Review

Hepatic Artery Infusion Chemotherapy of Hepatocellular Carcinoma: Clinical Advancements

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Review

Hepatic Artery Infusion Chemotherapy of Hepatocellular Carcinoma: Clinical Advancements

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Abstract: Hepatocellular carcinoma (HCC) in intermediate and advanced stages remains a therapeutic challenge. Hepatic artery infusion chemotherapy (HAIC) is a well-established locoregional therapy for unresectable HCC. HAIC, either alone or in combination with systemic therapies, has shown encouraging therapeutic outcomes for the treatment of HCC patients with intermediate and advanced diseases in recent studies. This review summarizes the clinical advances in HAIC for HCC, highlighting HAIC regimens and their therapeutic outcomes.

Keywords: hepatocellular carcinoma; hepatic artery infusion chemotherapy; clinical study

1. Introduction

Hepatocellular carcinoma (HCC) represents one of the most common malignancies globally and the third leading cause of cancer-related death [1]. China is a high-incidence region for HCC, accounting for approximately 50% of newly diagnosed cases worldwide. Additionally, the majority of HCC patients are diagnosed at intermediate or advanced stages, precluding them from potentially curative treatments such as surgical resection, liver transplantation, or ablation, leading to a relatively poor prognosis [2]. Based on the Barcelona Clinic Liver Cancer (BCLC) staging system, the standard treatment methods for intermediate and advanced HCC are transarterial chemoembolization (TACE) and systemic therapies, respectively [3]. However, their therapeutic efficacy is still unsatisfactory. Therefore, it is necessary to explore new treatment strategies, particularly using the combination of locoregional therapies and systemic ones [4,5].

Hepatic artery infusion chemotherapy (HAIC), also known as transcatheter arterial infusion (TAI), is a well-established locoregional therapy for HCC. Recently, with the improvement of the chemotherapy regimen and transcatheter technique, HAIC has achieved remarkable efficacy in the treatment of HCC. Moreover, the combination of HAIC with other treatment, such as molecular targeted therapy and immunotherapy, has demonstrated encouraging outcomes [6,7]. This article reviews the clinical advances in HAIC for HCC, with a focus on the current HAIC regimens and their therapeutic outcomes.

2. Definition and Technical Classification

2.1. Definition

HAIC is defined as the injection of chemotherapeutic agents in the hepatic artery via an intraarterially inserted catheter. In this way, highly concentrated doses of chemtherapy may effictively be delivered to the liver with reduced systemic toxicity [8]. HAIC is essentially a

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specialized form of chemotherapy, distinguished from conventional chemotherapy by its administration via the arterial route.

2.2. Technical Classification

HAIC primarily encompasses three procedural techniques: surgically implanted subcutaneous pump, temporary indwelling hepatic artery catheter, and percutaneously implanted port.

2.2.1. Surgically Implanted Subcutaneous Pump

The surgically implanted subcutaneous pump represents a classic technique for HAIC, which is still utilized in the United States and European countries. This procedure requires laparotomy under direct visualization to ensure precise catheter placement. Specifically, the catheter is inserted retrograde into the gastroduodenal artery (GDA) and secured with sutures. During the procedure, extrahepatic arterial branches are ligated to prevent extrahepatic chemotherapeutic exposure, while accessory hepatic arteries are occluded to minimize competitive intrahepatic flow. The catheter tip is precisely positioned at the GDA-common hepatic artery (CHA) junction to optimize hepatic perfusion. Finally, the pump is connected to the catheter and implanted in a subcutaneous pocket [9,10].

This technique utilizes a single catheter insertion, enabling repeated administration and adaptability to various chemotherapy regimens. However, several significant limitations exist. First, the procedure requires laparotomy performed by experienced surgeons and typically requires concomitant cholecystectomy, resulting in substantial invasiveness and potential surgical complications [11]. Second, although preoperative CT can assess hepatic arterial anatomy and the aberrant vessels can be managed, this technique demonstrates limited efficacy in controlling collateral arterial supply to HCC (e.g., subphrenic artery) and hepatic artery branches supplying extrahepatic regions (e.g., right gastric artery). Thirdly, catheter placement into arteries beyond the GDA is occasionally required, posing considerable technical difficulties [12]. These limitations collectively compromise the safety profile and therapeutic efficacy of HAIC.

2.2.2. Temporary Indwelling Hepatic Artery Catheter

The temporary indwelling hepatic artery catheter has been a popular technique in China in recent years [13]. This procedure involves the percutaneous insertion of a catheter in the proper hepatic artery or the tumor-feeding hepatic artery branch under digital subtraction angiography (DSA) guidance. The external end of the catheter is retained outside the skin of the arterial approach and connect with a infusion pump for chemotherapy. After the completion of single cession of chemotherapy, the catheter was removed with the puncture arterial hemostasis. It is noted that before the the indwelling catheter placement, routine arterial angiography is jperformed to evaluate hepatic arterial anatomy and tumor blood supply. When necessary, vascular embolization is employed to address hepatic artery variations or extrahepatic collateral blood supply, thereby ensuring selective drug distribution to the liver or the tumor [14]. This procedure needs to be repeated according to the HAIC treatment schedele.

As a minimally invasive interventional procedure, this technique offers several advantages, including operational simplicity and rapid postoperative recovery. The flexibility to adjust catheter positioning according to therapeutic requirements further enhances its clinical utility. However, certain limitations should be noted. Firstly, repeated catheterization and bedridden infusion chemotherapy may impair patient tolerance and compliance. Secondly, the tip of the indwelling catheter may dislocated due to vomiting, coughing or drastic positional changes, resulting in improper drug delivery. Finally, due to the limited duration of catheter placement, this approach is unsuitable for chemotherapy regimens requiring prolonged infusion or short-term repeated administration [11].

2.2.3. Percutaneously Implanted Port

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The percutaneously implanted port represents a significant advancement in HAIC technology, with widespread clinical adoption across Asian regions. This minimally invasive procedure employs the "tip-fixation method" to precisely position an indwelling side-holed catheter within GDA. The catheter is strategically placed with its side-hole aligned at the origin of the common hepatic artery. Through a coaxial approach, a microcatheter is advanced via the indwelling catheter, passing through the side-hole for optimal positioning. The distal tip of the indwelling catheter is then securely anchored within the GDA using either embolization coils or an NBCA-lipiodol mixture. Finally, the proximal end of the indwelling catheter is connected to an implantable port system for drug infusion [15–17].

This technique integrates the advantages of previous HAIC techniques, facilitating routine angiography and necessary procedures to redistribute intrahepatic or extrahepatic blood flow, thereby enhancing the efficacy and safety of chemotherapy. Additionally, it allows for multiple uses following a single catheterization, accommodating various chemotherapy regimens, improving patient comfort and compliance, and reducing overall treatment costs [18–22].

3. Therapeutic Mechanism and Chemotherapeutic Agents

3.1. Therapeutic Mechanism

The basis for the application of HAIC in treating hepatic malignancies lies in the disparity of blood supply between normal liver tissue and hepatic malignancies. Normal liver tissue derives approximately 75% of its blood supply from the portal vein, with the remaining 25% supplied by the hepatic artery. In contrast, hepatic malignancies are mainly nourished by the hepatic artery [23]. Therefore, it is reasonable to use the hepatic artery as an approach to deliver concentrated doses of chemtherapy to the tumor bed.

Precisely, intra-arterial administration augments the first-pass effect of drug within the liver and improve hepatic drug uptake. Studies have demonstrated that hepatic arterial infusion of floxuridine or 5-fluorouracil can achieve intrahepatic uptake rates of up to 90% and 19-90%, respectively. These rates significantly exceed those observed with conventional intravenous administration. Accordingly, intratumoral drug concentration are also markedly elevated [9,24]. In addition, transcatheter arterial infusion can enhance drug penetration, thus improving drug distribution within the tumor [25]. By leveraging these advantages, HAIC enhances chemotherapy efficacy for HCC while minimizing adverse events (AEs).

3.2. Drug Selection

When selecting chemotherapeutic agents for HAIC, it is crucial to adhere to the rational principles underlying conventional systemic chemotherapy, while also taking into account the unique characteristics of intra-arterial administration. Priority should be given to tumor-sensitive drugs and prototype drugs, with the use of combinations or sequential regimens of agents with differing mechanisms strategically designed to optimize the therapeutic efficacy [26,27]. Drugs that share similar toxic effects or exhibit cumulative hepatotoxicity, as well as those with antagonistic pharmacological effects or the potential to inactivate one another, should be avoided. The primary objective is to minimize toxicity while maximizing therapeutic efficacy against the tumor and decreasing side effects both systemically and within the liver.

Cell cycle–nonspecific drugs, which are concentration-dependent, encompass alkylating agents, antibiotics, platinum drugs, and miscellaneous antitumor agents. Their cytotoxic effects correlate directly with drug concentration, and thus short-term, high-dose infusion chemotherapy is generally adopted. For instance, platinu-based chemotherapeutic agents, such as oxaliplatin and cisplatin, are usually administered via rapid injection over a short period.

In contrast, cell cycle-specific drugs are time-dependent, meaning that after reaching an effective dose, prolonged exposure of the drug to the tumor is required to exert cytotoxic effects. Hence, continuous infusion chemotherapy is prevalently utilized, with the doses being adjusted by clinical

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experience. The time-dependent drugs commonly used in HAIC include fluorouracil and floxuridine, which are typically administered with continuous infusion [28,29].

4. Patient Selection and Perioperative Management

4.1. Patient Selection

HAIC is generally indicated for HCC patients with multiple intrahepatic lesions or massive tumors, portal vein invasion, liver function classified as Child-Pugh class A or B, and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2. Additionally, HAIC can also be an alternative option for advanced-stage patients with limited extrahepatic metastasis [6,7].

HAIC is currently recommended in several guidelines for the treatment of HCC. The clinical practice guidelines for HCC formulated by the Japanese Society of Hepatology (JSH) suggest HAIC as a treatment choice for patients with multiple intrahepatic lesions (n≥4) or vascular invasion [30]. The guidelines for the management of HCC developed by the Korean Liver Cancer Association - National Cancer Center (KLCA-NCC) recommend HAIC for those patients with portal vein invasion and without extrahepatic spread, who have either failed or are not eligible for first-line or second-line systemic therapy [31]. Notably, the guidelines for the diagnosis and treatment of primary liver cancer issued by the Chinese Society of Clinical Oncology (CSCO) have broadened the indications of HAIC. Specifically, it encompasses: 1) patients in Stage I b to II b with a single tumor larger than 7 cm who reject or are not suitable for surgical resection; 2) Stage III patients who decline molecular targeted therapy or systemic chemotherapy, or for whom such treatments prove ineffective; 3) Stage III b patients with certain extrahepatic metastases, where the application of HAIC can be determined at the clinician's discretion; 4) Stage IV patients who are unable or unwilling to undergo liver transplantation [13].

4.2. Perioperative Management

Before initiating HAIC treatment, a thorough assessment of the patient is essential. This assessment should include a detailed medical history, physical examination, laboratory tests, and imaging studies. Laboratory tests primarily focus on evaluating liver and renal function, tumor markers, coagulation status, and complete blood counts. Imaging studies typically involve dynamic contrast-enhanced CT or MRI, with PET-CT performed if necessary. In instances where the diagnosis of HCC is inconclusive, or there is suspicion of other hepatic malignancies, a biopsy should be conducted to establish a definitive pathological diagnosis.

Preoperative evaluation of patients focuses on liver function, performance status, and tumor burden. Regarding liver function, high-quality clinical trials typically include patients with compensated liver function (Child-Pugh A to B7) as candidates for HAIC alone or in combination with systemic therapy [32,33]. Other real-world studies have shown that patients with Child-Pugh B liver function generally tolerate HAIC well [6]. Similarly, most clinical trials adopt an ECOG performance status of 0-1 as the inclusion criterion for HAIC therapy [7], whereas an ECOG score of 0-2 is widely accepted in real-world studies [6]. In terms of tumor burden, HAIC is indicated for HCC patients with multiple intrahepatic lesions or massive tumors and portal vein invasion. However, when the tumor burden reaches ≥50% of the total liver volume, the efficacy of HAIC is compromised [34].

5. HAIC Chemotherapy Regimens and Outcomes

Currently, several HAIC regimens are used in clinical settings, including the FOLFOX regimen, the low-dose FP regimen, the FAIT regimen, the New FP regimen, and the oxaliplatin plus raltitrexed regimen. The reported outcomes for HCC vary depending on the chemotherapy regimen.

5.1. FOLFOX Regimen

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The FOLFOX regimen is the recommended first-line systemic chemotherapy for HCC in China and has been widely adopted in HAIC treatment [13]. The standard FOLFOX regimen for HAIC includes oxaliplatin (85 or 130 mg/m², administered via intra-arterial infusion over three hours on day 1), leucovorin (200 mg/m², delivered via intra-arterial infusion over three to five hours on day 1), and fluorouracil (400 mg/m² as an intra-arterial bolus, followed by a continuous infusion of 2400 mg/m² over 46 hours). Treatment is typically administered every three weeks for six cycles, with adjustments made based on tumor response [7]. The FOLFOX regimen combines the concentration-dependent effects of platinum-based chemotherapy agents and the time-dependent effects of fluorouracil, with leucovorin primarily used to enhance the efficacy of fluorouracil.

HAIC treatment has demonstrated significant survival benefits for patients with advanced HCC. A prospective, non-randomized Phase II study compared the efficacy of HAIC and TACE in patients with massive unresectable HCC. The results showed that HAIC achieved significantly higher partial response rates and disease control rates compared to TACE (52.6% vs. 9.8%, $P < 0.001$; 83.8% vs. 52.5%, $P < 0.01$) [35]. Another randomized controlled Phase III trial evaluated HAIC versus TACE in patients with unresectable HCC without vascular invasion or extrahepatic metastasis. HAIC as a first-line treatment significantly improved overall survival (OS) (23.1 months vs. 16.1 months, $P < 0.001$) and reduced the incidence of severe AEs (19% vs. 30%, $P = 0.03$) [36]. A recent randomized controlled Phase III trial comparing HAIC with sorafenib as first-line therapy for advanced HCC revealed that HAIC significantly prolonged OS compared to sorafenib (13.9 months vs. 8.2 months, $P < 0.001$) [32]. Additionally, a Phase III, multicenter, prospective, open-label, randomized controlled trial compared postoperative adjuvant HAIC with routine follow-up in HCC patients with microvascular invasion. HAIC significantly extended median disease-free survival (20.3 months vs. 10.0 months, $P < 0.001$) [37].

HAIC combined with targeted therapy has also emerged as a viable option for advanced HCC. An earlier randomized controlled trial compared sorafenib plus HAIC to sorafenib alone in patients with advanced HCC and portal vein invasion. The combination therapy resulted in longer OS (13.37 months vs. 7.13 months, $P < 0.001$), longer progression-free survival (PFS) (7.03 months vs. 2.6 months, $P < 0.001$), and a higher tumor response rate (40.8% vs. 2.46%, $P < 0.001$), although grade 3/4 AEs were more frequent in the combination group [38]. Another Phase II clinical trial confirmed the superior OS of sorafenib plus HAIC compared to sorafenib alone (16.3 months vs. 6.5 months, $P < 0.001$) in advanced HCC with major portal vein tumor thrombosis [33].

Combining HAIC with immunotherapy, as well as with both targeted therapy and immunotherapy, has also shown promising efficacy and safety [39–42]. A Phase II, single-center, single-arm study treated advanced, high-risk HCC patients with a combination of lenvatinib, toripalimab, and HAIC, achieving a 6-month PFS rate of 80.6% [41]. Another single-arm Phase II clinical study evaluated HAIC combined with camrelizumab and apatinib for advanced HCC, reporting an objective response rate of 77.1% and a median PFS of 10.38 months [42].

Other combination therapies, such as HAIC plus TACE or ablation, have also been explored [43,44]. A Phase II, prospective, non-randomized clinical study compared TACE combined with HAIC to TACE alone in unresectable HCC patients without extrahepatic metastasis. The combination therapy showed significant improvements in overall response rate and median PFS (68.9% vs. 45.9%, $P < 0.05$; 8 months vs. 4.5 months, $P < 0.001$) [44]. Several clinical trials of combination therapies are currently underway.

5.2. Low-Dose FP Regimen

The low-dose FP regimen was first introduced by Japanese researchers for HAIC chemotherapy, with its initial clinical application reported in 1999 [45]. The standard low-dose FP regimen consists of intra-arterial infusion of low-dose cisplatin (10 mg/day, infused over 30 minutes) followed by fluorouracil (250 mg/day, infused over 3–5 hours). This regimen is administered once daily for five consecutive days per week, with a two-day break, over a four-week treatment cycle. In this regimen, cisplatin functions primarily as a modulator rather than a direct effector, enhancing the antitumor

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activity of fluorouracil by increasing intracellular reduced folate concentrations, thereby creating a synergistic effect. The low-dose FP regimen requires frequent, short-duration intra-arterial administrations, making it particularly suitable for use with percutaneously implanted port-catheter systems.

Early retrospective studies evaluating the low-dose FP regimen as a standalone treatment for advanced HCC with portal vein invasion reported tumor response rates ranging from 20% to 71% and overall survival (OS) durations of 7.3 to 15.9 months [45–52]. A phase I/II study investigated the safety and efficacy of combining sorafenib with HAIC in patients with advanced HCC. The study demonstrated a response rate of 38.9%, a disease control rate of 77.8%, a median time-to-progression of 9.7 months, and a 1-year survival rate of 88.2% [53]. Additionally, an open-label, non-comparative phase II trial assessed survival outcomes in advanced HCC patients treated with HAIC or HAIC followed by sorafenib. The results revealed 1-year and 2-year survival rates of 64.0% and 48.3%, respectively [54].

A recent randomized controlled phase III trial compared low-dose FP combined with sorafenib to sorafenib monotherapy in advanced HCC. While no statistically significant difference in OS was observed between the two groups (11.8 months vs. 11.5 months, P = 0.955), subgroup analysis indicated that patients with main portal vein invasion who received the combination therapy had significantly longer median OS compared to those receiving sorafenib alone (11.4 months vs. 6.5 months, P = 0.05) [55]. These findings suggest that the combination of sorafenib and low-dose FP may offer a survival benefit for HCC patients with portal vein invasion compared to sorafenib monotherapy.

5.3. FAIT Regimen

The FAIT regimen was first reported for the treatment of HCC in 2002 [56]. This regimen combines intra-arterial infusion of fluorouracil with subcutaneous injection of interferon. In this regimen, fluorouracil is administered intra-arterially at a dose of either 500 mg/day or 300 mg/m²/day via continuous infusion for five consecutive days per week during the first two weeks, followed by a two-week break. Interferon is administered as a subcutaneous injection at 5 million U/day, three times per week for four weeks, with a total of 1–4 treatment cycles.

Studies have shown that the objective response rate of the FAIT regimen in HCC patients with portal vein invasion ranges from 24.6% to 73.0%, with overall survival (OS) ranging from 6.9 to 14.7 months [57–65]. Additionally, a Phase II clinical trial demonstrated that combining the FAIT regimen with cisplatin significantly improved both the objective response rate (45.6% vs. 24.6%, P = 0.03) and median OS (17.6 months vs. 10.5 months) compared to the FAIT regimen alone [62].

5.4. New FP Regimen

The new FP regimen combines cisplatin, lipiodol, and fluorouracil. It involves an intra-arterial infusion of 50 mg cisplatin mixed with 5–10 mL lipiodol, followed by a bolus injection of 250 mg fluorouracil and a continuous infusion of 1250 mg/m² fluorouracil over five days, with a two-day rest period. Treatment is administered weekly for two consecutive weeks. In this regimen, the therapeutic efficacy of cisplatin is enhanced by the tumor-targeting properties of lipiodol, while the dose of fluorouracil is increased to maximize antitumor effects.

Several retrospective studies have demonstrated that the new FP regimen achieves superior median overall survival (OS) in advanced HCC patients with vascular invasion compared to both the low-dose FP regimen and sorafenib (24.7 months vs. 16.1 months, $p < 0.05$; and 18 months vs. 9 months, $p < 0.0001$, respectively) [66,67]. Additionally, the combination of lenvatinib and the new FP regimen has shown an impressive objective response rate of 83% in advanced HCC [68]. A single-arm, multicenter Phase II clinical trial evaluating the new FP regimen in HCC patients with portal vein tumor thrombus reported a median disease-free survival of 8.6 months, an OS of 27 months, and an objective response rate of 75% [69].

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A non-randomized prospective cohort study comparing the new FP regimen to sorafenib in HCC patients with significant vascular invasion found that the new FP regimen significantly improved OS (30.4 months vs. 13.2 months, P = 0.013) and objective response rates (71% vs. 10%, P < 0.001) [70]. These findings have been further supported by recent multicenter, large-sample retrospective cohort studies, which indicate that HAIC treatment with the new FP regimen significantly extends OS in patients with locally advanced HCC compared to sorafenib (12 months vs. 7.9 months, P < 0.001) [71].

5.5. Other Regimens

Fluorouracil has a short plasma half-life, requiring prolonged continuous infusion or multiple short-term infusions to achieve its time-dependent chemotherapeutic effects. However, these administration methods can be inconvenient for patients undergoing chemotherapy. Raltitrexed, an alternative antimetabolite chemotherapy agent, is currently being explored for use in HAIC for HCC. Due to its longer plasma half-life compared to fluorouracil, raltitrexed combined with platinum-based drugs may enhance patient tolerance to HAIC [72].

A recent single-arm Phase II clinical trial evaluated the combination of oxaliplatin and raltitrexed in HAIC for intermediate- and advanced-stage HCC. The study reported an objective response rate of 51.4%, with a median progression-free survival (PFS) of 6.7 months, a median disease-free survival of 5.2 months, and a one-year survival rate of 43.2%. In this regimen, oxaliplatin was administered at a dose of 100 mg/m² over 4 hours, while raltitrexed was given at 3 mg/m² via a one-hour intra-arterial infusion, significantly reducing the overall infusion time. HAIC was repeated every three weeks, and no grade 4 treatment-related adverse events (AEs) were observed [73]. Another Phase II prospective clinical trial investigated the use of apatinib combined with HAIC of oxaliplatin and raltitrexed in HCC patients with extrahepatic metastasis who had progressed after first-line systemic therapy. The results demonstrated an objective response rate of 53.8% [74].

6. Adverse Events

AEs associated with HAIC can be broadly categorized into chemotherapy-related AEs and procedure-related AEs [9,75,76].

6.1. Chemotherapy-Related AEs

Gastrointestinal symptoms, particularly nausea and vomiting, are the most common chemotherapy-related AEs, occurring in over 30% of cases [9]. These symptoms can be effectively managed with antiemetic therapy. Acute upper abdominal pain, often caused by vasospasm induced by chemotherapeutic agents, can be alleviated by temporarily suspending the infusion or administering an appropriate dose of lidocaine through the catheter. Myelosuppression, characterized by reduced white blood cell and platelet counts, may require leukocyte- and platelet-boosting therapies or partial splenic artery embolization. Hepatotoxicity, indicated by elevated transaminase and bilirubin levels, necessitates hepatoprotective interventions. Nephrotoxicity can be mitigated through routine hydration during chemotherapy infusion to reduce renal damage. Additionally, certain chemotherapeutic agents may exhibit cardiotoxicity or gastrototoxicity, warranting routine supportive care, including energy supplementation, to support cardioprotective and gastroprotective measures.

6.2. HAIC Procedure-Related AEs

Procedure-related AEs primarily include pump pocket complications and catheter-related complications [75,76]. Pump pocket complications, occurring in 8% to 18% of patients, typically manifest as hematoma, infection, pump erosion, pump migration, or pump flipping [76]. Small hematomas can often be managed conservatively with compression dressings or abdominal binders. Infections or abscesses usually require drainage and may necessitate pump relocation or replacement

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[77]. Pump migration or flipping can typically be corrected surgically, while pump erosion or skin penetration generally requires the removal of the original pump and re-implantation at a new site. Catheter-related complications, affecting 10% to 26% of patients, primarily include catheter occlusion, dislodgement, and erosion [76,78]. These issues can usually be resolved through catheter repair, replacement, or repositioning.

The risk of HAIC procedure-related AEs can be minimized through standardized surgical techniques and meticulous postoperative care. For patients with percutaneous arterial ports, emphasis should be placed on proper wound care, maintenance of the arterial port reservoir, and careful management of the infusion catheter.

7. Conclusion

HAIC represents a safe and effective chemotherapeutic approach that has shown preliminary efficacy in the treatment of HCC, with widespread application in Asian regions. However, HAIC has not yet achieved global recognition as a recommended treatment for HCC. The current absence of a unified international standard for HAIC procedures undermines the consistency of treatment outcomes. Furthermore, despite the availability of a diverse range of HAIC regimens, they have not been fully optimized to cater to the requirements of different disease stages and individualized treatment plans. The synergistic mechanisms of combination therapies, including those involving targeted and immune therapies, remain to be further elucidated. These issues have impeded the further development and broader application of HAIC.

In order to advance the use of HAIC therapy in HCC, several key priorities must be addressed. First, the standardization of HAIC application should be advanced through multicenter studies and expert consensus to ensure the safety and consistency of treatment. Additionally, there is a need to optimize existing or develop innovative HAIC chemotherapy regimens to enhance the efficacy of HCC chemotherapy further and address the needs of different tumor stages. Lastly, with the advent of targeted-immune combination therapies and dual immune therapies, it is essential to clinically evaluate the efficacy and safety of HAIC in combination with these treatments, alongside conducting basic research to explore their potential synergistic mechanisms. Continued exploration and innovation in the field of HAIC are anticipated to offer new strategies for the comprehensive treatment of HCC, thereby improving overall therapeutic outcomes.

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References

1. Vogel, A.; Meyer, T.; Sapisochin, G.; Salem, R.; Saborowski, A. Hepatocellular Carcinoma. *Lancet* **2022**, *400*, 1345–1362, doi:10.1016/S0140-6736(22)01200-4.
2. Zeng, H.; Chen, W.; Zheng, R.; Zhang, S.; Ji, J.S.; Zou, X.; Xia, C.; Sun, K.; Yang, Z.; Li, H.; et al. Changing Cancer Survival in China during 2003-15: A Pooled Analysis of 17 Population-Based Cancer Registries. *Lancet Glob Health* **2018**, *6*, e555–e567, doi:10.1016/S2214-109X(18)30127-X.

 doi:10.20944/preprints202503.1424.v1

3. Reig, M.; Forner, A.; Rimola, J.; Ferrer-Fàbrega, J.; Burrel, M.; Garcia-Criado, Á.; Kelley, R.K.; Galle, P.R.; Mazzaferro, V.; Salem, R.; et al. BCLC Strategy for Prognosis Prediction and Treatment Recommendation: The 2022 Update. *J Hepatol* **2022**, *76*, 681–693, doi:10.1016/j.jhep.2021.11.018.
4. Vogel, A.; Martinelli, E.; ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org; ESMO Guidelines Committee Updated Treatment Recommendations for Hepatocellular Carcinoma (HCC) from the ESMO Clinical Practice Guidelines. *Ann Oncol* **2021**, *32*, 801–805, doi:10.1016/j.annonc.2021.02.014.
5. Hasegawa, K.; Takemura, N.; Yamashita, T.; Watadani, T.; Kaibori, M.; Kubo, S.; Shimada, M.; Nagano, H.; Hatano, E.; Aikata, H.; et al. Clinical Practice Guidelines for Hepatocellular Carcinoma: The Japan Society of Hepatology 2021 Version (5th JSH-HCC Guidelines). *Hepatol Res* **2023**, *53*, 383–390, doi:10.1111/hepr.13892.
6. Ueshima, K.; Komemushi, A.; Aramaki, T.; Iwamoto, H.; Obi, S.; Sato, Y.; Tanaka, T.; Matsueda, K.; Moriguchi, M.; Saito, H.; et al. Clinical Practice Guidelines for Hepatic Arterial Infusion Chemotherapy with a Port System Proposed by the Japanese Society of Interventional Radiology and Japanese Society of Implantable Port Assisted Treatment. *Liver Cancer* **2022**, *11*, 407–425, doi:10.1159/000524893.
7. Zhao, M.; Guo, Z.; Zou, Y.-H.; Li, X.; Yan, Z.-P.; Chen, M.-S.; Fan, W.-J.; Li, H.-L.; Yang, J.-J.; Chen, X.-M.; et al. Arterial Chemotherapy for Hepatocellular Carcinoma in China: Consensus Recommendations. *Hepatol Int* **2024**, *18*, 4–31, doi:10.1007/s12072-023-10599-6.
8. Ueshima, K.; Ogasawara, S.; Ikeda, M.; Yasui, Y.; Terashima, T.; Yamashita, T.; Obi, S.; Sato, S.; Aikata, H.; Ohmura, T.; et al. Hepatic Arterial Infusion Chemotherapy versus Sorafenib in Patients with Advanced Hepatocellular Carcinoma. *Liver Cancer* **2020**, *9*, 583–595, doi:10.1159/000508724.
9. Leal, J.N.; Kingham, T.P. Hepatic Artery Infusion Chemotherapy for Liver Malignancy. *Surg Oncol Clin N Am* **2015**, *24*, 121–148, doi:10.1016/j.soc.2014.09.005.
10. Van Nieuwenhove, Y.; Aerts, M.; Neyns, B.; Delvaux, G. Techniques for the Placement of Hepatic Artery Catheters for Regional Chemotherapy in Unresectable Liver Metastases. *Eur J Surg Oncol* **2007**, *33*, 336–340, doi:10.1016/j.ejso.2006.09.025.
11. Zheng, K.; Wang, X. Techniques and Status of Hepatic Arterial Infusion Chemotherapy for Primary Hepatobiliary Cancers. *Ther Adv Med Oncol* **2024**, *16*, 17588359231225040, doi:10.1177/17588359231225040.
12. Thiels, C.A.; D'Angelica, M.I. Hepatic Artery Infusion Pumps. *J Surg Oncol* **2020**, *122*, 70–77, doi:10.1002/jso.25913.
13. Zhou, J.; Sun, H.; Wang, Z.; Cong, W.; Zeng, M.; Zhou, W.; Bie, P.; Liu, L.; Wen, T.; Kuang, M.; et al. Guidelines for the Diagnosis and Treatment of Primary Liver Cancer (2022 Edition). *Liver Cancer* **2023**, *12*, 405–444, doi:10.1159/000530495.
14. Nagaoka, S.; Itano, S.; Nagamatsu, H.; Akiyoshi, J.; Kurogi, J.; Tajiri, N.; Kajiwara, M.; Sata, M. Temporary Indwelling Catheter System via the Left Brachial Artery: Evaluation in 83 Patients with Hepatic Tumors. *AJR Am J Roentgenol* **2007**, *188*, 652–658, doi:10.2214/AJR.05.0693.
15. Arai, Y.; Takeuchi, Y.; Inaba, Y.; Yamaura, H.; Sato, Y.; Aramaki, T.; Matsueda, K.; Seki, H. Percutaneous Catheter Placement for Hepatic Arterial Infusion Chemotherapy. *Tech Vasc Interv Radiol* **2007**, *10*, 30–37, doi:10.1053/j.tvir.2007.08.007.
16. Tanaka, T.; Arai, Y.; Inaba, Y.; Matsueda, K.; Aramaki, T.; Takeuchi, Y.; Kichikawa, K. Radiologic Placement of Side-Hole Catheter with Tip Fixation for Hepatic Arterial Infusion Chemotherapy. *J Vasc Interv Radiol* **2003**, *14*, 63–68, doi:10.1097/01.rvi.0000052292.26939.59.
17. Ganaha, F.; Sadaoka, S.; Yamada, T. Continuous Arterial Infusion Strategies Using Implanted Ports. *Tech Vasc Interv Radiol* **2002**, *5*, 170–176, doi:10.1053/tvir.2002.36417.
18. Herrmann, K.A.; Waggershauser, T.; Sittek, H.; Reiser, M.F. Liver Intraarterial Chemotherapy: Use of the Femoral Artery for Percutaneous Implantation of Catheter-Port Systems. *Radiology* **2000**, *215*, 294–299, doi:10.1148/radiology.215.1.r00ap14294.
19. Meyblum, L.; Faron, M.; Deschamps, F.; Kobe, A.; Bonnet, B.; Boileve, A.; Gelli, M.; Boige, V.; Hollebecque, A.; Durand-Labrunie, J.; et al. Safety and Efficacy of Percutaneous Arterial Port Implantation for Hepatic Arterial Infusion Chemotherapy. *Eur Radiol* **2024**, doi:10.1007/s00330-024-10887-1.

 doi:10.20944/preprints202503.1424.v1

20. Hu, J.; Zhu, X.; Wang, X.; Cao, G.; Wang, X.; Yang, R. Evaluation of Percutaneous Unilateral Trans-Femoral Implantation of Side-Hole Port-Catheter System with Coil Only Fixed-Catheter-Tip for Hepatic Arterial Infusion Chemotherapy. *Cancer Imaging* **2019**, *19*, 15, doi:10.1186/s40644-019-0202-z.
21. Matsumoto, T.; Yamagami, T.; Yoshimatsu, R.; Morishita, H.; Kitamura, N.; Sato, O.; Hasebe, T. Hepatic Arterial Infusion Chemotherapy by the Fixed-Catheter-Tip Method: Retrospective Comparison of Percutaneous Left Subclavian and Femoral Port-Catheter System Implantation. *AJR Am J Roentgenol* **2014**, *202*, 211–215, doi:10.2214/AJR.12.10502.
22. Yamagami, T.; Yoshimatsu, R.; Matsumoto, T.; Nishimura, T. Evaluation of Non-Target Arterial Patency after Implantation of Hepatic Arterial Catheter Using a Modified Implantation Technique with the Fixed Catheter Tip Method. *Clin Radiol* **2009**, *64*, 164–170, doi:10.1016/j.crad.2008.06.016.
23. Breedis, C.; Young, G. The Blood Supply of Neoplasms in the Liver. *Am J Pathol* **1954**, *30*, 969–977.
24. Barber, F.D.; Mavligit, G.; Kurzrock, R. Hepatic Arterial Infusion Chemotherapy for Metastatic Colorectal Cancer: A Concise Overview. *Cancer Treat Rev* **2004**, *30*, 425–436, doi:10.1016/j.ctrv.2004.04.002.
25. Liang, B.; Xiong, F.; Wu, H.; Wang, Y.; Dong, X.; Cheng, S.; Feng, G.; Zhou, G.; Xiong, B.; Liang, H.; et al. Effect of Transcatheter Intraarterial Therapies on the Distribution of Doxorubicin in Liver Cancer in a Rabbit Model. *PLoS One* **2013**, *8*, e76388, doi:10.1371/journal.pone.0076388.
26. Ikeda, M.; Morizane, C.; Ueno, M.; Okusaka, T.; Ishii, H.; Furuse, J. Chemotherapy for Hepatocellular Carcinoma: Current Status and Future Perspectives. *Jpn J Clin Oncol* **2018**, *48*, 103–114, doi:10.1093/jjco/hyx180.
27. Ensminger, W.D.; Gyves, J.W. Clinical Pharmacology of Hepatic Arterial Chemotherapy. *Semin Oncol* **1983**, *10*, 176–182.
28. Obi, S.; Sato, S.; Kawai, T. Current Status of Hepatic Arterial Infusion Chemotherapy. *Liver Cancer* **2015**, *4*, 188–199, doi:10.1159/000367746.
29. Nishikawa, H.; Osaki, Y.; Kita, R.; Kimura, T. Hepatic Arterial Infusion Chemotherapy for Advanced Hepatocellular Carcinoma in Japan. *Cancers (Basel)* **2012**, *4*, 165–183, doi:10.3390/cancers4010165.
30. Kokudo, N.; Takemura, N.; Hasegawa, K.; Takayama, T.; Kubo, S.; Shimada, M.; Nagano, H.; Hatano, E.; Izumi, N.; Kaneko, S.; et al. Clinical Practice Guidelines for Hepatocellular Carcinoma: The Japan Society of Hepatology 2017 (4th JSH-HCC Guidelines) 2019 Update. *Hepatol Res* **2019**, *49*, 1109–1113, doi:10.1111/hepr.13411.
31. Korean Liver Cancer Association (KLCA) and National Cancer Center (NCC) Korea 2022 KLCA-NCC Korea Practice Guidelines for the Management of Hepatocellular Carcinoma. *Clin Mol Hepatol* **2022**, *28*, 583–705, doi:10.3350/cmh.2022.0294.
32. Lyu, N.; Wang, X.; Li, J.-B.; Lai, J.-F.; Chen, Q.-F.; Li, S.-L.; Deng, H.-J.; He, M.; Mu, L.-W.; Zhao, M. Arterial Chemotherapy of Oxaliplatin Plus Fluorouracil Versus Sorafenib in Advanced Hepatocellular Carcinoma: A Biomolecular Exploratory, Randomized, Phase III Trial (FOHAIC-1). *J Clin Oncol* **2022**, *40*, 468–480, doi:10.1200/JCO.21.01963.
33. Zheng, K.; Zhu, X.; Fu, S.; Cao, G.; Li, W.-Q.; Xu, L.; Chen, H.; Wu, D.; Yang, R.; Wang, K.; et al. Sorafenib Plus Hepatic Arterial Infusion Chemotherapy versus Sorafenib for Hepatocellular Carcinoma with Major Portal Vein Tumor Thrombosis: A Randomized Trial. *Radiology* **2022**, *303*, 455–464, doi:10.1148/radiol.211545.
34. Murakami, E.; Aikata, H.; Miyaki, D.; Nagaoki, Y.; Katamura, Y.; Kawaoka, T.; Takaki, S.; Hiramatsu, A.; Waki, K.; Takahashi, S.; et al. Hepatic Arterial Infusion Chemotherapy Using 5-Fluorouracil and Systemic Interferon-α for Advanced Hepatocellular Carcinoma in Combination with or without Three-Dimensional Conformal Radiotherapy to Venous Tumor Thrombosis in Hepatic Vein or Inferior Vena Cava. *Hepatol Res* **2012**, *42*, 442–453, doi:10.1111/j.1872-034X.2011.00943.x.
35. He, M.-K.; Le, Y.; Li, Q.-J.; Yu, Z.-S.; Li, S.-H.; Wei, W.; Guo, R.-P.; Shi, M. Hepatic Artery Infusion Chemotherapy Using mFOLFOX versus Transarterial Chemoembolization for Massive Unresectable Hepatocellular Carcinoma: A Prospective Non-Randomized Study. *Chin J Cancer* **2017**, *36*, 83, doi:10.1186/s40880-017-0251-2.
36. Li, Q.-J.; He, M.-K.; Chen, H.-W.; Fang, W.-Q.; Zhou, Y.-M.; Xu, L.; Wei, W.; Zhang, Y.-J.; Guo, Y.; Guo, R.-P.; et al. Hepatic Arterial Infusion of Oxaliplatin, Fluorouracil, and Leucovorin Versus Transarterial

 doi:10.20944/preprints202503.1424.v1

Chemoembolization for Large Hepatocellular Carcinoma: A Randomized Phase III Trial. *J Clin Oncol* **2022**, *40*, 150–160, doi:10.1200/JCO.21.00608.

37. Li, S.-H.; Mei, J.; Cheng, Y.; Li, Q.; Wang, Q.-X.; Fang, C.-K.; Lei, Q.-C.; Huang, H.-K.; Cao, M.-R.; Luo, R.; et al. Postoperative Adjuvant Hepatic Arterial Infusion Chemotherapy With FOLFOX in Hepatocellular Carcinoma With Microvascular Invasion: A Multicenter, Phase III, Randomized Study. *J Clin Oncol* **2023**, *41*, 1898–1908, doi:10.1200/JCO.22.01142.
38. He, M.; Li, Q.; Zou, R.; Shen, J.; Fang, W.; Tan, G.; Zhou, Y.; Wu, X.; Xu, L.; Wei, W.; et al. Sorafenib Plus Hepatic Arterial Infusion of Oxaliplatin, Fluorouracil, and Leucovorin vs Sorafenib Alone for Hepatocellular Carcinoma With Portal Vein Invasion: A Randomized Clinical Trial. *JAMA Oncol* **2019**, *5*, 953–960, doi:10.1001/jamaoncol.2019.0250.
39. Tang, H.-H.; Zhang, M.-Q.; Zhang, Z.-C.; Fan, C.; Jin, Y.; Wang, W.-D. The Safety and Efficacy of Hepatic Arterial Infusion Chemotherapy Combined with PD-(L)1 Inhibitors and Molecular Targeted Therapies for the Treatment of Intermediate and Advanced Hepatocellular Carcinoma Unsuitable for Transarterial Chemoembolization. *J Hepatocell Carcinoma* **2023**, *10*, 2211–2221, doi:10.2147/JHC.S441024.
40. Yu, B.; Zhang, N.; Feng, Y.; Zhang, Y.; Zhang, T.; Wang, L. Tyrosine Kinase Inhibitors Plus Anti-PD-1 Antibodies with Hepatic Arterial Infusion Chemotherapy or Transarterial Chemoembolization for Unresectable Hepatocellular Carcinoma. *J Hepatocell Carcinoma* **2023**, *10*, 1735–1748, doi:10.2147/JHC.S431917.
41. Lai, Z.; He, M.; Bu, X.; Xu, Y.; Huang, Y.; Wen, D.; Li, Q.; Xu, L.; Zhang, Y.; Wei, W.; et al. Lenvatinib, Toripalimab plus Hepatic Arterial Infusion Chemotherapy in Patients with High-Risk Advanced Hepatocellular Carcinoma: A Biomolecular Exploratory, Phase II Trial. *Eur J Cancer* **2022**, *174*, 68–77, doi:10.1016/j.ejca.2022.07.005.
42. Zhang, T.-Q.; Geng, Z.-J.; Zuo, M.-X.; Li, J.-B.; Huang, J.-H.; Huang, Z.-L.; Wu, P.-H.; Gu, Y.-K. Camrelizumab (a PD-1 Inhibitor) plus Apatinib (an VEGFR-2 Inhibitor) and Hepatic Artery Infusion Chemotherapy for Hepatocellular Carcinoma in Barcelona Clinic Liver Cancer Stage C (TRIPLET): A Phase II Study. *Signal Transduct Target Ther* **2023**, *8*, 413, doi:10.1038/s41392-023-01663-6.
43. You, H.; Liu, X.; Guo, J.; Lin, Y.; Zhang, Y.; Li, C. Hepatic Arterial Infusion Chemotherapy and Sequential Ablation Treatment in Large Hepatocellular Carcinoma. *Int J Hyperthermia* **2022**, *39*, 1097–1105, doi:10.1080/02656736.2022.2112307.
44. Gao, S.; Zhang, P.-J.; Guo, J.-H.; Chen, H.; Xu, H.-F.; Liu, P.; Yang, R.-J.; Zhu, X. Chemoembolization Alone vs Combined Chemoembolization and Hepatic Arterial Infusion Chemotherapy in Inoperable Hepatocellular Carcinoma Patients. *World J Gastroenterol* **2015**, *21*, 10443–10452, doi:10.3748/wjg.v21.i36.10443.
45. Okuda, K.; Tanaka, M.; Shibata, J.; Ando, E.; Ogata, T.; Kinoshita, H.; Eriguchi, N.; Aoyagi, S.; Tanikawa, K. Hepatic Arterial Infusion Chemotherapy with Continuous Low Dose Administration of Cisplatin and 5-Fluorouracil for Multiple Recurrence of Hepatocellular Carcinoma after Surgical Treatment. *Oncol Rep* **1999**, *6*, 587–591, doi:10.3892/or.6.3.587.
46. Jeong, S.W.; Jang, J.Y.; Lee, J.E.; Lee, S.H.; Kim, S.G.; Cha, S.-W.; Kim, Y.S.; Cho, Y.D.; Kim, H.S.; Kim, B.S.; et al. The Efficacy of Hepatic Arterial Infusion Chemotherapy as an Alternative to Sorafenib in Advanced Hepatocellular Carcinoma. *Asia Pac J Clin Oncol* **2012**, *8*, 164–171, doi:10.1111/j.1743-7563.2012.01543.x.
47. Moriguchi, M.; Aramaki, T.; Nishiofuku, H.; Sato, R.; Asakura, K.; Yamaguchi, K.; Tanaka, T.; Endo, M.; Itoh, Y. Sorafenib versus Hepatic Arterial Infusion Chemotherapy as Initial Treatment for Hepatocellular Carcinoma with Advanced Portal Vein Tumor Thrombosis. *Liver Cancer* **2017**, *6*, 275–286, doi:10.1159/000473887.
48. Ando, E.; Tanaka, M.; Yamashita, F.; Kuromatsu, R.; Yutani, S.; Fukumori, K.; Sumie, S.; Yano, Y.; Okuda, K.; Sata, M. Hepatic Arterial Infusion Chemotherapy for Advanced Hepatocellular Carcinoma with Portal Vein Tumor Thrombosis: Analysis of 48 Cases. *Cancer* **2002**, *95*, 588–595, doi:10.1002/cncr.10694.
49. Yamasaki, T.; Kimura, T.; Kurokawa, F.; Aoyama, K.; Ishikawa, T.; Tajima, K.; Yokoyama, Y.; Takami, T.; Omori, K.; Kawaguchi, K.; et al. Prognostic Factors in Patients with Advanced Hepatocellular Carcinoma Receiving Hepatic Arterial Infusion Chemotherapy. *J Gastroenterol* **2005**, *40*, 70–78, doi:10.1007/s00535-004-1494-7.

 doi:10.20944/preprints202503.1424.v1

50. Ueshima, K.; Kudo, M.; Takita, M.; Nagai, T.; Tatsumi, C.; Ueda, T.; Kitai, S.; Ishikawa, E.; Yada, N.; Inoue, T.; et al. Hepatic Arterial Infusion Chemotherapy Using Low-Dose 5-Fluorouracil and Cisplatin for Advanced Hepatocellular Carcinoma. *Oncology* **2010**, *78 Suppl 1*, 148–153, doi:10.1159/000315244.
51. Niizeki, T.; Sumie, S.; Torimura, T.; Kurogi, J.; Kuromatsu, R.; Iwamoto, H.; Aino, H.; Nakano, M.; Kawaguchi, A.; Kakuma, T.; et al. Serum Vascular Endothelial Growth Factor as a Predictor of Response and Survival in Patients with Advanced Hepatocellular Carcinoma Undergoing Hepatic Arterial Infusion Chemotherapy. *J Gastroenterol* **2012**, *47*, 686–695, doi:10.1007/s00535-012-0555-6.
52. Nouso, K.; Miyahara, K.; Uchida, D.; Kuwaki, K.; Izumi, N.; Omata, M.; Ichida, T.; Kudo, M.; Ku, Y.; Kokudo, N.; et al. Effect of Hepatic Arterial Infusion Chemotherapy of 5-Fluorouracil and Cisplatin for Advanced Hepatocellular Carcinoma in the Nationwide Survey of Primary Liver Cancer in Japan. *Br J Cancer* **2013**, *109*, 1904–1907, doi:10.1038/bjc.2013.542.
53. Ueshima, K.; Kudo, M.; Tanaka, M.; Kumada, T.; Chung, H.; Hagiwara, S.; Inoue, T.; Yada, N.; Kitai, S. Phase I/II Study of Sorafenib in Combination with Hepatic Arterial Infusion Chemotherapy Using Low-Dose Cisplatin and 5-Fluorouracil. *Liver Cancer* **2015**, *4*, 263–273, doi:10.1159/000367751.
54. Hatooka, M.; Kawaoka, T.; Aikata, H.; Inagaki, Y.; Morio, K.; Nakahara, T.; Murakami, E.; Tsuge, M.; Hiramatsu, A.; Imamura, M.; et al. Hepatic Arterial Infusion Chemotherapy Followed by Sorafenib in Patients with Advanced Hepatocellular Carcinoma (HICS 55): An Open Label, Non-Comparative, Phase II Trial. *BMC Cancer* **2018**, *18*, 633, doi:10.1186/s12885-018-4519-y.
55. Kudo, M.; Ueshima, K.; Yokosuka, O.; Ogasawara, S.; Obi, S.; Izumi, N.; Aikata, H.; Nagano, H.; Hatano, E.; Sasaki, Y.; et al. Sorafenib plus Low-Dose Cisplatin and Fluorouracil Hepatic Arterial Infusion Chemotherapy versus Sorafenib Alone in Patients with Advanced Hepatocellular Carcinoma (SILIUS): A Randomised, Open Label, Phase 3 Trial. *Lancet Gastroenterol Hepatol* **2018**, *3*, 424–432, doi:10.1016/S2468-1253(18)30078-5.
56. Sakon, M.; Nagano, H.; Dono, K.; Nakamori, S.; Umeshita, K.; Yamada, A.; Kawata, S.; Imai, Y.; Iijima, S.; Monden, M. Combined Intraarterial 5-Fluorouracil and Subcutaneous Interferon-Alpha Therapy for Advanced Hepatocellular Carcinoma with Tumor Thrombi in the Major Portal Branches. *Cancer* **2002**, *94*, 435–442, doi:10.1002/cncr.10246.
57. Kasai, K.; Ushio, A.; Kasai, Y.; Sawara, K.; Miyamoto, Y.; Oikawa, K.; Kuroda, H.; Takikawa, Y.; Suzuki, K. Therapeutic Efficacy of Combination Therapy with Intra-Arterial 5-Fluorouracil and Systemic Pegylated Interferon α-2b for Advanced Hepatocellular Carcinoma with Portal Venous Invasion. *Cancer* **2012**, *118*, 3302–3310, doi:10.1002/cncr.26648.
58. Enjoji, M.; Morizono, S.; Kotoh, K.; Kohjima, M.; Miyagi, Y.; Yoshimoto, T.; Nakamuta, M. Re-Evaluation of Antitumor Effects of Combination Chemotherapy with Interferon-Alpha and 5-Fluorouracil for Advanced Hepatocellular Carcinoma. *World J Gastroenterol* **2005**, *11*, 5685–5687, doi:10.3748/wjg.v11.i36.5685.
59. Ota, H.; Nagano, H.; Sakon, M.; Eguchi, H.; Kondo, M.; Yamamoto, T.; Nakamura, M.; Damdinsuren, B.; Wada, H.; Marubashi, S.; et al. Treatment of Hepatocellular Carcinoma with Major Portal Vein Thrombosis by Combined Therapy with Subcutaneous Interferon-Alpha and Intra-Arterial 5-Fluorouracil; Role of Type 1 Interferon Receptor Expression. *Br J Cancer* **2005**, *93*, 557–564, doi:10.1038/sj.bjc.6602742.
60. Obi, S.; Yoshida, H.; Toune, R.; Unuma, T.; Kanda, M.; Sato, S.; Tateishi, R.; Teratani, T.; Shiina, S.; Omata, M. Combination Therapy of Intraarterial 5-Fluorouracil and Systemic Interferon-Alpha for Advanced Hepatocellular Carcinoma with Portal Venous Invasion. *Cancer* **2006**, *106*, 1990–1997, doi:10.1002/cncr.21832.
61. Nagano, H.; Wada, H.; Kobayashi, S.; Marubashi, S.; Eguchi, H.; Tanemura, M.; Tomimaru, Y.; Osuga, K.; Umeshita, K.; Doki, Y.; et al. Long-Term Outcome of Combined Interferon-α and 5-Fluorouracil Treatment for Advanced Hepatocellular Carcinoma with Major Portal Vein Thrombosis. *Oncology* **2011**, *80*, 63–69, doi:10.1159/000328281.
62. Yamashita, T.; Arai, K.; Sunagozaka, H.; Ueda, T.; Terashima, T.; Yamashita, T.; Mizukoshi, E.; Sakai, A.; Nakamoto, Y.; Honda, M.; et al. Randomized, Phase II Study Comparing Interferon Combined with Hepatic Arterial Infusion of Fluorouracil plus Cisplatin and Fluorouracil Alone in Patients with Advanced Hepatocellular Carcinoma. *Oncology* **2011**, *81*, 281–290, doi:10.1159/000334439.

63. Monden, M.; Sakon, M.; Sakata, Y.; Ueda, Y.; Hashimura, E.; FAIT Research Group 5-Fluorouracil Arterial Infusion + Interferon Therapy for Highly Advanced Hepatocellular Carcinoma: A Multicenter, Randomized, Phase II Study. *Hepatol Res* **2012**, *42*, 150–165, doi:10.1111/j.1872-034X.2011.00905.x.
64. Wu, J.; Huang, W.-J.; Wang, H.-Y.; Wang, Y.-F.; Peng, B.-G.; Zhou, Q. Arterial Infusion of 5-Fluorouracil Combined with Subcutaneous Injection of Pegylated Interferon Alpha-2b in Treating Unresectable Hepatocellular Carcinoma with Portal Vein Tumor Thrombus. *Med Oncol* **2015**, *32*, 65, doi:10.1007/s12032-015-0491-4.
65. Kaneko, S.; Urabe, T.; Kobayashi, K. Combination Chemotherapy for Advanced Hepatocellular Carcinoma Complicated by Major Portal Vein Thrombosis. *Oncology* **2002**, *62 Suppl 1*, 69–73, doi:10.1159/000048279.
66. Niizeki, T.; Iwamoto, H.; Shirono, T.; Shimose, S.; Nakano, M.; Okamura, S.; Noda, Y.; Kamachi, N.; Hiroyuki, S.; Sakai, M.; et al. Clinical Importance of Regimens in Hepatic Arterial Infusion Chemotherapy for Advanced Hepatocellular Carcinoma with Macrovascular Invasion. *Cancers (Basel)* **2021**, *13*, 4450, doi:10.3390/cancers13174450.
67. Iwamoto, H.; Niizeki, T.; Nagamatsu, H.; Ueshima, K.; Tani, J.; Kuzuya, T.; Kasai, K.; Kooka, Y.; Hiraoka, A.; Sugimoto, R.; et al. The Clinical Impact of Hepatic Arterial Infusion Chemotherapy New-FP for Hepatocellular Carcinoma with Preserved Liver Function. *Cancers (Basel)* **2022**, *14*, 4873, doi:10.3390/cancers14194873.
68. Maruta, S.; Koshima, Y.; Tsuchiya, T.; Tamura, R.; Takahashi, M.; Ohshima, T.; Ooka, Y. Combination Therapy of Lenvatinib and Hepatic Arterial Infusion Chemotherapy Using Cisplatin With Lipiodol and 5-Fluorouracil: A Potential Breakthrough Therapy for Unresectable Advanced Hepatocellular Carcinoma. *Cureus* **2024**, *16*, e66185, doi:10.7759/cureus.66185.
69. Nagamatsu, H.; Sumie, S.; Niizeki, T.; Tajiri, N.; Iwamoto, H.; Aino, H.; Nakano, M.; Shimose, S.; Satani, M.; Okamura, S.; et al. Hepatic Arterial Infusion Chemoembolization Therapy for Advanced Hepatocellular Carcinoma: Multicenter Phase II Study. *Cancer Chemother Pharmacol* **2016**, *77*, 243–250, doi:10.1007/s00280-015-2892-7.
70. Nakano, M.; Niizeki, T.; Nagamatsu, H.; Tanaka, M.; Kuromatsu, R.; Satani, M.; Okamura, S.; Iwamoto, H.; Shimose, S.; Shirono, T.; et al. Clinical Effects and Safety of Intra-Arterial Infusion Therapy of Cisplatin Suspension in Lipiodol Combined with 5-Fluorouracil versus Sorafenib, for Advanced Hepatocellular Carcinoma with Macroscopic Vascular Invasion without Extra-Hepatic Spread: A Prospective Cohort Study. *Mol Clin Oncol* **2017**, *7*, 1013–1020, doi:10.3892/mco.2017.1442.
71. Iwamoto, H.; Niizeki, T.; Nagamatsu, H.; Ueshima, K.; Nomura, T.; Kuzuya, T.; Kasai, K.; Kooka, Y.; Hiraoka, A.; Sugimoto, R.; et al. Survival Benefit of Hepatic Arterial Infusion Chemotherapy over Sorafenib in the Treatment of Locally Progressed Hepatocellular Carcinoma. *Cancers (Basel)* **2021**, *13*, 646, doi:10.3390/cancers13040646.
72. Feng, A.-W.; Guo, J.-H.; Gao, S.; Kou, F.-X.; Liu, S.-X.; Liu, P.; Chen, H.; Wang, X.-D.; Xu, H.-F.; Cao, G.; et al. A Randomized Phase II Trial of Hepatic Arterial Infusion of Oxaliplatin plus Raltitrexed versus Oxaliplatin plus 5-Fluorouracil for Unresectable Colorectal Cancer Liver Metastases. *Front Oncol* **2022**, *12*, 913017, doi:10.3389/fonc.2022.913017.
73. Chen, S.; Zhang, K.; Liu, W.; Yu, W. Hepatic Arterial Infusion of Oxaliplatin plus Raltitrexed in Patients with Intermediate and Advanced Stage Hepatocellular Carcinoma: A Phase II, Single-Arm, Prospective Study. *Eur J Cancer* **2020**, *134*, 90–98, doi:10.1016/j.ejca.2020.03.032.
74. Chen, S.; Wang, X.; Yuan, B.; Peng, J.; Zhang, Q.; Yu, W.; Ge, N.; Weng, Z.; Huang, J.; Liu, W.; et al. Apatinib plus Hepatic Arterial Infusion of Oxaliplatin and Raltitrexed for Hepatocellular Carcinoma with Extrahepatic Metastasis: Phase II Trial. *Nat Commun* **2024**, *15*, 8857, doi:10.1038/s41467-024-52700-z.
75. Allen, P.J.; Nissan, A.; Picon, A.I.; Kemeny, N.; Dudrick, P.; Ben-Porat, L.; Espat, J.; Stojadinovic, A.; Cohen, A.M.; Fong, Y.; et al. Technical Complications and Durability of Hepatic Artery Infusion Pumps for Unresectable Colorectal Liver Metastases: An Institutional Experience of 544 Consecutive Cases. *J Am Coll Surg* **2005**, *201*, 57–65, doi:10.1016/j.jamcollsurg.2005.03.019.
76. Sharib, J.M.; Creasy, J.M.; Wildman-Tobriner, B.; Kim, C.; Uronis, H.; Hsu, S.D.; Strickler, J.H.; Gholami, S.; Cavnar, M.; Merkow, R.P.; et al. Hepatic Artery Infusion Pumps: A Surgical Toolkit for Intraoperative

 doi:10.20944/preprints202503.1424.v1

Decision-Making and Management of Hepatic Artery Infusion-Specific Complications. *Ann Surg* **2022**, *276*, 943–956, doi:10.1097/SLA.0000000000005434.

77. Zhu, A.-L.; Liu, L.-X.; Piao, D.-X.; Lin, Y.-X.; Zhao, J.-P.; Jiang, H.-C. Liver Regional Continuous Chemotherapy: Use of Femoral or Subclavian Artery for Percutaneous Implantation of Catheter-Port Systems. *World J Gastroenterol* **2004**, *10*, 1659–1662, doi:10.3748/wjg.v10.i11.1659.
78. Laface, C.; Laforgia, M.; Molinari, P.; Ugenti, I.; Gadaleta, C.D.; Porta, C.; Ranieri, G. Hepatic Arterial Infusion of Chemotherapy for Advanced Hepatobiliary Cancers: State of the Art. *Cancers (Basel)* **2021**, *13*, 3091, doi:10.3390/cancers13123091.