Hepatic Arterial Infusion Chemotherapy Is a Feasible Treatment Option for Hepatocellular Carcinoma: A New Update

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Abstract

Background: Hepatic arterial infusion chemotherapy (HAIC) is one option for treating massive tumors and unresectable hepatocellular carcinoma (HCC). However, there is a lack of remedial treatment after these treatments are ineffective or failed. ***Summary:*** Some studies have discovered that HAIC has greater survival in patients with advanced HCC. A previous study has shown that HAIC is effective in the treatment of advanced HCC, and the data on randomized clinical trials are limited and unclear. ***Key Message:*** More clinical trials and research are needed in order to make HAIC a standard and recommended therapy for advanced HCC. Our review focuses on the clinical applications of hepatic artery infusion treatment.

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Introduction

Regardless of gender or country, there is an increase in the number of yearly diagnosed cancer cases. Cancer is a progressive and, in many cases, deadly disease of multicellular insurrection. The latest global cancer estimates from the International Agency for Research on Cancer (IARC) indicate that around 19.3 million cancer cases and 10.0 million cancer deaths occurred worldwide in 2020 [1]. Hepatocellular carcinoma (HCC) is the seventh most common malignancy in the world and is the third most frequent cause of cancer-related death [2]. A total of 840,000 new cases of liver cancer and 780,000 related deaths were recorded in 2018 [3]. According to previous studies, the 5-year relative survival rate of liver cancer patients was 18.4% (2009–2015) and 14.1% (2010–2014) in the USA and China [4, 5]. According to comparative studies, results may differ between Asia-Pacific and Western patients and between different etiologies for the same therapeutic modalities [6, 7]. In a couple of regions, early-stage HCC benefits from potentially curative therapies [8, 9]. 25–70% of the patients are diagnosed with intermedi-

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ate or advanced HCC, where treatment options are limited and prognosis is poor [10–12]. Approximately 75% of patients are in the Asia-Pacific region, and their cases are caused by hepatitis B virus (HBV) and/or hepatitis C virus (HCV). More than 50% of cases of HCC occur in China, and an estimated 360,000 patients residing in east Asian countries, including China, Japan, Korea, and Taiwan, die from this disease each year [13–15]. Incidences of HCC are likely to increase over the next 10–20 years and to peak around 2030 [16]. Sorafenib and regorafenib could be of benefit, increase survival rates, and become the standard treatments for advanced HCC [17, 18]. Another study showed that the promising systemic chemotherapeutic agent sorafenib only demonstrated relatively limited benefits rather than eradicating the microscopic residue and curing patients with advanced HCC. Therefore, sorafenib is beneficial in only around 30% of patients, and resistance often develops within 6 months [19]. The study by Jackson and his team [20] was consistent with evidence that the effectiveness of sorafenib on overall survival (OS) is dependent on patients' hepatitis status. There is an improved OS for patients negative for HBV but positive for HCV when treated by sorafenib. HCC related to infection with the HCV has become the fastest-rising cause of cancer-related death in the USA during the past 2 decades. The 5-year survival rate for HCC has remained below 12% [21]. According to a huge population-based study of individuals diagnosed with advanced HCC, the USA has not widely adopted sorafenib since FDA approval in 2007. Although sorafenib treatment is associated with a lower risk of mortality, this finding can be used to further the discussion surrounding appropriate adoption of sorafenib with clear and ongoing discussions of promoting cancer prevention [22, 23].

Treatment Option for Patients with Advanced-Stage HCC

Liver cancer (HCC) remains a major problem for health care systems around the world, and surgeons are facing the challenge of providing the most appropriate treatment for patients with HCC. The evaluation of prevention strategies, regular monitoring, and early diagnosis lead to good treatment options. Furthermore, immunotherapy drugs have brought new breakthroughs in the treatment of HCC [24, 25]. The American Association for the Study of Liver Diseases (AASLD) published practice guidelines on the management of HCC in 2005. Since then, new information has emerged that requires the

guidelines to be updated [26]. According to a publication by Bruix and colleagues [27], HCC patients have been defined (whether the nodules are 1 or 2 cm), and effective treatment is available for tumors detected at an early stage. Several approaches are available at the intermediate-advance stage including radiofrequency ablation, transarterial chemoembolization, and radioembolization, and sorafenib remains the best option for advanced-stage treatment [27]. However, a preliminary study by the SHARP-ORIENTAL Investigators Study Group showed that patients with advanced HCC, who received sorafenib treatment, had a median survival of nearly 10.7 months, as compared with 7.9 months [28]. Regorafenib is shown to provide survival benefits in HCC patients when added to sorafenib treatment, and 1-year survival is 33 and 44%. Immune checkpoint inhibitors or oral multikinase inhibitors have been approved, notably lenvatinib (Lenvima; Eisai and Merck & Co.), regorafenib (Stivarga; Bayer), cabozantinib (Cabometyx; Exelixis/Ipsen/Takeda), Ramucirumab (Cyramza; Eli Lilly), programmed cell death protein 1 (PD1) inhibitor nivolumab Opdivo (Opdivo; Bristol-Myers Squibb/Ono Pharmaceutical), PD1 inhibitor pembrolizumab (Keytruda; Merck & Co.), the PD1 ligand 1 (PDL1) inhibitor, atezolizumab (Tecentriq; Roche/Genentech/Chugai), and the PDL1 inhibitor durvalumab (Imfinzi; AstraZeneca). The FDA granted atezolizumab plus bevacizumab breakthrough designation status as a first-line treatment for advanced or metastatic disease. Moreover, it is being evaluated in unresectable HCC and in patients with advanced or metastatic disease. Yet, the disease control rate was 35% in the dose-escalation phase and 100% in the dose-expansion phase, which could have positively affected OS [29–31].

Although there have been significant advances in HCC treatment over the past decade, evidence is still lacking on therapeutics that can stop increasing incidence rates of HCC. Recently, the guidelines for the management of Chinese HCC patients were updated. The treatment of patients with HCC often necessitates multidisciplinary care (MDT). It includes the involvement of hepatologists, diagnostic and interventional radiologists, transplant surgeons, medical and surgical oncologists, and pathologists. The European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD) updated the clinical practical guidelines on the management of HCC in 2018, in line with typical standard management. Furthermore, the Asian Pacific Association for the Study of the Liver (APASL) HCC guidelines were published in 2010 and are the oldest of the major guidelines. The NCCN Guidelines

for hepatobiliary cancers provide treatment recommendations for HCC [16, 32, 33]. China and other countries have established their guidelines for heterogeneity in the prevalence, phenotype, and treatment responses of HCC. The guidelines specific to Chinese patients were updated in 2019 based on an accumulation of new evidence [34, 35]. The study by Hatooka and colleagues [36] compared the evidence to determine whether hepatic arterial infusion chemotherapy (HAIC) or sorafenib is superior. In advanced-stage patients, they found favorable outcomes in patients who were treated with HAIC. Among responders, a better prognosis was expected with HAIC compared to sorafenib, while HAIC nonresponders had a poor prognosis at 6 months in previous studies, and 1- and 2-year survival rates were higher. Therefore, it is necessary to identify HAIC nonresponders as early as possible. Also, the patients in the HAIC group remain alive for over 10 years [36].

Comparison of Outcome of HAIC and Sorafenib in Patients with HCC Advanced Stage

Recently, a few centers reported the outcomes of an interesting, randomized phase II trial comparing sorafenib alone (Sor) with sorafenib plus HAIC with cisplatin (SorCDDP) in advanced HCC. The median survivals in the Sor and SorCDDP arms were 8.7 and 10.6 months. The HR stratified by the allocation factors, including the presence/absence of portal vein tumor thrombosis (PVTT) and extrahepatic metastases (95% CI), was 0.60 (0.38–0.96) (p value 0.031). The crude HR (95% CI) was 0.68 (0.44–1.049) (p = 0.073). In brief, the administration of sorafenib before HAIC could lead to better clinical outcomes considering the sensitized and synergistic effect with cisplatin and the antiangiogenic activity of sorafenib. In a Korean study by Song and colleagues [39], on advanced-stage HCC and PVTT, 50 patients were treated with HAIC and 60 patients were treated with sorafenib. The median OS was significantly longer in the HAIC group than in the sorafenib group (7.1 vs. 5.5 months, p = 0.011). The median time to progression was also significantly longer in the HAIC group than in the sorafenib group (3.3 vs. 2.1 months, p = 0.034). So, HAIC shows more favorable responses compared to sorafenib [39].

Another randomized trial from Japan by Kudo and colleagues [40] (SILIUS) selected patients with advanced HCC not suitable for resection, local ablation, or transarterial chemoembolization. The outcome showed that HAIC plus sorafenib has shown promising tumor control

and a manageable safety profile in patients in advanced stages and unresectable HCC. The median OS was similar for sorafenib plus HAIC and sorafenib (11.8 months [95% CI: 9.1–14.5] vs. 11.5 months [8.2–14.8]; hazard ratio 1.009 [95% CI: 0.743–1.371]; p = 0.955). Grade 3–4 adverse events (AEs) are more frequent in the sorafenib plus HAIC group than in the sorafenib group. Japanese Randomized HAIC outcomes are favorable and showed better responses for HCC patients exhibiting macroscopic vascular invasion when treated with HAIC rather than sorafenib [40]. Another Japanese review that reported treatment strategies for advanced HCC recommended sorafenib as the primary treatment for cases without macroscopic vascular invasion or Child-Pugh A and HAIC for those with macroscopic vascular invasion or Child-Pugh A or B [41]. However, future research and further investigation is required for HAIC to become a standard treatment for HCC.

HAIC, a Potential Therapeutic Option for HCC

HAIC has been shown to be an effective treatment for advanced HCC in Asian countries, especially Japan [44]. According to the recent clinical practice guidelines for HCC in Japan (J-HCC 2013) [42], HAIC is one of the standard treatments for patients with advanced HCC. The clinical response was significant, and the responders had the best survival rates from 7 to 81%, with a median survival time (MST) of approximately 6–15.9 months [43]. Theoretically, HAIC has a chemotherapeutic effect and a favorable toxicity profile in patients with advanced HCC. HAIC is one of the few remaining treatment options for advanced HCC patients in these predicaments because advanced HCC derives almost all of their blood supply from the hepatic artery. In HAIC, a highly concentrated chemotherapeutic agent is injected into the liver via the hepatic artery. The consequent concentration of the agent at the tumor site would be expected to increase antitumor effects [45]. Additionally, the liver derives about 70% of its blood supply from the portal vein. HAIC requires the insertion of a catheter into the hepatic artery. In single-administration HAIC, the catheter is inserted for a sole application of the chemotherapeutic agent each time. The methods for administering HAIC are dependent on certain agents. Epirubicin hydrochloride, mitomycin C, cisplatin, and miriplatin are suitable for single administration, and the agents suitable for continuous administration include anthracycline-based agents, mitomycin C, and fluorouracil (5-FU) [43]. HAIC, on the

other hand, is not recommended and should not be used as a standard of care. There is not enough convincing clinical evidence because large randomized studies of HAIC in advanced HCC patients have not been conducted. Recent studies continue to show high response rates, up to 52.6%, and OS up to 36.8 months, using various combinations of modern agents. See Table 1.

FAIT Therapeutic Option

Fluorouracil arterial infusion plus interferon therapy (FAIT) was evaluated in patients with HCC with a high degree of vascular invasion associated with poor prognosis. FAIT showed beneficial effects for a combination therapy of interferon (IFN) and 5-FU, for advanced HCC with tumor thrombi in the major branches of the portal vein. The survival rates were from 30 to 40%, with an MST of approximately 8.4–10.5 months [46–49]. A previous study by Obi and colleagues [46] evaluated FAIT in 116 patients; 19 patients (16%) showed complete response and another 42 patients (36%) showed partial response, with the response rate of 52.6%, a median survival of 6.9 months, and a 1-year survival of 34%, and prognosis improved when compared with a historical control [46]. Ota et al. [50] investigated FAIT in 55 patients with HCC and reported a response rate of 43.6%, a median survival of 11.8 months, and a 1-year survival of 48.9% [50]. Recently, Yamashita et al. [47] reported that the response rate of FAIT was 24.6% (14 out of 57 patients), and the median survival was 10.5 months in patients with unresectable HCC, primarily due to high degrees of vascular invasion or multiple intrahepatic metastases [47]. Based on these findings (IFN and 5-FU), the authors evaluated the efficacy and safety of FAIT. FAIT may be a strategy of worth trying for advanced HCC with a high degree of vascular invasion.

The Role of Low-Dose Cisplatin plus 5-FU for Treatment of Advanced and Recurrent HCC

The efficacy of combination chemotherapy consisting of 5-FU and cisplatin (FP therapy) utilizing biochemical modulation for advanced HCC has been recently reported. Various regimens of HAIC have been tried individually or in combination, mainly using 5-FU or CDDP. 5-FU-based continuous infusion chemotherapy (FP or 5-FU/IFN) and CDDP monotherapy are typical regimens in Japan. However, there are few reports comparing the efficacy and safety of these regimens, and the basis of their selection is unclear [51–53]. One study by Nouso and colleagues [51] reported results of 476 patients with HCC who underwent HAIC with 5-FU and cisplatin (HAIC) compared with 1,466 patients who did not receive active therapy. The HAIC (HR, 0.48; 95% CI: 0.41–0.56; $p < 0.0001$) was associated with better survival. The MSTs were 14.0 months (HAIC group) and 5.2 months (no therapy group), so survival was significantly higher in the HAIC group ($p < 0.0001$). Hazard ratio of HAIC in this propensity score-match was 0.60 (95% CI: 0.49–0.73; $p < 0.0001$).

Most of the HCC treatment guidelines recommend chemotherapy for patients with Child-Pugh A/B disease who have portal vein invasion and/or >3 tumors. In cases of Child-Pugh A/B disease with >3 tumors, MST was 13.9 months (HAIC) and 3.7 months (without therapy), and the survival benefit of HAIC treatment was observed ($p < 0.0001$). For other cases observed with Child-Pugh A/B disease with PVTT, MST was 7.9 months (HAIC) and 3.1 months (no therapy) [51]. Our findings and the previous study suggest that IFN with CDDP and 5-FU are currently used as HAIC regimens in Japan. The regimen containing IFN has not become widespread because there were not many clinical trials for these drugs. Low-dose FP is the most common regimen used for HAIC, and it has demonstrated a favorable outcome and can be important for achieving long-term survival in the future.

Low-Dose Cisplatin Monotherapy Alone

In Japan, CDDP has been available for intra-arterial infusion for the treatment of HCC since 2004. Recent studies reported that CDDP alone had an overall response rate of 33.8%. The 1-year survival rate was 67.5%, and the 2-year survival rate was 50.8% [54, 55]. HAIC has been used as a treatment option because of the efficacy and safety of HAIC using cisplatin for patients with early-stage HCC [56]. One Japanese study by Ishikawa and colleagues [57] studied the high efficacy and safety of using CDDP in patients with early-stage HCC. Some patients received radical local treatment with TACE and radiofrequency ablation, and other patients did not receive HAIC before radical local treatment. Outcomes showed that the cumulative survival rates at 1, 3, and 5 years in the non-HAIC group were 77.4, 69.2, and 55.3% and in the HAIC group were 97.4, 87.0, and 84.4% ($p = 0.023$). The survival time was prolonged significantly in the HAIC group compared with the non-HAIC group. Based on these re-

sults, treatments consisting of whole-liver HAIC with CDDP to all patients with early-stage HCC were appropriate for radical local treatment [57]. Also, anticancer agents are commonly used for the treatment of advanced HCC. Based on this finding, the cisplatin infusion significantly prolonged survival without increasing the incidence of AEs. These outcomes suggest that CDDP may play a leading role in determining that all-liver HAIC with CDDP is more beneficial as neoadjuvant or adjuvant therapy for HCC in the future.

Potential Responders to FOLFOX Therapy

Clinical activity of several regimens containing oxaliplatin in advanced and unresectable HCC has been demonstrated in phase II studies. FOLFOX (infusional fluorouracil, leucovorin, and oxaliplatin) administered to patients with advanced and unresectable HCC in Asia and the patients who were ineligible for curative resection or localize therapies could provide a survival benefit and greater efficacy compared with chemotherapy doxorubicin [58]. A Chinese study by Min and colleagues [59] compared the safety and efficacy of HAIC with FOLFOX versus TACE in patients with massive tumor and unresectable HCC. This study demonstrated encouraging outcomes for both efficacy and safety of HAIC with FOLFOX. The results of using HAIC with the FOLFOX group show higher and more significant partial responses and disease control rates than the TACE group rates. The results were 52.6 versus 9.8%, $p < 0.001$; 83.8 versus 52.5%, $p = 0.004$. The median survival rate in both HAIC and TACE groups was 5.87 and 3.6 months (HR = 2.35, 95% CI = 1.16–4.76, $p = 0.015$). The number of patients who underwent surgical resection in the HAIC group was higher than the TACE group (10 vs. 3, $p = 0.033$). The result was not significant in either group. Also, the proportions of grade 3–4 AEs and serious AEs were lower in the HAIC group than in the TACE group (AEs: 13 vs. 27, $p = 0.007$; severe AEs: 6 vs. 15, $p = 0.044$). Based on their findings, HAIC + FOLFOX yielded significant and better treatment responses and less serious toxicity than TACE and HAIC. FOLFOX might be a better choice for patients with unresectable HCC [59]. According to another study by Ning Lyu et al. [60], with a total of 55 enrolled patients with advanced HCC, almost 49 patients had cirrhosis caused by HBV infection. The aim of their study was to investigate the effect and safety of a HAIC + FOLFOX regimen in patients with advanced HCC. The responders had the best survival rates from 55.1 to 71.4%, and the median survival rates were 6 and 12 months [60]. On the other hand, 2 studies SHARP-ORIENTAL Investigators Study Group and Barcelona Clinic Liver Cancer (BCLC) Group recommended sorafenib as the standard treatment for BCLC-C advanced-stage HCC [60]. Recently, the study by Ning Lyu et al. [60] treated 232 of 412 patients with sorafenib, and 180 patients were given HAIC + FOLFOX therapy. The median age range was 16–82 years old. The results in both disease-free survival and OS in the HAIC + F group were significantly longer than those in the sorafenib group (disease-free survival 7.1 vs. 3.3 months; OS 14.5 vs. 7.0 months, $p < 0.001$). This study found that HAIC + FOLFOX therapy may improve survival compared to sorafenib in patients with advanced HCC. Thus, HAIC + F is an alternative therapy for advanced HCC and is urgently required [61]. In brief, the combination of the HAIC with FOLFOX regimen in patients with advanced HCC has favorable survival rates, 6 and 12 months, high response rate, and acceptable toxicity and improves life quality; this strategy may provide a promising therapeutic option for advanced HCC.

Prognostic Factors in Patients with HCC Receiving HAIC

The safety and benefits of neoadjuvant HAIC in advanced HCC patients according to the Child-Pugh score and alpha-fetoprotein (AFP) level and the response to HAIC could certainly have survival benefits and may be a useful therapeutic option for patients with advanced HCC liver function and should be considered carefully when dealing with HAIC [62–64]. The radiological response to therapy was assessed by modified response evaluation criteria in both solid tumors and classified as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). Early response was defined as the achievement of CR or PR, and disease control was defined as the achievement of CR, PR, or SD. To evaluate biologic tumor response, the alterations in AFP were analyzed based on primer AFP value after treatment [64], according to Miyaki et al. [63]. The early response results and outcomes of HAIC and MST with early imaging response are MST in PR, 20.6; SD, 11.4; and PD, 5.0 months ($p < 0.0001$). The MST was significantly different in patients with AFP and DCP of ≤1 or >1. Worse MST of 6.5 months was seen in patients with an AFP ratio of >1 and a DCP ratio of >1. Yet, decreases in both AFP and DCP in early-stage therapy with HAIC were significant,

Table 1. Different studies of HAIC with systemic therapy for liver cancer [37, 38, 47, 51, 57, 59, 61, 63]

Study	Study design	Year	Patients, n	Median age, years	Treatment	RR, %	OS, months
Ikeda et al. [37]	Multicenter RCT	2016	65	64	Sorafenib + HAIC (cisplatin)	21.7	10.6
Song et al. [38]	Multicenter RCT	2014	50	55.1	HAIC and sorafenib, cisplatin + 5-FU	24.0	7.1
Yamashita et al. [47]	Single-center RCT	2011	57	65	Hepatic arterial infusion of fluorour acil plus cisplatin	45.6	10.5
Nouso et al. [51]	Multicenter RCT	2013	476	–	Cisplatin + 5-FU	40.5	14.0
Ishikawa et al. [57]	Single-center RCT	2014	79	67.8	HAI with DDP-H	–	36.8
Min et al. [59]	Single-center prospective	2017	38	71.1	HAIC (mFOLFOX)	52.6	5.87
Lyu et al. [61]	Single-center RCT	2017	180	51	Hepatic arterial infusion of oxaliplatin plus fluorouracil/leucovorin	49.7	14.5
Miyaki et al. [63]	Single-center RCT	2012	249	66	HAIC (intra-arterial low-dose cisplatin + 5-FU/IFN)	27.3	9.2

HAIC, hepatic artery infusion chemotherapy; 5-FU, 5-fluorouracil; RCT, randomized controlled trial; RR, response rate; OS, overall survival; IFN, interferon; DDP-H, cis-diamminedichloroplatinum; HAI, hepatic arterial infusion.

and independent prognostic factors associated with OS in all patients [63]. See Table 1.

Another study by Niizeki and colleagues [65] reported the serum vascular endothelial growth factor levels and the therapeutic effect of HAIC with advanced HCC patients. Various chemotherapeutic regimens are used for HAIC, with the combination of cisplatin (CDDP) and 5-FU being one of the most common and standard regimens, and the serum vascular endothelial growth factor level was an important predictive factor of the therapeutic effect and survival in patients with advanced HCC undergoing HAIC [65]. Ando et al. [62] first reported that repeated HAIC using low-dose CDDP and 5-FU was useful for patients with advanced HCC and tumor thrombus in the portal vein [62, 66]. A previous study by Ota and colleagues [50] reported the beneficial effects of combination therapy of IFN-α/5-FU which is promising for advanced HCC with tumor [50]. In addition, a study by Tajiri and colleagues [67] reported on 26 patients with advanced HCC who were treated by HAIC using arterial cisplatin plus continuous 5-FU. The neutrophil/lymphocyte ratio (NLR) was assessed to determine its effectiveness as a prognostic indicator of HAIC. The response rate was 42.3% and was independent of liver function. Response rate was significantly lower in patients with an NLR of 4. Therefore, the significance of NLR in predicting the effects of HAIC-FP remains uncertain. So, investigations are required [67]. Finally, and briefly, inflammation plays a critical role in tumors, and the oncogenic change induces an inflammatory microenvironment that promotes the development of tumors.

Conclusion

Our conclusion is that HAIC is a promising and acceptable approach for the management of advanced HCC with tolerable toxicities. Furthermore, various novel combinations of chemotherapeutic regimens have been recognized to be useful as standard treatments for advanced HCC patients. The previous randomized trials of combination therapies showed better benefits in patients who were treated with a combination of cisplatin + 5-FU, HAIC + sorafenib, FOLFOX, and INF + 5-FU. On the basis of these findings, we hope future studies will demonstrate more attractive results and publish more trials. Recently, HAIC has been researched widely. Thus, further improvements in the treatment outcomes of patients with advanced HCC are expected in the near future.

Conflict of Interest Statement

The authors declare that they have no conflicts of interest.

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Author Contributions

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