9 vs. 5.3 months, $p = 0.002$) and progression-free survival (median survival, 3.9 vs. 2.1 months, $p = 0.048$). The findings of these studies indicate that HAIC plus RT may yield favorable ORRs and survival benefits; nevertheless, evidence from prospective randomized controlled studies is still unavailable.

3.4. HAIC Plus Immunotherapy

Immune checkpoint inhibitor–based combinations have changed the treatment paradigm for advanced HCC [53][54] and are likely to remain the cornerstone of systemic treatment in the next few years. The IMbrave150 trial compared treatment with atezolizumab plus bevacizumab and treatment with sorafenib; they reported an impressive ORR of 30% and an unprecedented OS benefit for the combination treatment over sorafenib (median survival, 19.2 vs. 13.4 months, HR 0.66) [54][55]. Several ongoing Phase 3 trials testing immune checkpoint inhibitors in combinations with other immuno-oncology agents or multikinase inhibitors (MKIs) are ongoing.

Chemotherapeutic modalities have been proved to be synergistic with anti-PD1/PD-L1 antibodies in several cancers, such as those of the lung and breast [56][57]. HAIC may also induce substantial local immune modulation in the intrahepatic tumor microenvironment of HCC. Whether HAIC plus PD1/PD-L1 blockade would have synergistic effects warrants further investigations. Preliminary results of early phase trials of PD-1 blockade plus MKIs have been promising [53], and investigations of triplet therapy, namely anti-PD-1, MKIs, and HAIC, are ongoing. Gu et al. [43] reported a single-center experience for six patients who received HAIC combined with apatinib and toripalimab as the first-line treatment for advanced HCC. All six patients responded to treatment (ORR, 100%), and three of the patients (50%) exhibited complete responses. He et al. [44] presented a retrospective study in which 71 patients underwent treatment involving a combination of HAIC, lenvatinib, and toripalimab; they reported a high ORR (59%) after treatment. These encouraging results support further research on HAIC combined with other immune-based therapeutic agents.

In summary, many studies have shown positive signs for HAIC combination treatments. In particular, for patients with major PVT, HAIC plus sorafenib provided a longer OS [39][41]. Regarding the combination of HAIC with other therapeutic modalities, HAIC plus RT or PD-1/PD-L1 blockade also demonstrated promising results [43][44][46][47][48]. It's believed that these HAIC-based combination treatments will become the dominant trend in clinical practice and clinical trials.

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