



Arterial chemotherapy for hepatocellular carcinoma in China: consensus recommendations

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Abstract

Hepatocellular carcinoma (HCC) is one of the most common malignancies and the third leading cause of cancer-related deaths globally. Hepatic arterial infusion chemotherapy (HAIC) treatment is widely accepted as one of the alternative therapeutic modalities for HCC owing to its local control effect and low systemic toxicity. Nevertheless, although accumulating high-quality evidence has displayed the superior survival advantages of HAIC of oxaliplatin, fluorouracil, and leucovorin (HAIC-FOLFOX) compared with standard first-line treatment in different scenarios, the lack of standardization for HAIC procedure and remained controversy limited the proper and safe performance of HAIC treatment in HCC. Therefore, an expert consensus conference was held on March 2023 in Guangzhou, China to review current practices regarding HAIC treatment in patients with HCC and develop widely accepted statements and recommendations. In this article, the latest evidence of HAIC was systematically summarized and the final 22 expert recommendations were proposed, which incorporate the assessment of candidates for HAIC treatment, procedural technique details, therapeutic outcomes, the HAIC-related complications and corresponding treatments, and therapeutic scheme management.

Keywords Hepatocellular carcinoma · Hepatic arterial infusion chemotherapy · Consensus · FOLFOX

Abbreviations

AEs	Adverse events	HCC	Hepatocellular carcinoma
AFP	Alpha-fetoprotein	ICIs	Immune checkpoint inhibitors
BTC	Betacellulin	MTAs	Molecular targeting agents
CCL28	C–C motif chemokine ligand 28	MVI	Macrovascular invasion
c-TACE	Conventional TACE	OS	Overall survival
CTLA-4	Cytotoxic T lymphocyte-associated antigen 4	PDGFR	Platelet-derived growth factor receptor
DCR	Disease control rate	PD-L1	Programmed cell death 1
DEB-TACE	Drug-eluting bead TACE	PVTT	Portal vein tumor thrombosis
EHS	Extrahepatic spread	RCTs	Randomized controlled trials
FOLFOX	The combined chemotherapeutic regimen of oxaliplatin, leucovorin, and fluorouracil	TACE	Transarterial chemoembolization
GRADE	The grading of recommendations assessment, development, and evaluation system	TARE	Transarterial radioembolization
HAIC	Hepatic arterial infusion chemotherapy	TRAE	Treatment-related adverse events
HBV	Hepatitis B virus	TKIs	Tyrosine kinase inhibitors
		VEGFR	Vascular endothelial growth factor receptor

Extended author information available on the last page of the article

Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies and the third leading cause of cancer-related deaths worldwide [1]. More than half of HCC is at an advanced stage when initially diagnosed. China accounts for more than 50% of newly diagnosed cases and related deaths annually, and most of the cases are diagnosed with intermediate or advanced stage due to the insidious onset [2].

Since the global SHARP study reported that sorafenib could modestly prolong the survival period of patients with median overall survival (OS) of 10.7 months in 2008, it was approved as the first tyrosine kinase inhibitors (TKIs) for treating advanced HCC [3]. However, a parallel phase 3 study revealed a low response and limited survival advantage with a median OS of 6.5 months in patients in the Asia Pacific region, where hepatitis B virus (HBV) infection is the predominant etiological factor [4]. Another TKI, lenvatinib, has received approval as a first-line systemic treatment for unresectable HCC following the findings of the global REFLECT study in 2018. The study demonstrated the non-inferiority of lenvatinib compared to sorafenib. Notably, the median OS for patients receiving lenvatinib was reported as 13.6 months, while for those treated with sorafenib, it was 12.3 months. These results provide robust evidence supporting the use of lenvatinib as an effective therapeutic option for patients with unresectable HCC [5]. With decades of development, two recent phase 3 studies (the IMbrave150 and HIMALAYA trial) demonstrated that immunotherapy of programmed cell death ligand 1 (PD-L1) checkpoint inhibitor (atezolizumab or durvalumab) combined with either anti-angiogenesis (bevacizumab) or cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) blockade (tremelimumab) are improved first-line systemic options for patients with unresectable HCC, which have shown to prolong OS compared with sorafenib [6, 7].

In Asia, especially China, the area with the highest incidence of advanced HCC, newly diagnosed mega liver masses are more commonly associated with macrovascular invasion (MVI) (62.8%) than with extrahepatic spread (EHS) [8, 9]. A recent large cohort study with consecutive populations by the Italian Liver Cancer (ITA.LI.CA) group showed that among the newly diagnosed HCC cases, the prevalence of tumor-related MVI was approximately twice than that of EHS [10]. However, in clinical trials from western countries, IMbrave150, HIMALAYA, SHARP, and Asia-Pacific SHARP, the percentage of EHS reached a range of 53%–68.7%, while MVI accounted for 25.4–38% [3, 4, 6, 7]. IMbrave150 recently proved that atezolizumab plus bevacizumab had a clinically relevant

treatment benefit versus sorafenib with a median OS of 19.2 versus 13.4 months; nevertheless, in the post hoc subgroup analysis of IMbrave150 study, the median OS for high-risk patients receiving atezolizumab plus bevacizumab was reported as 7.6 months, while for those treated with sorafenib, it was 5.5 months. Although there is a trend indicating improved OS in the experimental group (HR 0.62, 95% CI 0.39–1.00), the efficacy analyses were described without statistically analyzed *p*-values, which possibly suggested that the clinical benefit of atezolizumab plus bevacizumab in high-risk patients might potentially be limited [11, 12]. Another study, the REFLECT, excluded the population with Vp4 PVTT or intrahepatic occupation exceeding 50%, indicating that the efficacy of lenvatinib is still uncertain in patients with high hepatic tumor burden.

Additionally, among recent international phase 3 clinical trials including ORIENT-32 (Sintilimab plus a bevacizumab biosimilar (IBI305) versus sorafenib), RATIONALE-301 (tislelizumab versus sorafenib), and CARES-310 (camrelizumab plus rivoceranib versus sorafenib), the proportion of patients with MVI only reached 28%, 14.9%, and 14.7%, respectively [13–15]. So far, there are no consensus treatment guidelines for liver-confined advanced-stage HCC, especially in a population with a high liver tumor burden associated with MVI.

Hepatic arterial infusion chemotherapy (HAIC) has been performed mainly in Asia as the alternative option for patients with unresectable HCC [16–18]. HAIC is a transarterial treatment that directly delivers chemotherapeutic agents into tumor-associated hepatic arterial branches to increase local concentrations, and thus effectively reduce the tumor burden with lower systemic toxicity through a greater first-pass effect in the liver [19, 20]. HAIC has been widely adopted as an alternative treatment option by multiple Asian HCC guidelines. The Japan Society of Hepatology practice guidelines for HCC have recognized HAIC as an effective treatment for locally advanced HCC since 1995 [16, 21]. According to the Korean practice guidelines for HCC management, HAIC is recommended for patients with advanced HCC who do not have EHS and have either failed or are unsuitable for systemic therapies [18, 22–24]. Additionally, in cases where PVTT is present, HAIC has also been recommended as a preferred treatment option according to the Taiwan management consensus guideline for HCC [25, 26]. And HAIC-FOLFOX regimen (a combined chemotherapeutic regimen of oxaliplatin, leucovorin, and fluorouracil) is recommended as the alternative therapy for advanced HCC by the Chinese Society of Clinical Oncology [27]. There is increasing evidence for the adaption of HAIC treatment in the treatment algorithm of HCC patients [20, 28–32]. Recently, two phase 3 randomized controlled trials (RCTs) in China further demonstrated the solid efficacy and

tolerable safety profile of oxaliplatin-based HAIC treatment with or without sorafenib versus sorafenib alone in patients with extensively macrovascular tumor thrombosis [29, 32]. Besides, HAIC-FOLFOX combined with systemic immunologic antibodies and targeted drugs showed potentially anti-tumor activity in single-arm phase 2 studies [33, 34]. For example, a promising result with the progression-free survival (PFS) of 10.4 months was achieved by performing HAIC-FOLFOX plus lenvatinib and toripalimab in patients with high-risk advanced HCC (MVI rate: 86.1%) [33]. Considering the limited tumor response of current first-line systemic therapy and unsatisfactory survival advantage in specific patient subgroups (i.e., patients with intrahepatic high-risk factors), HAIC-FOLFOX alone or in combination with alternative therapies with different anti-tumor mechanism seems to be promising approaches for those who have limited benefits from systemic standard care, such as patients with high intrahepatic tumor burden or PVTT [17].

Nevertheless, HAIC has not been applied as a recommended treatment option worldwide. One of the main reasons is the lack of a unified technical standard for HAIC procedure. This considerable ambiguity may lead to a wide range of practice pattern variations for HCC and the heterogeneity of efficacy. Therefore, there is an urgent need for relevant guidelines/consensus as a reference to ensure the standardization of the HAIC procedure. With the endorsement of most national experts in the field of HAIC treatment of HCC, we organized a conference that aimed to reach a wide consensus on various aspects of the appropriate application of oxaliplatin-based HAIC for patients with HCC. Given that a recent Japanese guideline concerning HAIC treatment with a port system has systematically elaborated the status and principles of cisplatin-based HAIC treatment [35], our consensus focuses on providing a deep understanding of HAIC-FOLFOX-based monotherapy or combination therapeutic strategies in China.

Method of consensus development

Considering the variability of therapeutic regimens and the heterogeneity of study quality of HAIC in treating HCC, a standard consensus clustering the latest clinical evidence and the experts' opinions on HAIC was urgently needed to optimize clinical practice and improve the prognosis of HCC patients. For this purpose, we first searched the literature on HAIC with FOLFOX regimen through PubMed and the World Health Organization International Clinical Trials Registry Platform databases for evidence to summarize and support consensus statements about using HAIC with FOLFOX for HCC. During the manual search of published studies and ongoing clinical trials, the expert committee reached an agreement that the initial publication date was set to 2008 because since then the management strategies of unresectable HCC were fundamentally changed by tyrosine kinase targeted therapies. 105 relevant papers were identified and reviewed for the development of this consensus. The evidence quality and recommendations strength were determined according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system. As shown in Table 1, the level of the evidence was classified as high, moderate, or low, and the strength of the recommendation was classified as either strong or weak. Then statements and clinical questions were circulated among all members by email. In Mar 2023, a pre-consensus meeting was held in Guangzhou, China, for extensive discussion and content corrections before finalizing the consensus statements. Dr. MZ chaired the panel, and all panel members were nationally recognized interventional radiologists with extensive experience in HAIC treatment and patient management for HCC.

The present consensus was prepared by a writing committee (JZY and YMZ) and reviewed by the chair (MZ).

Table 1 Levels of evidence and grade of recommendation (adapted from the GRADE system)

Level of evidence	Description	Study characteristic
High	Further research is unlikely to change our confidence in the estimate of benefit and risk	Systematic review and meta-analysis of high-quality RCT High-quality RCT
Moderate	Further research is likely to have an impact on our confidence in the estimate of benefit and risk and may change the estimate	Low-quality RCT Multiple non-randomized cohort studies
Low	Any estimate of the effect is uncertain	Single non-randomized cohort study Retrospective study
Recommendation grade	Description	Strength
Strong	Sufficient evidence for efficacy and benefits outweighs the risk or the disadvantages	Strongly recommended
Weak	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages	Generally recommended or optional

RCT randomized controlled trial, GRADE grading of recommendations assessment, development, and evaluation system

The final version of the manuscript was approved by each panel member, and the details of key recommendations are summarized in Table 2 and Table S1.

Definition and status of HAIC-FOLFOX

HAIC-FOLFOX is an image-guided approach achieved by selectively administering the combinations of chemotherapeutic agents including infusional oxaliplatin, fluorouracil, and leucovorin to the feeding artery of the intrahepatic tumor through an arterial catheter, which has been proved to be a promising and acceptable approach for the management of unresectable or advanced HCC with low systemic toxicities [28–32, 36, 37]. Before the approval of sorafenib, HAIC was routinely applied for patients with advanced HCC in the Asian region, especially in Japan and Korea [38, 39]. However, HAIC has not become a widely recognized and standard care for HCC patients due to the various outcome reported in clinical studies of various regimens, such as doxorubicin, cisplatin–fluorouracil, and FOLFOX [40, 41]. FOLFOX regimen was first used in colorectal cancer with liver metastases both by systemic and HAIC and then applied to unresectable or transarterial chemoembolization (TACE)-refractory advanced HCC [42–44]. In 2013, a randomized phase 3 trial (EACH) revealed the survival advantage of systemic FOLFOX regimen compared with doxorubicin for advanced HCC in the first-line setting, with the PFS of 2.93 versus 1.77 months and median OS of 6.40 versus 4.97 months. And this regimen had no significant increased toxicity over doxorubicin [45]. Then, the FOXAI phase 2 study exploring the modified FOLFOX regimen revealed that hepatic arterial infusion of oxaliplatin, fluorouracil, and leucovorin was an effective and well-tolerated strategy in patients with advanced HCC, with a 12-month survival rate of 55.1% and objective response rate (ORR) of 40.8% according to modified RECIST [36]. Subsequent prospective clinical studies further demonstrated that modified FOLFOX regimen alone or combination strategies such as FOLFOX plus sorafenib in HAIC treatment yields improved survival benefits for patients with unresectable or advanced HCC [29, 30, 37].

Currently, the application of cisplatin-based HAIC treatment lacks reliable high-level evidence of efficacy. The recent SCOOP-2 multicenter randomized phase 2 trial and SILIUS multicenter randomized phase-3 trial estimating the combination of cisplatin–fluorouracil and sorafenib compared with sorafenib in advanced HCC patients reported negative results as well [46, 47]. The pharmacokinetic advantage of oxaliplatin has been reported, attributed to its distinct pharmacological and cytotoxic properties that differentiate it from cisplatin [48, 49]. Studies have demonstrated that the combination of oxaliplatin with fluorouracil

(5-FU) exhibits synergistic anti-tumor cytotoxic effects [50]. Oxaliplatin exhibited a broad spectrum of antineoplastic activity and a lack of cross-resistance with other platinum compounds [51, 52]. Preclinical investigations have described a more pronounced inhibition of DNA synthesis and greater cytotoxic activity of oxaliplatin compared to cisplatin against tumor cells, including those resistant to other drugs [53, 54]. In the context of FOLFOX therapy, a preclinical study utilizing colorectal cancer cell lines proposed a mechanism for the observed synergism. It was suggested that 5-FU mediates the suppression of ATP7B and induces overexpression of MRP2, a glutathione exporter. Consequently, this process leads to a significant sensitization of tumor cells to oxaliplatin [50]. Furthermore, available preclinical evidence indicated that oxaliplatin is capable of inducing immunogenic tumor cell death (ICD) [55, 56]. The activation of this process suggests the potential superiority of oxaliplatin when combined with immune checkpoint inhibitors (ICIs)-based systemic treatment. Additionally, a preclinical study conducted in a rabbit VX2 liver tumor model suggested a pharmacokinetic advantage associated with the use of oxaliplatin for HAIC compared to intravenous administration [57]. A series of phase 3 studies that directly compared oxaliplatin-based regimens with standard first-line treatment have demonstrated that HAIC-FOLFOX with or without sorafenib is active against HCC [29, 31, 32]. Based on these findings, FOLFOX has been the major regimen of HAIC in China and further exploration of HAIC-FOLFOX-based combination strategies is ongoing (Fig. 1 and Table S2).

Recommendation: FOLFOX is one of the main regimens used in the HAIC treatment of HCC patients worldwide, and the antitumor efficacy and safety profile of HAIC-FOLFOX treatment in HCC have been validated. (evidence level: high; recommendation strength: strong; agree level: 97.3%) (No. 1 in Table 2).

Patient selection

HAIC treatment is generally indicated for HCC patients with intrahepatic tumor burden, and also an alternative option for those with extrahepatic oligo-metastasis spread when intrahepatic tumor burden or liver function influence their prognosis (Fig. 2 and Table 3). In recent clinical trials involving HAIC-FOLFOX, patients with compensated liver function, classified from Child–Pugh A to B7, have shown substantial tolerance to both single HAIC therapy and the combination of HAIC with systemic treatment [30, 32]. Moreover, HAIC treatment seems to be a suitable perioperative strategy to reduce the recurrence risk in HCC patients and thus improve the postoperative prognosis. The tumor situations appropriated for HAIC treatment are described below.

Table 2 Recommendations of the HAIC-FOLFOX consensus statement

No	Consensus recommendation	Grade quality of evidence	Strength of recommendation	Level of agreement (%) *
General recommendations				
1	FOLFOX is the main regimen used in the HAIC treatment of HCC patients in China, and the antitumor efficacy and safety profile of HAIC-FOLFOX treatment in HCC have been validated	High	Strong	97.3%
2	Repetitive catheterization without an implanted port system is the preferred administration of HAIC-FOLFOX treatment, it can readjust the catheter position to achieve the optimal antitumor effect and avoid port system-related AEs	High	Strong	91.9%
3	The current mainstream therapeutic scheme includes oxaliplatin (130 or 85 mg/m ² infusion for 3 h on day 1), leucovorin (200 mg/m ² at hours 3 to 5 on day 1), and fluorouracil (400 mg/m ² in bolus, and then 2,400 mg/m ² continuous infusion 46 h)	High	Strong	86.5%
4	The dose of oxaliplatin, whether the fluorouracil is retained, and the infusion time of fluorouracil should be adjusted according to particular situations, such as the tumor blood supply, general status of patients, and other combined treatments	High	Strong	89.2%
5	The management principle of HAIC-related AEs: Grade 1–2 AEs, symptomatic treatment, no dose adjustment; For grade 3 or grade 4 AEs, the appropriate perfusion should be terminated, and active symptomatic treatment should be carried out. The dose of chemotherapy drugs should be adjusted accordingly in the next course of treatment, and HAIC therapy should be terminated if necessary	High	Strong	100%
6	HAIC-FOLFOX responders generally obtain better clinical outcomes than HAIC-FOLFOX non-responders, early identification of potential responders would be essential for formulating an efficient HCC management with a satisfactory prognosis	Moderate	Strong	100%
Candidate for HAIC treatment				
7	Neoadjuvant HAIC therapy may reduce the risk of postoperative recurrence and death in patients with a high risk of relapse	Low	Weak	75.7%
8	For HCC patients with microvascular invasion after hepatectomy, adjuvant HAIC therapy may reduce the risk of postoperative recurrence and prolong survival time, and adjuvant HAIC therapy is recommended within 1 to 2 months after hepatectomy	High	Strong	81.1%
9	When HAIC was used for conversion therapy, surgical resection can be considered when all the following criteria are met: (1) Tumor response evaluated as the complete or partial response, or the stable disease status maintains for more than 3 months. (2) Sufficient residual liver volume for hepatectomy. (3) R0 resection can be achieved. (4) Without common surgical contraindications	Low	Weak	94.6%
10	Imaging assessment is recommended every 2–3 cycles of HAIC during conversion therapy	Moderate	Weak	91.9%
11	Conversion surgery is suggested to be operated on within 3–4 weeks after the last course of HAIC treatment when it is used as the conversion therapy for HCC patients	Low	Weak	81.1%
12	The interval between the last course of HAIC treatment and conversion surgery is suggested to be extended to at least 6 weeks if the additional anti-angiogenesis drugs were combined with the HAIC treatment	Low	Weak	72.9%
13	Single HAIC-FOLFOX treatment might be an effective and safe first-line option for locally advanced HCC with or without extrahepatic oligometastasis #	High	Strong	75.6%
14	FOLFOX-based HAIC treatment combined with sorafenib showed superior survival advantages than single sorafenib and can be used in patients with advanced HCC, especially those with portal vein tumor thrombus	High	Strong	81.1%
15	HAIC-FOLFOX combined with ICIs or the triple therapy scheme of TKIs, ICIs and HAIC-FOLFOX show favorable efficacy and safety profile and may be appropriate for advanced HCC	Low	Weak	94.6%
16	TACE combined with HAIC may be used for patients with multiple tumor lesions located in different liver lobes	Low	Weak	89.2%
17	If the lesions have multiple blood supply sources, TACE can be performed to embolize the non-main tumor-feeding artery while HAIC can be performed to perfusion the main tumor-feeding artery	Low	Weak	83.7%
18	If the lesions have an abnormally rich blood supply, TACE can be used to embolize part of the tumor-feeding artery first and then combined with HAIC	Low	Weak	81.1%
19	If some active tumor lesions remain after multiple courses of HAIC treatments, combined TACE can be performed for embolization	Low	Weak	97.3%

Table 2 (continued)

No	Consensus recommendation	Grade quality of evidence	Strength of recommendation	Level of agreement (%) *
Therapeutic scheme management				
20	It is suggested to maintain HAIC treatment for at least 4 courses if no obvious progression of the lesions was observed in the first follow-up evaluation	High	Weak	75.7%
21	If extrahepatic lesions progress while intrahepatic lesions are under control, concurrent systemic therapies on the basis of HAIC treatment are recommended	Moderate	Strong	94.5%
22	HAIC treatment discontinuation should be considered if obvious intrahepatic lesions progression or intolerable toxicities occurs	High	Strong	97.3%

AEs adverse events, *FOLFOX* a combined chemotherapeutic regimen of oxaliplatin, leucovorin, and fluorouracil, *GRADE* grading of recommendations assessment, development, and evaluation system, *HAIC* hepatic arterial infusion chemotherapy, *HCC* hepatocellular carcinoma, *ICIs* immune checkpoint inhibitors, *TACE* trans-arterial chemoembolization, *TKI* tyrosine kinase inhibitors

*Percentage of expert advisors who either strongly agreed or agreed (based on a five-point Likert scale, comprising: strongly disagree, disagree, neutral, agree, and strongly agree)

#Extrahepatic oligometastasis was defined as up to three metastatic lesions in up to two organs with the largest diameter ≤ 3 cm

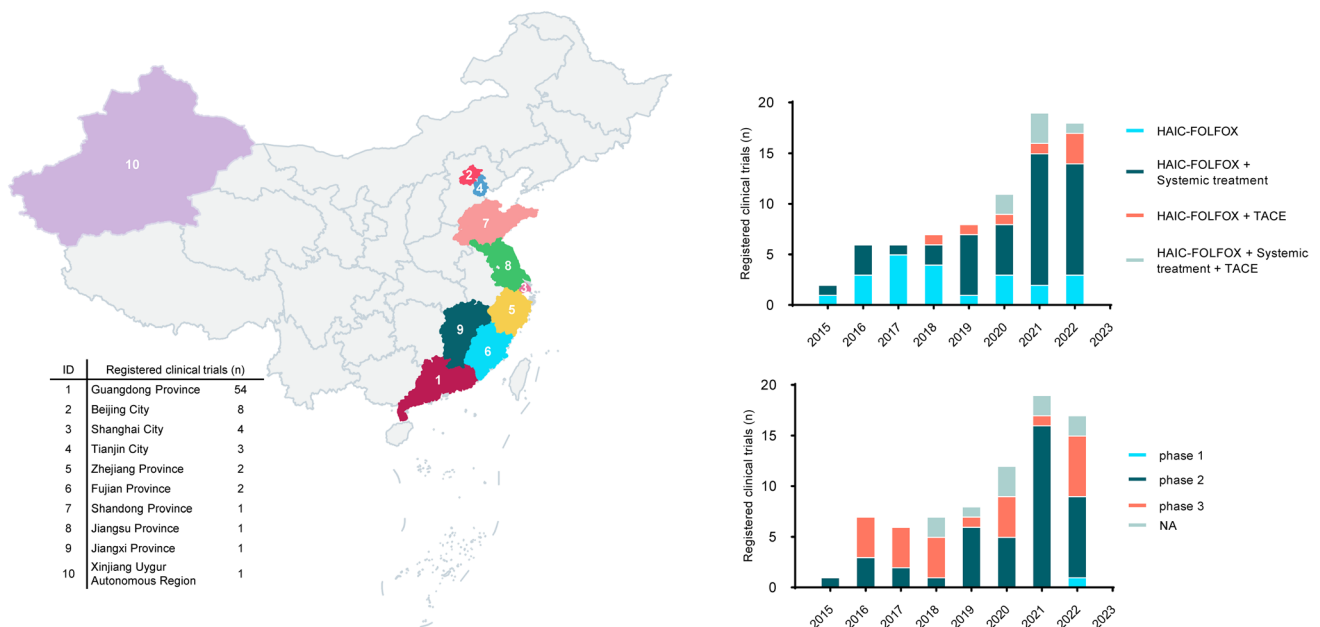


Fig. 1 Geographical distribution and the annual number of the registered trials of oxaliplatin-based HAIC treatment for HCC since 2015. *FOLFOX* a combined chemotherapeutic regimen of oxaliplatin, leu-

covorin, and fluorouracil, *HAIC* hepatic arterial infusion chemotherapy, *HCC* hepatocellular carcinoma, *TACE* transarterial chemoembolization

Resectable HCC

Several studies have reported that a certain portion of HCC patients with potentially resectable tumors (BCLC stage B/C HCC or BCLC stage A beyond Milan criteria) obtained improved survival benefits through receiving hepatectomy [58, 59]. However, the high percentage of postoperative recurrence in these patients limits the benefits of surgery, and perioperative strategies are proposed to improve the postoperative prognosis. Preliminary evidence has supported HAIC as the neoadjuvant or adjuvant treatment for patients

in such a setting, which enables precise delivery of high concentrations of anticancer reagents into the tumor-feeding artery to limit or eliminate the tumor while minimizing chemotherapy-related injuries [60, 61].

Moreover, the rapid tumor shrinkage through HAIC treatment preoperatively may increase the efficacy of postoperative multimodality treatments [32]. A retrospective study has compared patients receiving the neoadjuvant HAIC-FOLFOX regimen with those receiving adjuvant portal vein perfusion chemotherapy. The result suggested that neoadjuvant HAIC is an efficient and well-tolerated strategy


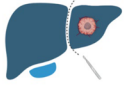

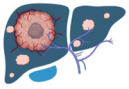

Stage	Purpose		Therapeutic regimen	Strong of recommendation	Level of evidence	Level of agreement	Indication
Early stage beyond Milan criteria	neoadjuvant prior to resection		HAIC-FOLFOX	weak	low	75.7%	alternative
Early stage with microvascular invasion	adjuvant after resection		HAIC-FOLFOX	strong	high	81.1%	recommended
Intermediate stage with unresectable lesions (i.e., a largest lesion ≥ 7 cm)	conversion to resectable		HAIC-FOLFOX	weak	low	94.6%	alternative
Advanced stage with high live tumor burden (i.e., tumor volume >50% occupied the liver), macrovascular invasion, or minimal or uncertain metastasis	alternative first-line		HAIC-FOLFOX	strong	high	75.6%	recommended
Advanced stage with extensively extrahepatic metastasis	alternative first-line		HAIC-FOLFOX + sorafenib	strong	high	81.1%	recommended
			HAIC-FOLFOX + lenvatinib and toripalimab	weak	low	94.6%	alternative

Fig. 2 Indications of oxaliplatin-based HAIC treatment for HCC. HAIC hepatic artery infusion chemotherapy, HCC hepatocellular carcinoma

without grade 3 or higher severe adverse events (AEs) in patients with BCLC stage B/C resectable HCC [60]. In the neoadjuvant HAIC group, the overall cumulative 3-year OS rates were 78.3%, and the 3-year event-free survival rates were 32.0% [62]. The results of a multicenter phase 3 RCT showed that neoadjuvant HAIC could significantly improve the prognosis of patients with resectable BCLC A/B HCC that beyond Milan criteria, with the pathological complete response rate of 10.1% and ORR of 63.6% [63]. And the 3-year OS rate of neoadjuvant HAIC group is 63.5%, which is significantly higher than that of 46.3% in patients receiving operation directly. The 6-, 12-, and 18-month recurrence-free survival (RFS) rates for the neoadjuvant HAIC group were 63.8%, 47.3%, and 47.3% respectively, while they were 52.7%, 42.8%, and 34.8% for the control group. However, there was no statistically significant difference in RFS between the two groups ($p=0.385$). Moreover, neoadjuvant HAIC may filter a cluster of patients with poor treatment responses to HAIC therapy, and thus the remaining HCC patients who demonstrated acceptable responses tended to benefit from further surgical treatment [28].

Most postoperative recurrences of HCC are confined to the liver [64]. Compared with the systemic adjuvant treatment, local adjuvant treatments, such as TACE and transarterial radioembolization (TARE), might be the more suitable choice in HCC patients with high risks of local recurrence [65]. However, owing to toxicity and potential liver function impairment, adjuvant TACE may even worsen the survival outcomes of these patients [66]. In addition, TARE has been reported to cause hypothyroidism and radiation injury

to normal organs, but its efficacy remains controversial in intermediate and advanced-stage HCC [65]. To evaluate the feasibility of HAIC-FOLFOX regimen as a postoperative adjuvant treatment option, Li et al. conducted a phase 3 RCT enrolled 315 HCC patients with microvascular invasion who experienced curative resection [67]. And the results indicated that adjuvant HAIC treatment after hepatectomy could bring better survival advantages for the adjuvant HAIC group (treatment group) than the group without adjuvant treatment (control group), with the median disease-free survival of 20.3 months versus 10.0 months (HR = 0.59; 95% CI 0.43–0.81; $p=0.001$). The OS rate was similar in the two groups (HR = 0.64; 95% CI, 0.36–1.14; $p=0.130$), and the 1-, 2- and 3-year OS rates of the treatment group and the control group were 93.8%, 86.4%, and 80.4% versus 92.0%, 86.0%, and 74.9%, respectively. Moreover, the operation-related AEs incidence in adjuvant HAIC group was similar to that in control group ($p=0.60$), and the majority were grade 1 AEs. Adjuvant HAIC precisely administers the high concentration of chemotherapeutic drug to eliminate the small residual foci after hepatectomy.

Recommendation (1): Neoadjuvant HAIC therapy may reduce the risk of postoperative recurrence and death in patients with high risk of relapse. (evidence level: low; recommendation strength: weak; agree level: 75.7%) (No. 7 in Table 2).

(2) For HCC patients with microvascular invasion after hepatectomy, adjuvant HAIC therapy may reduce the risk of postoperative recurrence and prolong survival time, and adjuvant HAIC therapy is recommended within 1 to

Table 3 Chemotherapeutic regimens used in the HAIC-FOLFOX treatment

Year	Journal (ISO ABBREVIATION)	Corresponding institution	Study design	Oxaliplatin (mg/m ²)	Fluorouracil bolus (mg/m ²)	Fluorouracil infusion < 24 h (mg/m ²)	Fluorouracil infusion for 24–48 h (mg/m ²)	Concomitant antitumor treatment	Any grade 3/4 adverse events (%)	Grade 3/4 adverse events > 10%
Early stage (within up-to-seven criteria)										
2020	Ann. Surg. Oncol [61]	SYSUCC	Phase 3	85	400	–	2400	No	12.1	No
2022	J. Clin. Oncol [67]	SYSUCC	Phase 3	85	400	–	2400	No	1.4	No
Intermediate stage (beyond up-to-seven criteria, but no macrovascular tumor invasion or extrahepatic metastasis)										
2017	Chin. J. Cancer [37]	SYSUCC	Phase 2	85	400	–	2400	No	34.2	Vomiting
2021	Ann. Surg. Open [119]	SYSUCC	No	85	400	–	2400	TACE (using iodized oil)	NA	Abdominal pain; Vomiting; Elevated AST
2022	J. Clin. Oncol [31]	SYSUCC	Phase 3	130	400	2400	–	No	NA	Elevated AST
2022	J. HEPATO-CELL. CARCINOMA [74]	SYSUCC	No	130	0	1200	–	No	NA	No
Advanced stage (with intrahepatic high-risk factors, macrovascular tumor invasion, or extrahepatic metastasis)										
2017	Gut [36]	SYSUCC	Phase 2	130	400	–	2400	No	11	No
2018	J. Hepatol [28]	SYSUCC	No	130	400	–	2400	No	9	No
2018	Cardiovasc. Interv. Radiol [97]	SYSUCC	Phase 2	85	400	–	2400	TKIs (sorafenib)	51.4	Elevated AST; Hand-foot syndrome; Thrombocytopenia
2019	J. Vasc. Interv. Radiol [85]	SYSUCC	No	130	400	–	2400	No	NA	No
2019	JAMA Oncol [29]	SYSUCC	Phase 3	85	400	–	2400	TKIs (sorafenib)	53.2	Elevated AST; Thrombocytopenia
2020	Eur. J. Cancer [94]	Fujian Medical University Cancer Hospital	Phase 2	100	raltitrexed 3 mg/m ² instead of fluorouracil	–	–	No	23.1	Elevated AST
2021	Acad. Radiol [83]	Zhongshan Hospital, Fudan University	No	130	400	–	2400	No	NA	No
2021	J. HEPATO-CELL. CARCINOMA [101]	SYSUCC	No	135	400	–	2400	No	5.4	No

Table 3 (continued)

Year	Journal (ISO ABBREVIATION)	Corresponding institution	Study design	Oxaliplatin (mg/m ²)	Fluorouracil bolus (mg/m ²)	Fluorouracil infusion <24 h (mg/m ²)	Fluorouracil infusion for 24–48 h (mg/m ²)	Concomitant antitumor treatment	Any grade 3/4 adverse events (%)	Grade 3/4 adverse events > 10%
2021	Front. Oncol [100]	SYSUCC	No	85	400	–	2400	No	39.7	Elevated AST; Elevated ALT
2021	Hepatobil. Surg. Nutr [84]	SYSUCC	No	135	400	–	2400	No	19.1	No
2021	Biomed Res. Int [75]	Peking University Cancer Hospital and Institute	No	85	0	1500	–	TACE (using iodized oil)	23.3	Elevated AST; Elevated ALT
2021	J. HEPATOCELL. CARCINOMA [76]	Second Affiliated Hospital of Guangzhou Medical University,	No	85	400	–	2400	TACE (using drug-eluting beads)	37.7	Abdominal pain; Thrombocytopenia
2021	Front. Oncol [100]	SYSUCC	No	85	400	–	2400	TKIs (sorafenib)	51.5	Elevated AST; Elevated ALT; Hand-foot syndrome
2021	J. HEPATOCELL. CARCINOMA [101]	SYSUCC	No	135	400	–	2400	ICIs (toripalimab)	6.2	No
2021	Technol. Cancer Res. Treat [102]	SYSUCC	No	85	400	–	2400	ICIs (toripalimab)	NA	Elevated AST
2021	Front. Oncol [127]	SYSUCC	No	135	400	–	2400	TKIs + ICIs (tenvatimib plus toripalimab)	8.9	No
2021	BMC Cancer [111]	First Affiliated Hospital, Sun Yat-sen University	No	85	400	–	2400	TKIs + ICIs (tenvatimib plus pembrolizumab)	NA	NA
2021	Ther. Adv. Med. Oncol [114]	SYSUCC	No	85	400	–	2400	TKIs + ICIs (tenvatimib plus toripalimab)	NA	Elevated AST; Hypertension
2022	J. Clin. Oncol [32]	SYSUCC	Phase 3	130	400	–	2400	No	20.3	Thrombocytopenia; Elevated AST

Table 3 (continued)

Year	Journal (ISO ABBREVIATION)	Corresponding institution	Study design	Oxaliplatin (mg/m ²)	Fluorouracil bolus (mg/m ²)	Fluorouracil infusion <24 h (mg/m ²)	Fluorouracil infusion for 24–48 h (mg/m ²)	Concomitant antitumor treatment	Any grade 3/4 adverse events (%)	Grade 3/4 adverse events > 10%
2022	Radiology[30]	Peking University Cancer Hospital and Institute	Phase 2	105 (35 mg/m ² once a day for three days)	NA	–	1800 (600 mg/m ² once a day for three days)	TKIs (sorafenib)	59.4	Thrombocytopenia; Diarrhea; Hand-foot syndrome Elevated AST
2022	J. Gastrointest. Surg [71]	Fujian Medical University Cancer Hospital	No	100	raltitrexed 3 mg/m ² instead of fluorouracil	–	–	No	NA	NA
2022	Front. Oncol [103]	Xiangya Hospital	No	85	400	–	2400	ICIs (pembrolizumab)	NA	NA
2022	Int. J. Hyperthermia[128]	First Affiliated Hospital of Jinan University	No	130	400	–	2400	No	4.4	No
2022	Ann. Surg. Oncol [60]	SYSUCC	No	130	400	–	2400	No	0	0
2022	Eur. J. Cancer[33]	SYSUCC	Phase 2	85	400	2400	–	TKIs + ICIs (tenvatnib plus toripalimab)	72.2	Thrombocytopenia; Elevated AST; Hypertension
2022	Front. Immunol [115]	Affiliated Cancer Hospital of Zhengzhou University	No	85	400	–	2400	ICIs + Anti-angiogenesis drug (atezolizumab plus bevacizumab)	NA	NA

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *FOLFOX* a combined chemotherapeutic regimen of oxaliplatin, leucovorin, and fluorouracil, *HAIC* hepatic arterial infusion chemotherapy, *ICIs* immune checkpoint inhibitors, *NA* not applicable, *SYSUCC* Sun Yat-sen University Cancer Center, *TACE* trans-catheter arterial chemoembolization, *TKIs* tyrosine kinase inhibitors

2 months after hepatectomy. (evidence level: high; recommendation strength: strong; agree level: 81.1%) (No.8 in Table 2).

Unresectable HCC without EHS and PVTT

The treatment of large unresectable HCC is still a major challenge, and the efficacy of TACE as standard care in patients with particularly large HCC (longest diameter ≥ 7 cm) is far from satisfactory [68, 69]. And HAIC was proposed as a feasible first-line option in such situations, which delivers sustained chemotherapeutic drugs and avoids embolization-related AEs (i.e., serious postembolization syndrome and liver/renal dysfunction) [70]. Recent studies have demonstrated that the HAIC-FOLFOX yield improved OS and higher tumor response than TACE in patients with unresectable large HCC [31, 37, 71]. In a multicenter phase 3 RCT, the median OS in the HAIC-FOLFOX group was 23.1 months versus 16.1 months in the TACE group [31]. In addition, the incidence of serious AEs in the HAIC-FOLFOX group was 19%, which is significantly lower than 30% in the TACE group.

Successful conversion therapy could obviously improve the prognosis of HCC patients with initially unresectable diseases [72, 73]. In recent studies, patients initially diagnosed with unresectable HCC are typically those presenting an intrahepatic tumor burden exceeding the up-to-7 criteria, macrovascular tumor thrombosis, or insufficient future liver remnants post-resection (estimated to be less than 40% for cirrhotic cases and under 30% for non-cirrhotic cases) [31, 74]. FOLFOX-based HAIC with or without other treatment modalities seems to be an attractive conversion strategy for unresectable patients [29, 32], which has been used for initially unresectable HCC and achieved conversion to curative surgery resection in about 23.8% of cases [74]. A single-center real-world study indicated that, although the HAIC-surgery group had a higher incidence of surgery-related complications than the surgery group, there exists no significant difference in recurrence-free survival between these two groups [74]. In the HAIC-surgery group, increased preoperative HAIC cycles were correlated with increased risks of abdominal bleeding and decreased liver function. The rate of pathological complete response after 3–5 HAIC cycles was 29.4%, which was significantly higher than that of 13.2% after 1–2 cycles.

In addition, compared with HAIC, lipiodol-based embolization could occlude tumor-feeding vessels to achieve tumor control. Several retrospective studies have revealed better survival benefits and conversion rates of the TACE-HAIC regimen than conventional TACE (c-TACE) or drug-eluting bead TACE (DEB-TACE) [75, 76]. Therefore, the synergistic effect of TACE and HAIC may lead to tumor shrinkage and reduced risk of tumor

progression. On the basis of these previous clinical studies, the "SYSU Criterion" was proposed by the Sun Yat-sen University Cancer Center, and the HAIC-FOLFOX-based treatment may be the preferred conversion treatment options for patients who meet the criteria as follows: (1) Single or multiple tumors located in one lobe of the liver. (2) Without tumor thrombus in portal vein main trunk or inferior vena cava, no EHS. (3) With the ECOG PS score 0–1 and the liver function of Child–Pugh A.

Regarding the appropriate timing of conversion surgery, the safety of surgical treatment should be considered as a priority. HAIC-FOLFOX is a periodic regimen in which patients receive chemotherapeutic agents via infusion every 3 or 4 weeks. Once successful conversion is achieved through HAIC monotherapy, it is suggested that the radical resection be performed 3–4 weeks after the last HAIC cycle. It is worth noting that although combining HAIC with systemic treatment has shown a higher conversion rate, the addition of anti-angiogenesis drugs such as bevacizumab may increase the risk of surgical bleeding and affect wound healing [77, 78]. Bevacizumab is a monoclonal antibody that targets VEGF and inhibits angiogenic signaling, thereby suppressing tumor cell growth. However, it can also lead to adverse effects related to VEGF inhibition, such as hypertension, proteinuria, and bleeding [6, 12]. Additionally, the use of bevacizumab has been associated with an increased incidence of delayed surgical wound healing. Therefore, it is necessary to have a proper discontinuation period of bevacizumab prior to liver resection in order to prevent such complications [77]. In the case of liver resection for colorectal liver metastases, the colorectal cancer NCCN guideline recommended an interval of at least 6 weeks (equivalent to 2 half-lives of bevacizumab) between the last dose of bevacizumab and surgery [79]. Based on the half-life of bevacizumab and the experience with liver resection for colorectal liver metastases, it is suggested that if the anti-angiogenesis drugs are combined with the HAIC treatment, the interval between the last HAIC cycle and conversion surgery should be extended to at least 6 weeks. However, caution should be exercised when considering this recommendation due to the limited availability of prospective evidence regarding the preoperative use of bevacizumab in the treatment of HCC.

Recommendation: (1) When HAIC was used for conversion therapy, surgical resection can be considered when the following criteria are met: (1) Tumor response evaluated as CR or PR, or the stable disease status maintains for more than 3 months. (2) Sufficient residual liver volume for hepatectomy. (3) R0 resection can be achieved. (4) Without commonly surgical contraindications. (evidence level: low; recommendation strength: weak; agree level: 94.6%) (No.9 in Table 2).

(2) Imaging assessment is recommended every 2–3 cycles of HAIC during conversion therapy (evidence level:

moderate; recommendation strength: weak; agree level: 91.9%) (No.10 in Table 2).

(3) Conversion surgery is suggested to be operated on within 3–4 weeks after the last course of HAIC treatment when it is used as the conversion therapy for HCC patients. (evidence level: low; recommendation strength: weak; agree level: 81.1%) (No.11 in Table 2).

(4) The interval between the last course of HAIC treatment and conversion surgery is suggested to be extended to at least 6 weeks if the additional anti-angiogenesis drug were combined with the HAIC treatment. (evidence level: low; recommendation strength: weak; agree level: 72.9%) (No.12 in Table 2).

Advanced HCC with EHS and/or PVTT

Previous studies have revealed that severe intrahepatic tumor burden and decompensated liver function influence the prognosis of patients with advanced HCC [80, 81], which may cause tumor progression and liver functional failure [82]. Given the unsatisfactory efficacy of systemic treatment for advanced patients with high intrahepatic tumor burden, HAIC treatment that effectively reduces the tumor burden appears appropriate for patients in such setting [28, 32, 83, 84]. A previous retrospective study indicated that HAIC was found to be suitable for advanced HCC with extrahepatic oligo-metastasis (up to three metastatic lesions in up to two organs with the largest diameter ≤ 3 cm). However, the presence of lung metastases may serve as a negative prognostic factor for patients undergoing HAIC-FOLFOX treatment [85]. In a recent phase 3 RCT, Lyu et al. directly compared the HAIC-FOLFOX regimen with sorafenib as the first-line therapy in advanced HCC patients with or without extrahepatic oligometastasis. The results showed the improved survival benefits of HAIC-FO compared with sorafenib in advanced HCC, with the median OS of 13.9 months in HAIC group and 8.2 months in sorafenib group (HR = 0.408; 95% CI 0.30–0.55; $p < 0.001$) [32].

Portal vein tumor thrombosis (PVTT) was observed in approximately 10–40% of cases; despite breakthroughs like atezolizumab combined with bevacizumab in the systemic treatment of advanced HCC occurred recently, the clinical outcomes of patients with major PVTT remained unsatisfactory, with the median OS of 3.1–7.6 months [5, 12, 86, 87]. These patients seem to benefit more from additional HAIC treatment, and the superior efficacy of HAIC-FOLFOX combined with sorafenib than sorafenib alone has been supported by phase 2 and phase 3 RCTs; thus, sorafenib plus HAIC of FOLFOX may be a favorable option for HCC patients with major PVTT [29, 30]. The median OS in the combination group was significantly longer than that in the sorafenib group (13.4–16.3 months versus 6.5–7.1 months). Moreover, in the aforementioned phase 3 RCT comparing HAIC plus

sorafenib versus sorafenib alone in advanced HCC patients with PVTT, the proportion of patients with EHS was 30.4% in the combination group and 34.4% in sorafenib group. The subgroup analysis of OS indicated that HAIC plus sorafenib may significantly improve the survival outcome of patients with concurrent PVTT and EHS compared to sorafenib alone (HR = 0.52; 95% CI 0.32–0.84) [29]. It is worth noting that although the grade 3/4 AEs more frequently occurred in the sorafenib-HAIC group, these AEs are manageable by dose reduction or treatment interruption.

Recommendation: (1) Single HAIC-FOLFOX treatment might be an effective and safe first-line option for locally advanced HCC with or without extrahepatic oligometastasis. (evidence level: high; recommendation strength: strong; agree level: 75.6%) (No.13 in Table 2).

(2) FOLFOX-based HAIC treatment combined with sorafenib showed superior survival advantages than single sorafenib and can be used in patients with advanced HCC, especially those with portal vein tumor thrombus. (evidence level: high; recommendation strength: strong; agree level: 81.1%). (No.14 in Table 2).

Summary

In the era of systemic therapy based on ICIs and MTAs, there still exists a non-negligible portion of HCC patients who may not benefit from systemic treatment in real-world practice [88, 89]. Data from several RCTs, including IMbrave 150, HIMALAYA, REFLECT, ORIENT-32, RATIONALE-301, and CARES-310 study, have demonstrated a notable improvement in survival for patients primarily with EHS. However, the extent of this benefit may be limited for individuals with intrahepatic high-risk factors. Generally, HCC patients with high-risk characteristics, including tumor occupancy of $> 50\%$ of the liver, tumor invasion of the main-branch or trunk of the portal vein, and/or invasion of the bile duct, often have accompanying severe portal hypertension, decompensated liver function, and a decline in physical status. In the subgroup analysis of the IMbrave150 trial, it was observed that the rate of variceal hemorrhage was higher in the Vp4-PVTT subgroup than in the remainder of the total population (13.6% versus 2.5%). The unique toxicity profile of this combination can significantly increase medical risk, which needs to be taken into consideration when determining the appropriate treatment plan. Therefore, treatments with low toxicity are preferred for this specific population. Currently, the tolerable safety and promising efficacy of HAIC-FOLFOX regimens have been demonstrated by several RCTs in China. Unlike previous clinical trials carried out in systemic therapies, studies involving HAIC-FOLFOX mainly included patients with locally advanced HCC with high-risk factors or unresectable HCC with large liver lesions. Consequently, in cases

of unresectable/advanced HCCs where there is a liver-only disease or oligometastatic disease, loco-regional FOLFOX-HAIC might be considered as an alternative initial therapy when systemic options are unsatisfying.

The post HAIC-FOLFOX therapeutic management varied depending on the type of tumor response. Suitable patients with deep response were advised to consider switching to curative treatment options, such as surgical resection or thermal ablation, when the disease has been down-staged to an early stage. This recommendation is based on evidence from subgroup analysis of several phase 3 RCTs that demonstrated significant improvements in survival for patients who received radical resection after conversion from HAIC. Moreover, in some patients, the tumors may remain stable during HAIC treatment. When the upper limit number of HAIC (typically 6–8 cycles) is reached, it is recommended for these patients to switch to systemic treatment.

For patients who experience recurrence or tumor progression, the treatment approach varies depending on the pattern of progression. In cases where there is extrahepatic progression (intrahepatic lesions remain stable while metastases occur outside the liver), HAIC therapy can be continued to control intrahepatic tumors, while systemic therapy should be added to target the extrahepatic lesions. In cases of intrahepatic progression, HAIC treatment should be discontinued as the tumors have shown resistance to chemotherapeutic drugs. These patients should then switch to systemic treatment options. The post-progression treatment options for HCC mainly included ICIs, MTAs, anti-angiogenesis, and their combinations (i.e., atezolizumab and bevacizumab, tremelimumab and durvalumab, or lenvatinib). Preliminary evidence suggested that immunotherapy-based strategies had promising survival benefits for patients with advanced HCC refractory to HAIC [90].

Procedural technique

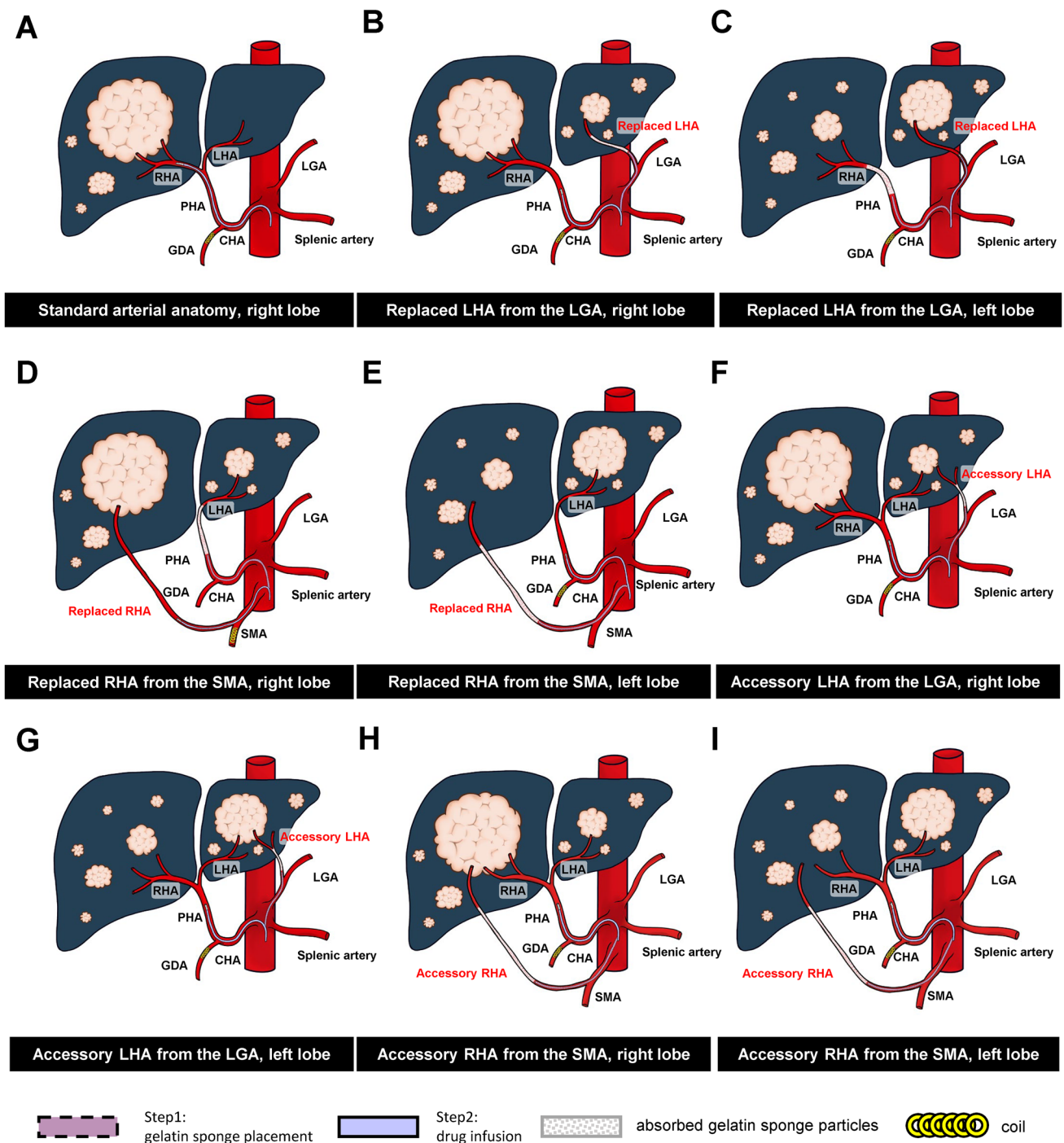
In the procedure of HAIC treatment, the FOLFOX regimen was administered through a microcatheter with or without a percutaneously implanted port catheter system. Currently, repetitive single administration of the FOLFOX regimen is the preferred arterial infusion technique used in routine clinical practice or most studies about HAIC-FOLFOX for HCC patients (Supplementary Fig. 1).

The drug delivery port system of HAIC has been widely utilized in Asia, including Japan, Korea, and Taiwan. This system effectively eliminates the need for repeated femoral arterial puncture and catheterization, thereby enhancing patient compliance with long-term infusion of time-dependent cytotoxic antitumor agents such as fluorouracil. However, in cases of tumors with multiple feeding arteries, the main tumor-feeding artery may change during

multiple HAIC sessions, while the catheter position may not be adjusted promptly when employing an implanted port system. In the phase 3 randomized SILIUS study, which investigated the combination of sorafenib and HAIC (cisplatin combined with fluorouracil) versus sorafenib alone, safety data revealed that 12% of patients in the sorafenib plus HAIC group experienced grade 3/4 port-related complications [47]. If catheter dislocation or occlusion occurs, it renders the HAIC treatment technically unfeasible, potentially necessitating either re-implantation of the port system or discontinuation of treatment. Furthermore, HAIC utilizing repeated catheterization instead of a port system is also employed when administering drugs such as cisplatin. Several phase 2 studies utilizing the cisplatin-HAIC regimen have described this approach [91, 92].

Compared with a catheter connected to an indwelling reservoir system, repetitive puncture and catheterization could more selectively infuse the chemotherapeutic drugs into the tumor-feeding artery (Fig. 3) [93]. During the HAIC treatment, a catheter is selectively inserted into the main tumor-feeding artery of the primary lesions to deliver chemotherapeutic drugs. In patients with standard arterial anatomy, the catheter is typically placed in the left or right hepatic artery if the tumors are confined to one lobe of the liver (Fig. 3A). If the tumors are distributed in both lobes of the liver, it is recommended to insert the catheter into the proper hepatic artery so that the chemotherapeutic drugs can be infused into the lesions in both lobes. However, it is important to note that hepatic arterial variants are relatively common (Fig. 3B–I). In fact, the prevalence of hepatic arterial variant seen at angiography was nearly 40% in a large cohort study containing six hundred patients [93]. In HCC patients with hepatic arterial variants, the intrahepatic tumor lesions may receive blood supply from tumor-feeding arteries other than the hepatic artery, such as branches of the superior mesenteric artery or left gastric artery. In such cases, the subordinate blood supply arteries are embolized using absorbed gelatin sponge particles to occlude the blood supply. This step ensures that the majority of blood flow is directed toward the main tumor-feeding artery. Once the subordinate blood supply arteries are embolized, the catheter can be inserted into the main tumor-feeding artery to deliver the chemotherapeutic drugs specifically to the target lesions. The micro-catheter position can be precisely readjusted to the tumor-feeding artery in each HAIC cycle to achieve a better antitumor response by maximizing the local drug concentration in the tumor surrounding tissue [28].

Additionally, several large-scale phase 3 RCTs of HAIC-FOLFOX regimen alone or with sorafenib showed that HAIC was minimally invasive and repeatable, which also avoided implanted port catheter system-related AEs, such as port-related infection, dislocation of the catheter tip, and thrombosis [29, 31, 32]. According to the data from clinical



trials, HAIC procedure-related complications occurred in 2%–8% of patients, and all the complications were mild. The common procedure-related adverse events associated with HAIC include spasm (2%), collateralization (4%), and stenosis of hepatic artery (7%) as well as hemorrhage of the femoral artery puncture site (4%). In addition, the incidence of procedure-related complications was not obviously increased in patients who underwent multiple cycles of HAIC [36]. A recent retrospective study performed an analysis of the

correlation between HAIC treatment-related complications and the HAIC cycles [74]. The results indicated that pleural effusion (56.1%), ascites effusion (17.8%), biliary leakage (10.3%), and abdominal bleeding (10.3%) were the common complications after HAIC conversion surgery, and only the incidence of abdominal bleeding was positively correlated with the number of HAIC cycles among these complications. As the number of HAIC cycles increases, the incidence of abdominal bleeding gradually increases, and

Fig. 3 (A) Pattern diagram of HAIC treatment for HCC patients with classic hepatic arterial anatomy. Generally, the arterial catheter was inserted using an image-guided procedure through the femoral artery and then located at the common hepatic artery or proper hepatic arterial branch (tumor-feeding artery). When blood flows into the gastroduodenal artery was confirmed by micro-catheter angiography, the route was embolized with a coil or micro-coil to prevent reflux of chemotherapeutic drugs to the stomach and duodenum. Considering the latent possibility of changes in the main tumor lesion's location, catheter insertion was repeatedly performed before every HAIC cycle for the catheter reposition if necessary. (B–I) Pattern diagram of HAIC treatment for HCC in several commonly observed arterial anatomic variants. Anatomic variants and tumor location are two common specific situations to face in the process of hepatic arterial infusion. No matter which situation, anatomic variants or tumor location, when more than one feeding artery of liver tumor lesions was detected, the principle is that the smaller arteries would be embolized with absorbed gelatin sponge particles. In summary, the above charts selectively show the HAIC procedure for HCC patients with either classic hepatic arterial anatomy or several commonly observed arterial anatomic variants according to the study by Covey et al. (*Radiology*, 2002), which account for approximately 86% of the population. The classic hepatic arterial anatomy was observed in more than 61.3% of the patients, and the above representative arterial anatomic variants were observed in approximately 24.5% of the population (accessory LHA from LGA 10.7%, Replaced RHA 8.7%, Replaced LHA 3.8%, and accessory RHA from SMA 1.5%). *CHA* common hepatic artery, *GDA* gastroduodenal artery, *HAIC* hepatic artery infusion chemotherapy, *HCC* hepatocellular carcinoma, *LGA* left gastric artery, *LHA* left hepatic artery, *PHA* proper hepatic artery, *RHA* right hepatic artery, *SMA* superior mesenteric artery

receiving 3–8 cycles of HAIC treatment was more likely to cause abdominal bleeding (16.7% versus 3.8%, $p = 0.028$) than receiving 1–2 cycles of HAIC. Therefore, the number of HAIC procedures and the duration of HAIC treatment should be individually determined to avoid serious vascular AEs or liver function injuries.

It is recommended to conduct routine follow-up imaging evaluations after every 2–3 cycles of HAIC-FOLFOX treatment to assess its efficacy. In most prospective studies, patients with advanced HCC typically undergo the first imaging assessment after 2 courses of HAIC [29–33, 94]. If there is no significant tumor progression observed in the initial imaging evaluation, patients are advised to receive an additional 2 courses of HAIC before the next follow-up assessment of efficacy. Data from RCT studies have shown that the disease control rate, which includes complete response, partial response, and stable disease according to RECIST 1.1 criteria, for HAIC is around 82% for unresectable intermediate HCC and 77.7% for advanced HCC [31, 32]. This suggests that the majority of patients may benefit from receiving at least 4 cycles of HAIC treatment, equivalent to 2 additional cycles. Furthermore, a treatment interval of 3–4 weeks between HAIC sessions is commonly implemented to ensure continuous anti-tumor effects and allow sufficient time for HCC patients to recover liver and body functions. A phase 3 RCT investigating HAIC-FOLFOX

treatment for advanced HCC reported a median time to response of 9.3 weeks [32]. Considering that the HAIC regimen in this study was administered every 3 weeks, these results indicate that most responders achieved complete or partial response within the initial 4 cycles of HAIC. Therefore, it is suggested to continue HAIC treatment for at least 4 courses if no significant progression of the lesions is observed in the first follow-up evaluation. This approach may allow for an adequate assessment of treatment efficacy and provide an opportunity for patients to benefit from the anti-tumor effects of HAIC-FOLFOX.

Recommendation: (1) Repetitive catheterization without an implanted port system is the preferred administration of HAIC-FOLFOX treatment, it can readjust the catheter position to achieve the optimal antitumor effect and avoid port system-related AEs. (evidence level: high; recommendation strength: strong; agree level: 91.9%) (No.2 in Table 2).

(2) It is suggested to maintain HAIC treatment for at least 4 courses if no obvious progression of the lesions was observed in the first follow-up evaluation. (evidence level: low; recommendation strength: weak; agree level: 75.7%) (No.20 in Table 2).

(3) If extrahepatic lesions progress while intrahepatic lesions are under control, concurrent systemic therapies on the basis of HAIC treatment are recommended. (evidence level: moderate; recommendation strength: strong; agree level: 94.5%). (No.21 in Table 2).

(4) HAIC treatment discontinuation should be considered if obvious intrahepatic lesions progression or intolerable toxicities occurs. (evidence level: high; recommendation strength: strong; agree level: 97.3%) (No.22 in Table 2).

HAIC therapeutic outcome

The therapeutic outcomes of HAIC vary depending on the regimen. The commonly used regimens in oxaliplatin-based HAIC treatment include the HAIC-FOLFOX regimen alone, HAIC combined with molecular targeting agents (MTAs), HAIC combined with ICIs, the triple regimen of HAIC, ICIs and MTAs, and HAIC combined with TACE (Fig. 4). The results of various treatment scheme are summarized in Table 4.

HAIC-FOLFOX

Recently, two high-quality large-scale RCTs from China have further demonstrated the better survival outcomes of the HAIC-FOLFOX regimen as the first-line option compared with TACE or sorafenib in unresectable intermediate to advanced-stage HCC [31, 32]. This therapeutic FOLFOX scheme includes oxaliplatin (130 or 85 mg/m² infusion for 3 h on day 1), leucovorin (200 mg/m² at hours 3 to 5 on day

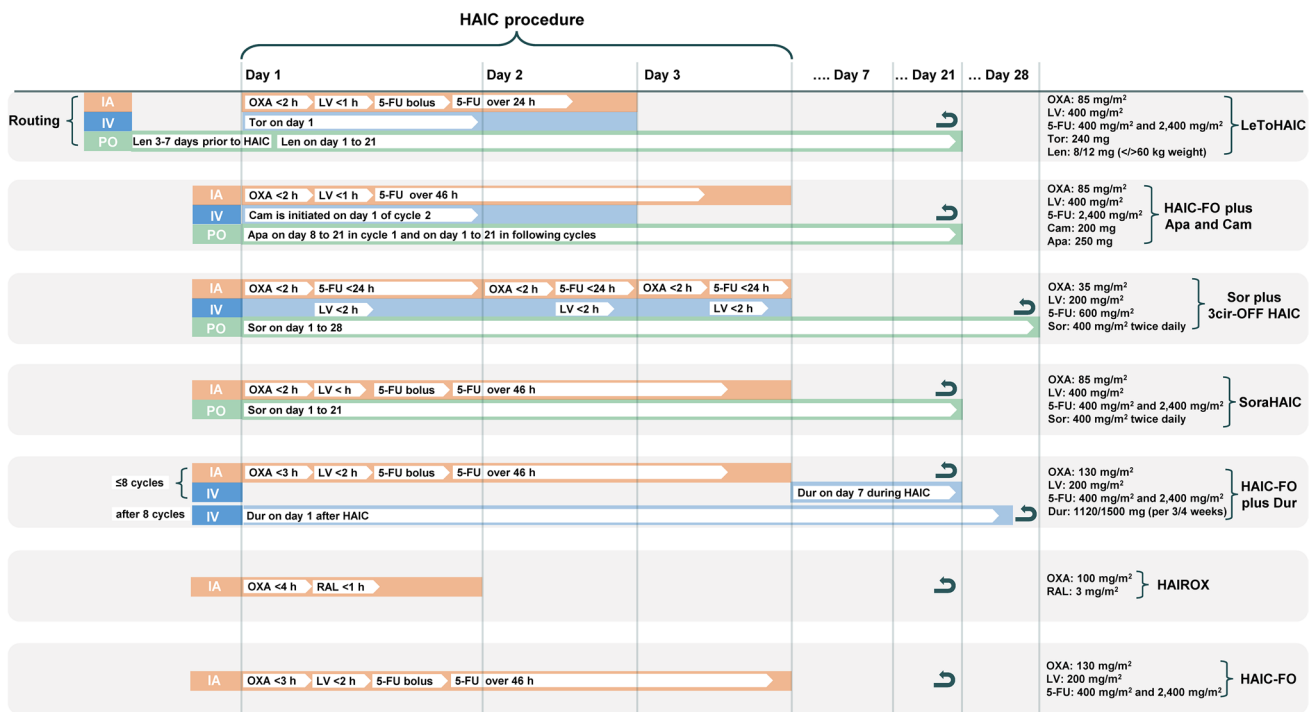


Fig. 4 Current main infusion chemotherapeutic regimen of oxaliplatin-based HAIC treatment for HCC. *Apa* apatinib, *Cam* Camrelizumab, *Dur* Durvalumab, *FU* fluorouracil, *FO* FOLFOX, a combined chemotherapeutic regimen of oxaliplatin, leucovorin, and fluorouracil, *HAIC* hepatic artery infusion chemotherapy, *HCC* hepatocellular carcinoma, *IA* Intra-arterial infusion, *IV* intravenous infusion, *Len* Lenvatinib, *LV* leucovorin, *Oxa* oxaliplatin, *PO* oral administration, *Ral* raltitrexed, *Sor* sorafenib, *Tor* toripalimab

1) and fluorouracil (400 mg/m² in bolus, and then 2,400 mg/m² continuous infusion 46 h).

Notably, it seems that fluorouracil is inconvenient for infusion chemotherapy due to its short plasma concentration half-life and prolonged infusion time of over 46 h [28, 29]. Conversely, based on the longer half-life of plasma concentrations, raltitrexed (another antimetabolic agent) could be applied in short-term infusion [95, 96]. A single-arm phase 2 trial was conducted to evaluate the feasibility of HAIC containing raltitrexed in patients with BCLC B/C stage HCC [94]. Objective response was observed in 46.2% of patients, the 12-month survival rates were 43.2%, and grade 4 treatment-related adverse events (TRAEs) or deaths were not reported. The median time to progression was 6.7 months, and the median PFS was 5.2 months. The strength of this regimen is the relatively short infusion time, and it warrants further comparison with HAIC-FOLFOX and other standard first-line treatments in future phase 3 RCT.

Recommendation: (1) The current mainstream therapeutic scheme includes oxaliplatin (130 or 85 mg/m² infusion for 3 h on day 1), leucovorin (200 mg/m² at hours 3 to 5 on day 1) and fluorouracil (400 mg/m² in bolus, and then 2,400 mg/m² continuous infusion 46 h). (evidence level: high; recommendation strength: strong; agree level: 86.5%) (No.3 in Table 2).

(2) The dose of oxaliplatin, whether the fluorouracil is retained, and the infusion time of fluorouracil should be adjusted according to particular situations, such as the tumor blood supply, general status of patients, and other combined treatments. (evidence level: high; recommendation strength: strong; agree level: 89.2%) (No.4 in Table 2).

HAIC-FOLFOX combined with MTAs/ICIs

HAIC could effectively lower the tumor burden, whereas the effectiveness of sorafenib obtains better anti-tumor effect in patients with lower tumor burdens, and thus the combination of them may benefit advanced HCC patients more than sorafenib [91, 97]. The synergistic effect between chemotherapy and MTAs has been demonstrated in several preclinical studies. MTAs, such as sorafenib and lenvatinib, exert inhibitory effects on multiple targets, including Raf-1, platelet-derived growth factor receptor (PDGFR)-β, Braf, and vascular endothelial growth factor receptor (VEGFR)-1–3. These inhibitory effects may have the potential to induce apoptosis in tumor cells and enhance their sensitivity to FOLFOX agents [98]. Furthermore, the anti-angiogenic properties of MTAs may alter the structure and function of tumor vasculature, thereby promoting vessel normalization within the tumor tissue.

Table 4 Clinical outcomes of patients receiving HAIC-FOLFOX-based treatment for HCC

Year of publication	Corresponding author(s)	Therapy	Study design	Sample size	Median tumor size (cm)	PVTT (%)	EHM (%)	ORR by RECIST 1.1	ORR by mRECIST	PFS	OS
Early stage (adjuvant treatment after resection)											
2020	Guo [61]	HAIC-FOLFOX routine follow-up	Phase 3	63	NA	0	0	NA	NA	NA	NA
2022	Guo et al. [67]	HAIC-FOLFOX routine follow-up	Phase 3	157	NA	0	0	NA	NA	20.3	NA
Intermediate stage (beyond up-to-seven criteria, but no macrovascular tumor invasion or extrahepatic metastasis)											
2017	Shi [37]	HAIC-FOLFOX cTACE	Phase 2	38	NA	0	0	54.1	NA	NA	NA
2021	Yuan [119]	HAIC-FOLFOX plus cTACE	Phase 2	41	NA	0	0	9.8	NA	NA	NA
2022	Shi [31]	HAIC-FOLFOX cTACE	Retrospective study	41	NA	0	0	14.6	65.9	NA	NA
2022	Zhou and Zhang [74]	HAIC-FOLFOX plus surgery	Retrospective study	42	NA	0	0	2.4	16.7	9.2	13.5
2022	Zhou and Zhang [74]	HAIC-FOLFOX plus surgery	Phase 3	159	NA	0	0	45.9	48.4	9.6	23.1
2022	Zhou and Zhang [74]	HAIC-FOLFOX plus surgery	Phase 3	156	NA	0	0	17.9	32.7	5.4	16.1
2022	Zhou and Zhang [74]	HAIC-FOLFOX plus surgery	Retrospective study	131	NA	0	0	NA	NA	38.7	NA
2022	Zhou and Zhang [74]	HAIC-FOLFOX plus surgery	Retrospective study	217	NA	0	0	NA	NA	22.9	NA
Advanced stage (with intrahepatic high-risk factors, macrovascular tumor invasion, or extrahepatic metastasis)											
2017	Zhao [36]	HAIC-FOLFOX	Phase 2	49	10.9	57.1	NA	28.6	40.8	7.1	NA
2018	Zhao [28]	HAIC-FOLFOX TKIs (sorafenib)	Retrospective study	180	11.7	54.4	60	29.4	47.8	7.1	14.5
2018	Shi [97]	HAIC-FOLFOX plus TKIs (sorafenib)	Retrospective study	232	11.6	55.6	58.6	3	9.1	3.3	7.0
2019	Zhao [85]	HAIC-FOLFOX	Phase 2	35	10.8	100	31.4	40	62.8	6.7	13.2
2019	Shi [29]	HAIC-FOLFOX plus TKIs (sorafenib)	Retrospective study	116	NA	63.8	43.1	NA	28.4	NA	12.5
2020	Yu [94]	HAIC of oxaliplatin and raltitrexed	Phase 3	125	10.1	100	30.4	40.8	54.4	7	13.4
2021	Chen [83]	HAIC-FOLFOX	Phase 2	39	NA	64.1	0	46.2	NA	5.2	NA
2021	Guo and Wei [101]	HAIC-FOLFOX	Retrospective study	87	7.1	69	31	13.8	NA	3.7	9
2021	Guo and Wei [101]	HAIC-FOLFOX plus ICI (toripalimab)	Retrospective study	148	NA	55	26	30	NA	5.6	14.6
2021	Shi and Li [100]	HAIC-FOLFOX	Retrospective study	81	NA	64	17	38	NA	10	18
2021	Guo [84]	HAIC-FOLFOX plus TKIs (sorafenib)	Retrospective study	99	NA	NA	39.4	37.4	NA	7	12.9
2021	Zhu [75]	HAIC-FOLFOX cTACE	Retrospective study	126	NA	NA	40.5	36.5	NA	5.3	10.5
2021	Zhu [75]	HAIC-FOLFOX plus cTACE	Retrospective study	95	9.8	94.7	18.9	NA	44.3	6.6	27.8
2021	Zhu [75]	HAIC-FOLFOX plus cTACE	Retrospective study	273	9.4	86.8	21.6	NA	7.7	2.8	7.1
2021	Zhu [75]	HAIC-FOLFOX plus cTACE	Retrospective study	89	8.5	65.2	49.4	NA	1.3	3.2	7.4
2021	Zhu [75]	HAIC-FOLFOX plus cTACE	Retrospective study	86	9.5	100	37.2	NA	24.4	6	8
2021	Zhu [75]	HAIC-FOLFOX plus cTACE	Retrospective study	69	9.9	100	37.7	NA	5.8	2	5

Table 4 (continued)

Year of publication	Corresponding author(s)	Therapy	Study design	Sample size	Median tumor size (cm)	PVTT (%)	EHM (%)	ORR by RECIST 1.1	ORR by mRECIST	PFS	OS
2021	Zhu and Lu [76]	HAIC-FOLFOX plus DEB-TACE	Retrospective study	69	10.4	49.3	0	NA	71	9.3	19
		DEB-TACE	Retrospective study	64	9.7	46.7	0	NA	53.1	6.3	14
2021	Li and Shi [102]	HAIC-FOLFOX plus ICIs (toripalimab) TKIs (lenvatinib)	Retrospective study	53	NA	77.4	32.1	47.2	NA	9.3	17.1
2021	Guo and Li [127]	HAIC-FOLFOX plus TKIs and ICIs (lenvatinib and toripalimab)	Retrospective study	65	NA	70.8	36.9	9.2	NA	4.8	10.1
			retrospective study	45	11.2	80	33.3	40	NA	8.8	15.9
		TKIs and ICIs (lenvatinib and toripalimab)	Retrospective study	25	10.9	72	52	16	NA	5.4	8.6
2021	Guo and Li [111]	HAIC-FOLFOX plus TKIs and ICIs (lenvatinib and pembrolizumab)	Retrospective study	84	NA	58.3	23.8	46.4	59.5	10.9	17.7
		TKIs and ICIs (lenvatinib and pembrolizumab)	Retrospective study	86	NA	64.0	27.9	30.2	41.9	6.8	12.6
2021	Shi and Li [114]	HAIC-FOLFOX plus TKIs and ICIs (lenvatinib and toripalimab)	Retrospective study	71	NA	77.5	22.5	59.2	67.6	11.1	NA
		TKIs (lenvatinib)	Retrospective study	86	NA	72.1	29.1	9.3	16.3	5.1	11
2022	Zhao [32]	HAIC-FOLFOX	Phase 3	130	11.7	68.5	33.8	31.5	35.4	7.8	13.9
		TKIs (sorafenib)	Phase 3	132	10.8	62.9	34.8	1.5	5.3	4.3	8.2
2022	Wang [30]	HAIC-FOLFOX plus TKIs (sorafenib)	Phase 2	32	10.6	100	12	40.6	50	9	16.3
		TKIs (sorafenib)	Phase 2	32	10.7	100	16	3.1	3.1	2.5	6.5
2022	Chen and He [71]	HAIC of oxaliplatin and raltitrexed	Retrospective study	113	NA	51.6	0	54.8	59.7	6.7	15
2022	Shi [103]	HAIC-FOLFOX plus ICIs (pembrolizumab)	Retrospective study	52	NA	100	23.1	57.7	NA	7.1	15.6
2022	Li [128]	HAIC-FOLFOX	Retrospective study	135	10.8	48.9	40	NA	53.3	4.6	14.5
		HAIC-FOLFOX plus ablation	Retrospective study	93	10.1	37.6	24.7	NA	96.8	8.5	22.2
2022	Xu [60]	HAIC-FOLFOX	Retrospective study	36	8.1	66.7	0	NA	NA	9.1	NA
		portal vein perfusion chemotherapy	Retrospective study	28	9.6	64.3	0	NA	NA	3.2	19.5
2022	Shi and Kan [33]	HAIC-FOLFOX plus TKIs and ICIs (lenvatinib and toripalimab)	Phase 2	36	11.2	86.1	27.8	63.9	66.7	10.4	17.9
2022	Zhou et al. [115]	HAIC-FOLFOX plus ICIs and Anti-angiogenesis (atezolizumab and bevacizumab)	Retrospective study	52	10.2	71.1	50	44.3	67.3	10.6	NA

cTACE conventional transarterial chemoembolization using lipiodol, *DEB-TACE* transarterial chemoembolization using drug-eluting beads, *EHM* extrahepatic metastasis, *FOLFOX* a combined chemotherapeutic regimen of oxaliplatin, leucovorin, and fluorouracil, *DFS* disease-free survival, *HAIC* hepatic arterial infusion chemotherapy, *HCC* hepatocellular carcinoma, *ICIs* immune checkpoint inhibitors, *mRECIST* modified RECIST, *NA* not applicable, *OS* overall survival, *ORR* objective response rate, *PD-1* programmed death ligand 1, *PFS* progression-free survival, *PVTT* portal vein tumor thrombosis, *RECIST* Response Evaluation Criteria in Solid Tumors, *TKIs* tyrosine kinase inhibitors

Consequently, this leads to enhanced delivery of the chemotherapeutic agent, increasing the exposure of tumor cells to these agents and subsequently augmenting their cell-killing effects [99].

In a previous multicenter phase 3 study, the feasibility of HAIC combined with sorafenib versus sorafenib was estimated in patients with portal vein invasion [29]. At the data cutoff, the median OS was 13.37 months in the SoraHAIC group versus 7.13 months in the sorafenib group. The soraHAIC group showed a higher ORR (40.8% versus 2.46%; $p < 0.001$) and a longer median PFS (7.03 months versus 2.6 months; $p < 0.001$) than the sorafenib group. Although more grade 3 or 4 AEs were observed in the SoraHAIC group than in the sorafenib group, they were manageable by dose modification or treatment interruption. Recently, a novel treatment scheme of sorafenib plus 3cir-OFF HAIC for HCC patients with PVTT was investigated in a phase 2 RCT; the enrolled patients in the soraHAIC group received 3cir-OFF HAIC treatment with concurrent oral sorafenib (400 mg twice daily) [30]. Similar survival advantages and acceptable safety profiles were observed in the soraHAIC group compared with the sorafenib group.

Currently, it has not been determined whether sorafenib combined with HAIC is more effective than HAIC alone, and whether the survival benefits of HAIC-FOLFOX plus sorafenib were attributed to HAIC alone or the synergistic effect of HAIC and sorafenib remains unclear. A retrospective study was conducted to compare HAIC-FOLFOX plus sorafenib with HAIC alone in patients with advanced HCC [100]. Patients in the soraHAIC group obtained a longer median OS (12.9 months versus 10.5 months; $p = 0.025$) and better PFS (7.0 months versus 5.3 months; $p = 0.046$) than the HAIC alone group. And the disease control rate (DCR) was significantly higher in the soraHAIC group than in the HAIC alone group according to RECIST 1.1 criteria (74.8% versus 61.1%, $p = 0.03$). Collectively, the addition of sorafenib to HAIC-FOLFOX treatment may delay tumor progression and extend patients' survival period through the disease stabilization of sorafenib and local tumor burden control of HAIC.

In recent years, HAIC-FOLFOX and ICIs have shown promising efficacy in advanced HCC, and several retrospective studies also indicated that ICIs combined with HAIC-FOLFOX could achieve better survival benefits and tumor response rate [101–103]. Mei et al. conducted a retrospective study and compared the efficacy of HAIC plus anti-PD-1 inhibitors (HAICAP) with HAIC in advanced HCC [101]. The reported results indicated that HAICAP gained better treatment response and more survival benefits than HAIC alone, with a median OS of 18.0 months versus 14.6 months and a median PFS of 10.0 months versus 5.6 months respectively in the HAICAP cohort and HAIC cohort. The intrahepatic response (85% versus 74%; $p = 0.045$) and DCR (83%

versus 66%; $p = 0.006$) were higher in the HAICAP cohort than in the HAIC cohort.

The combination of chemotherapy and ICIs has been recommended as the first-line treatment for various malignancies, such as lung cancer and gastric cancer [104–106]. The potential mechanisms underlying the synergistic effects between chemotherapy and ICIs have been explored using preclinical models. Oxaliplatin, a component of the FOLFOX regimen, has been shown to increase the expression of human leucocyte antigen (HLA) and enhance T cell stimulation, thereby activating the adaptive immune system [107]. Platinum compounds may also disrupt immunosuppression by dephosphorylating STAT6, resulting in decreased expression of the T cell inhibitory molecule programmed death receptor–ligand 2 on human tumor cells and increased T cell-stimulating potential of dendritic cells. This restoration of immuno-surveillance may help counteract tumor immune evasion [108]. Furthermore, oxaliplatin may increase the antigenicity of tumor cells by inducing immunogenic cell death and reducing immunosuppression within the tumor microenvironment [56, 109]. In syngeneic tumor graft models, the combination of oxaliplatin and anti-PD-1 agent was found to achieve superior outcomes than single anti-PD-1 drugs, by inhibiting the HCC tumor growth and TGF- β secretion and augmenting the inflammatory cytokine secretion [109]. Taken together, these preclinical findings provided a biological rationale for the therapeutic potential of combining ICIs with HAIC-FOLFOX for the treatment of HCC.

Triple therapy scheme of MTAs, ICIs, and HAIC-FOLFOX

HCC is a complex disease with multiple signaling pathways involved in its carcinogenesis [110]. Recently, immune-based combination therapies like dual ICIs [111], ICIs combined with MTAs [6, 112], and ICIs combined with local treatment have shown promising antitumor activity and clinical outcomes combined with systemic monotherapy [113]. In addition, a few studies have reported that HAIC might yield a synergistic effect in combination with MTAs or ICIs, as described above. A multicenter retrospective study was conducted to investigate the efficacy and safety profile of lenvatinib, toripalimab, plus HAIC (LeToHAIC) versus lenvatinib for patients with advanced HCC [114]. The LeToHAIC group showed a longer median PFS (11.1 months versus 5.1 months, $p < 0.001$) and a higher ORR (RECIST: 59.2% versus 9.3%, $p < 0.001$) than the lenvatinib group. Moreover, complete response was observed in 14.1% of patients in the LeToHAIC group. Another phase 2 single-arm trial concerning HAIC plus Lenvatinib and toripalimab as the first-line treatment in patients with high-risk advanced

HCC further demonstrated the encouraging antitumor efficacy and acceptable toxicity profile of this scheme [33]. The median OS was 17.9 months after the follow-up was extended, and the median PFS was 10.4 months. The ORR was 63.9% per RECIST and 66.7% per mRECIST. The most common TRAEs included hypoalbuminemia (69.4%), elevated AST (66.7%), elevated ALT (63.2%), thrombocytopenia (52.8%), and anemia (50%).

The encouraging clinical outcomes of a combination of pembrolizumab and lenvatinib have been reported in a phase I trial enrolling 104 patients with unresectable HCC [112]. To determine whether the incorporation of pembrolizumab plus lenvatinib into HAIC obtains improved survival outcomes, a multicenter retrospective study was conducted to investigate the efficacy and safety of pembrolizumab plus lenvatinib plus HAIC (PLH) versus pembrolizumab plus lenvatinib (PL) in patients with unresectable HCC exhibiting PD-L1 staining [111]. At the final follow-up, the longer median OS (17.7 months versus 12.6 months; $p=0.001$) and longer median PFS (10.9 months versus 6.8 months; $p=0.001$) were observed in the PLH group than in the PL group. No significant difference was detected in the incidence of each AE between groups, and these AEs were controllable. Nowadays, atezolizumab plus bevacizumab demonstrated better survival benefits versus sorafenib in patients with unresectable HCC in the IMbrave150 trial and were approved as the first-line systemic therapy for these patients [6]. However, the updated result of IMbrave 150 indicated that this combination had limited antitumor activity in high-risk advanced HCC [12]. Recently, Xin et al. conducted a multicenter retrospective study to explore the preliminary evidence of triple therapy with atezolizumab, bevacizumab, and HAIC for advanced HCC patients [115]. The ORR in the 52 eligible patients was 44.2% and 67.3% based on RECIST1.1 and mRECIST criteria. The median PFS of patients was 10.6 months, and 6- and 12-month OS rates were 96.2% and 86.5%, respectively. Atezolizumab plus bevacizumab combined with HAIC appear to have a significant therapeutic effect in advanced HCC and the AEs are manageable, which need to be further confirmed by more prospective trials.

Recommendation: (1) FOLFOX-based HAIC treatment combined with sorafenib showed superior survival advantages than single sorafenib and can be used in patients with advanced HCC, especially those with portal vein tumor thrombus. (evidence level: high; recommendation strength: strong; agree level: 81.1%). (No.14 in Table 2).

(2) HAIC-FOLFOX combined with ICIs or the triple therapy scheme of MTAs, ICIs, and HAIC-FOLFOX show favorable efficacy and safety profile and may be appropriate for advanced HCC. (evidence level: low; recommendation strength: weak; agree level: 94.6%). (No.15 in Table 2).

HAIC-FOLFOX combined TACE

TACE is a common regimen as the first-line treatment for initially unresectable HCC without EHS [116]. However, the clinical outcomes of c-TACE or DEB-TACE in some subgroups such as HCC patients with large unresectable HCC or HCC patients with PVTT are still not satisfactory [117, 118]. It has been proposed that TACE combined with HAIC could make up for the deficiency of each other and yield the enhanced anti-tumor effect and mild AEs [75, 76]. TACE could delay the flow within the tumor-feeding artery and significantly prolongs the contact time between tumors and chemotherapeutic agents [76]. Additionally, HAIC enhances drug exposure by delivering a high concentration of chemotherapy drugs, which may clear most residual lesions and avoid embolization-related AEs. A retrospective study evaluating the feasibility of DEB-TACE combined with HAIC-FOLFOX in patients with large unresectable HCC showed that the TACE-HAIC combination was tolerable and obtained better OS than DEB-TACE [76]. The patients receiving TACE-HAIC treatment had longer median OS (19.0 months versus 14.0 months; $p=0.008$), median PFS (9.3 months versus 6.3 months; $p=0.005$), and higher ORR (71.0% versus 53.1%, $p=0.033$) than those who received DEB-TACE. And the grade 3 or 4 AEs incidence was similar between the two groups (37.7% versus 28.1%, $p=0.242$). Another retrospective study suggested that TACE-HAIC treatment was a more efficient strategy for patients with initially unresectable HCC [119], with a higher conversion rate (48.8% versus 9.5%; $p<0.001$) and a longer median PFS (not available versus 9.2 months; $p=0.003$). And similar rates of grade 3 or 4 AEs were observed in these groups. To investigate the efficacy and safety of TACE combined with HAIC-FOLFOX for patients with HCC and PVTT, Li et al. conducted a retrospective study enrolling HCC patients with PVTT undergoing cTACE-HAIC treatment or cTACE alone [75]. The results of a propensity score-matched analysis showed that patients obtained a longer median OS (9.0 months versus 5.0 months, $p=0.018$) and a longer median PFS (6.0 months versus 2.0 months, $p=0.045$) in cTACE-HAIC group than cTACE group. Similarly, the matched groups did not differ regarding grade 3 or 4 AEs.

Recommendation: (1) TACE combined with HAIC may be used for patients with multiple tumor lesions located in different liver lobes. (evidence level: low; recommendation strength: weak; agree level: 89.2%). (No.16 in Table 2).

(2) If the lesions have multiple blood supply sources, TACE can be performed to embolize the non-main tumor-feeding artery while HAIC can be performed to perfusion the main tumor-feeding artery. (evidence level: low; recommendation strength: weak; agree level: 83.7%). (No.17 in Table 2).

(3) If the lesions have an abnormally rich blood supply, TACE can be used to embolize part of the tumor-feeding artery first and then combined with HAIC. (evidence level: low; recommendation strength: weak; agree level: 81.1%). (No.18 in Table 2).

(4) If some active tumor lesions remain after multiple courses of HAIC treatments, combined TACE can be performed for embolization. (evidence level: low; recommendation strength: weak; agree level: 97.3%). (No.19 in Table 2).

Summary

Currently, both HAIC-FOLFOX monotherapy and the combination of HAIC-FOLFOX with sorafenib have demonstrated superior survival benefits compared to sorafenib alone for advanced HCC patients in phase 3 RCTs. However, further studies are needed to compare the safety and efficacy of HAIC alone and the combination of HAIC and sorafenib. As a first-line therapeutic option for unresectable large HCC, single HAIC-FOLFOX has been validated to show better tumor response, longer PFS, and lower toxicities when compared to TACE. For patients with microvascular invasion HCC, adjuvant single HAIC-FOLFOX therapy has shown potential in improving the median disease-free survival after resection. Moreover, neoadjuvant HAIC-FOLFOX monotherapy has demonstrated an increase in the 3-year overall survival rate for patients with resectable HCC beyond the Milan criteria.

The complications of HAIC and corresponding treatments

The complications of HAIC-FOLFOX-based treatment are mainly categorized into HAIC procedure-related AEs, infusion-related reactions, and drug-related toxicities caused by FOLFOX regimens or other additional agents, such as MTAs and ICIs. Overall, HAIC-FOLFOX treatment appears to be a minimally invasive and safe therapeutic scheme, treatment-related death is rarely reported in current studies, and the incidence of AEs is relatively low, most of which could be resolved by symptomatic treatment, dose reduction, dose interruption, or dose discontinuations.

Catheter occlusion attributable to thrombus formation or dislocation of the catheter tip is the common HAIC procedure-related AEs [120]. The heparin was injected to prevent thrombotic obstruction of the catheter once it was placed. When the subsequent injection is difficult, the catheter should be checked by injecting heparin, and the catheter should be replaced if occlusion of the catheter is confirmed. If the dislocation of the catheter tip happens, patients should be transferred to the digital subtraction angiography room for catheter repositioning [31].

Additionally, it should be noted that the operation for puncture and catheterization should be gentle and standardized to prevent the vascular complication (i.e., stenosis, occlusion, or pseudo-aneurysm) of the blood vessel, which is occasionally observed in the HAIC procedure, and the anticoagulants such as rivaroxaban can be used if necessary.

Specific abdominal pain is frequently observed in clinical trials and routine clinical practice, possibly due to the rapid tumor-shrinking or arterial spasm associated with oxaliplatin infusion [32]. Generally, such pain was mostly minded and observed during the oxaliplatin infusion process and was shortly relieved after the infusion. However, in a small portion of patients, this pain can be acute and severe but is quickly relieved by suspending the infusion of oxaliplatin or symptomatic treatments, such as lidocaine for analgesia and anisodamine for spasmolysis [28]. For infusion-related reactions, the infusion rate might be modified as follows: Grade 1, slowed by 50% with the original protocol; Grade 2, interrupted and symptomatic treatment was to be administered, and once the infusion-related reaction was decreased to grade 1 or resolved, the infusion rate could be resumed at 50% with the original protocol; Grade 3 or 4, interrupted and symptomatic treatment to be administered, and the patient was to be discontinued from HAIC [28, 32].

Chemo-therapeutics-related toxicity in HAIC treatment is generally tolerable and mild compared with systemic chemotherapy or TKIs, and the common AEs, including thrombocytopenia, neutropenia, vomiting, diarrhea, liver function injuries (i.e., alanine aminotransferase increased, aspartate aminotransferase increased, total bilirubin increased) and renal function injuries (i.e., creatinine elevation) [121]. Additional complications, such as hand-foot syndrome and hypertension, are also reported in studies of HAIC-based combination strategies associated with the combined drugs [29, 114]. In principle, the drug-related complications in HAIC-FOLFOX-based treatment are acceptable and could be resolved by symptomatic treatments (i.e., increasing WBC or PLT, antibiotic therapy, antiemetics, and hepatic functional protection). However, suppose serious AEs like hepatic failure, gastrointestinal bleeding, or ascites happen, clinicians should pause the current HAIC treatment and perform the symptomatic treatments such as endoscopic hemostasis or medical treatment in time, and the HAIC treatment discontinuation may be considered if necessary.

Recommendation: The management principle of HAIC-related adverse reactions: Grade 1–2 adverse events, symptomatic treatment, no dose adjustment; For grade 3 or 4 adverse events, the appropriate perfusion should be terminated, and active symptomatic treatment should be carried out. The dose of chemotherapy drugs should be adjusted accordingly in the next course of treatment, and HAIC therapy should be terminated if necessary. (evidence level: high;

recommendation strength: strong; agree level: 100%). (No.5 in Table 2).

Predictive factors of treatment response to HAIC treatment

The modality of HAIC-FOLFOX has shown promising anti-tumor activities in advanced HCC, and the HAIC-FOLFOX responders are proven to have superior survival advantages with longer PFS and OS than the HAIC-FOLFOX non-responders [29, 32]. However, due to the heterogeneity of tumors, the sensitivity of advanced HCC to chemotherapy varies greatly. With the development of novel promising systemic treatments and growing demand for efficient alternative therapy for HCC patients with nonresponse features, it is necessary to identify the potential responder of HAIC-FOLFOX treatment and switch to other therapeutic regimens early for potential HAIC-FOLFOX non-responders, which may maximize the survival benefits of the whole population. For advanced HCC, few validated predictive response biomarkers have yet to be identified. The potential predictive biomarkers, such as alpha-fetoprotein (AFP), serum VEGF level (≥ 100 pg/mL), neutrophil-to-lymphocyte ratio, and des- γ -carboxy-prothrombin, have been supported by preliminary evidence of several studies of HAIC treatment for HCC, which need to be further validated in large-scale prospective trials [122–125]. In a recent phase 3 study of HAIC-FOLFOX treatment in patients with advanced HCC, Lyu et al. performed a genetic profiling in the tumor and the corresponding liver tissue biopsies of available patients and built a newly developed 15-mutant-gene (*PIK3CD*, *HNRN-PCL4*, *NBPF20*, *TCHH*, *RAB3-GAP2*, *FGFR4*, *ARID1B*, *AGO2*, *PGR*, *KMT2A*, *SLX4*, *NF1*, *ERBB2*, *AXIN2*, and *PRKD2*) prediction model, which could identify 83% of patients with response to HAIC-FOLFOX treatment [32]. Additionally, the data suggested that an early decrease in the AFP concentration in the first two cycles of HAIC is associated with imaging response, which was beneficial for early determining disease courses and formulating treatment plans. Another biomolecular exploratory phase 2 study of the combination treatment of HAIC-FOLFOX, lenvatinib, and toripalimab for patients with high-risk advanced HCC showed that patients with low levels of both C–C motif chemokine ligand 28 (CCL28) and betacellulin (BTC) had poor prognosis (10.2 versus 20.3 months; $p < 0.001$) [33]. Therefore, the levels of CCL28 or BTC before the treatment may serve as a predictive biomarker for HCC patients receiving this triple combination treatment.

Recommendation: HAIC-FOLFOX responders generally obtain better clinical outcomes than HAIC-FOLFOX non-responders; early identification of potential responders would be essential for formulating an efficient HCC

management with a satisfactory prognosis. (evidence level: moderate; recommendation strength: strong; agree level: 100%). (No.6 in Table 2).

Perspective

Currently, the promising efficacy of HAIC-FOLFOX regimens has been validated by several high-quality clinical trials. Considering that atezolizumab plus bevacizumab is the new front-line owing to the encouraging efficacy reported in the IMbrave150 study, HAIC-FOLFOX should be compared with the front-line atezolizumab plus bevacizumab combination in future research to clarify its role in current clinical practices, especially in high-risk locally advanced HCC treatment. HAIC-based combination strategies have played an important role in advanced HCC management. However, with the emergence of novel systemic drugs in recent years, more scheme combinations would be proposed, and several questions need to be further explored: (1) What systemic regimen can be combined with HAIC therapy? (2) How to combine systemic regimens with HAIC treatment? (i.e., optimal dose, infusion time, number, of course, schedule of administration) (3) How to adjust the combination strategies once tumor progression or unacceptable toxicities occur?

Finally, major participants in current clinical trials of HAIC-FOLFOX treatment were infected with HBV; the superior benefit of HAIC-FOLFOX to sorafenib was still unclear for patients with extensive liver involvement caused by other etiology like hepatitis C virus infection or alcohol, which may impact the generalizability of the results to a broader population. Although sorafenib plus systemic FOLFOX regimen yielded favorable survival benefits in a phase 2 study, and the participants mainly consisted of HCC patients caused by alcohol, hepatitis C virus infection, or metabolic syndrome, the global multicenter RCTs are required to support the use of FOLFOX regimen in HAIC treatment for HCC patients of various etiologies [126]. In conclusion, the HAIC-FOLFOX regimen and the related combination strategies have been proven to prolong the survival time and improve the prognosis of HCC patients, but there is still a need for large sample size RCTs to provide more high-level evidence support. With the participation of more medical centers and ongoing HAIC-related clinical studies, HAIC-FOLFOX-based monotherapy or combination strategies may provide an alternative front-line option for HCC patients worldwide.

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Data availability All data included in this study are available upon request by contact with the corresponding author (drmingzhao@outlook.com).

Declarations

Conflict of interest Ming Zhao, Zhi Guo, Ying-Hua Zou, Xiao Li, Zhi-Ping Yan, Min-Shan Chen, Wei-Jun Fan, Hai-Liang Li, Ji-Jin Yang, Xiao-Ming Chen, Lin-Feng Xu, Yue-Wei Zhang, Kang-Shun Zhu, Jun-Hui Sun, Jia-Ping Li, Yong Jin, Hai-Peng Yu, Feng Duan, Bin Xiong, Guo-Wen Yin, Hai-Lan Lin, Yi-Long Ma, Hua-Ming Wang, Shan-Zhi Gu, Tong-Guo Si, Xiao-Dong Wang, Chang Zhao, Wen-Chang Yu, Jian-Hai Guo, Jian Zhai, Yong-Hui Huang, Wei-Yu Wang, Hai-Feng Lin, Yang-Kui Gu, Jin-Zhang Chen, Jian-Peng Wang, Yi-Min Zhang, Jun-Zhe Yi, Ning Lyu declare no potential conflicts of interest.

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