Current Status of Hepatic Arterial Infusion Chemotherapy

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Abstract
Background: Hepatic arterial infusion chemotherapy (HAIC) is frequently used to treat advanced hepatocellular carcinoma (HCC) in Asian countries. However, there is a lack of evidence supporting the use of HAIC. Summary: Many studies report high response rates in patients with advanced HCC receiving HAIC, and clinical responses translate to survival benefits. Therefore, prediction of an antitumor response is important in selecting appropriate treatments. There are no proven post-sorafenib therapeutic measures or procedures for HCC patients with poor liver function, and HAIC is one of the few options for patients in these situations. Despite studies showing its effectiveness, the use of HAIC for treatment of advanced HCC is unclear because convincing data from large-scale randomized clinical trials are lacking. For HAIC to become a standard treatment for HCC, such trials must establish its efficacy compared with other HCC therapies; prediction of antitumor response in HAIC may aid trial design, and a multi-center, open-labelled, randomized clinical trial of HAIC in advanced HCC is currently in progress. Optimization of HCC treatment protocols and regimens is also required. Key message: We think that both HAIC and sorafenib are effective treatments for advanced HCC, and this review presents evidence supporting this contention.

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer in the world. In recent years, its incidence has risen in many countries, including those in America, Europe, and
Asia [1]. Most cases of HCC develop in individuals with advanced chronic liver disease, which results from chronic hepatitis B or C virus infection, aflatoxin B1 exposure, or alcohol abuse. However, the etiology of HCC in 15%–50% of new HCC cases remains unclear, suggesting that other risk factors underlie its rising incidence. Risk factors in these “non-B, non-C” cases may include nonalcoholic fatty liver disease, which has received more attention in the last few years because of its high prevalence worldwide [2]. Because a surveillance system has not been established for non-B, non-C HCC [3–6], it is sometimes detected at an advanced stage. Additionally, the long-term prognosis of HCC remains far from satisfactory, mainly because of its frequent recurrence [7]; therefore, treatment of advanced HCC is important.

The purpose of this review is to provide an update of the current status of hepatic arterial infusion chemotherapy (HAIC). This review is based on PubMed searches (from 2010 to 2014) using the search terms “hepatic arterial infusion chemotherapy” and “hepatocellular carcinoma.”

**Guidelines for Advanced HCC**

The Barcelona Clinic Liver Cancer (BCLC) staging system has become widely accepted in clinical practice and has been used in many clinical trials evaluating new drugs for HCC treatment [4]. There are five HCC stages: very early stage (performance status (PS) 0, Child-Pugh A, single nodule <2 cm diameter), early stage (PS0, Child-Pugh A or B, single nodule and 2 or 3 nodules <3 cm diameter), intermediate stage (PS0, Child-Pugh A or B, multinodular), advanced stage (PS1–2, Child-Pugh A or B, portal invasion, lymph node involvement (N1), metastases (M1)), and terminal stage (PS>2, Child-Pugh C).

According to the American Association for the Study of Liver Diseases (AASLD) practice guidelines for HCC management, sorafenib is now considered the first-line treatment for patients with advanced stage HCC with good liver function (Child-Pugh A) [3]. Sorafenib inhibits the activity of several kinases, including Raf-1, B-Raf, vascular endothelial growth factor (VEGF) receptor 2, platelet-derived growth factor receptor, and c-Kit. It produces a clinically relevant increase in time to progression and length of survival, and its associated toxicity is easily managed without treatment-related mortality [8, 9].

On the other hand, in spite of its high antitumor efficacy, HAIC is not generally recommended as standard of care for HCC because it has not been tested in large-scale randomized clinical trials [3]. The BCLC staging classification and treatment schedule does not include HAIC on its list of treatment options for HCC [3], nor does the Asian Pacific Association for the Study of the Liver [5]. Although the 2010 version of the practice guidelines for hepatobiliary cancers developed by the National Comprehensive Cancer Network supports the use of systemic single- or multiple-agent chemotherapy or HAIC for unresectable HCC, it restricts these treatments to patients participating in clinical trials [10]. Cytotoxic drugs are not routinely recommended for HCC treatment but they may be considered in highly selected patients whose general and hepatic conditions are adequate [5].

According to the most recent version of the clinical practice guidelines for HCC in Japan (J-HCC 2013) [11], and a study comparing HAIC with historical controls [12], HAIC may improve prognosis. At present, sorafenib remains the standard treatment for advanced HCC worldwide. Studies showing whether HAIC improves HCC prognosis relative to sorafenib are required in the future.
Systemic Chemotherapy with Sorafenib for Advanced HCC

In patients with untreated advanced stage HCC, prognosis is poor, with a median survival time (MST) of approximately 5–7 months, although this varies depending on liver function [13]. Although cytotoxic agents are used for advanced HCC, systemic chemotherapy has not demonstrably improved survival despite decades of efforts by numerous investigators. HCC is often accompanied by liver cirrhosis and pancytopenia, thus making highly myelosuppressive chemotherapy more difficult to perform [14].

In 2008, the pivotal Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol trial showed that sorafenib significantly increased median overall survival (OS) by approximately three months relative to placebo (10.7 months vs 7.9 months, respectively; p<0.001) in patients with advanced HCC [8]. These findings were confirmed in a randomized controlled trial in the Asia-Pacific area (OS of 6.5 months for sorafenib vs 4.2 months for placebo, respectively; p<0.014) [9]. On the basis of these strong clinical findings, sorafenib is now considered the first-line treatment for patients with advanced stage HCC with good liver function worldwide [3–5, 11].

HAIC for Advanced HCC

HAIC has been shown to be an effective treatment for advanced HCC in Asian countries, especially Japan [15]. High response rates (RRs) and consequent survival benefits have been reported [12, 15–17]. Advanced HCCs derive 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 [18]. Liver parenchyma derives about 70% of its blood supply from the portal vein. Because the therapeutic agent first passes through the liver, the organ involved in its eventual metabolism, fewer systemic side effects are anticipated [18].

There are two methods for administering HAIC: bolus injection and continuous infusion. Concentration-dependent agents such as epirubicin hydrochloride, mitomycin C, cisplatin, and miriplatin are suitable for single-administration HAIC. Agents suitable for continuous HAIC include anthracycline-based agents; mitomycin C; fluorouracil (5-FU), which is time-dependent; and cisplatin, which is administered intermittently in accordance with the concept of biochemical modulation [19]. 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. In continuous HAIC, a reservoir system is sited subcutaneously for continuous infusion or repetitive applications. Presumably due to technical improvements, only 0–4% of patients develop catheter-related complications, such as port migration, catheter dislocation, arterial occlusion, port-catheter system occlusion, subcutaneous hematoma, or infection [12, 15, 16, 20].

Standard Protocols for HAIC

Several HAIC regimens, including single or combined administration of doxorubicin, epirubicin, mitomycin C, 5-FU, zinostatin stimalamer, cisplatin, miriplatin, and oxaliplatin, have been reported. However, relatively few large-scale, randomized controlled studies have investigated the efficacy of chemotherapy for treatment of HCC in contrast to other malignant tumors; the optimal regimen for HAIC in the treatment of HCC therefore remains unknown.
Cisplatin

Cisplatin exerts its anticancer effects by forming intra- and inter-strand covalent bonds with deoxyribonucleic acid via direct interaction with guanine or adenine at the N-7 position [21]. It has both time-dependent and concentration-dependent features. The RR for cisplatin administered via HAIC in advanced HCC ranges from 14% to 42% [22]. A 28% RR was demonstrated in a recent phase II study of HCC patients with portal vein tumor thrombosis (PVTT) [23]. The median progression-free survival (PFS) and the OS times in this study were 3.6 and 7.6 months, respectively. Four of the seven patients who showed a response survived for more than three years, and moderate cisplatin activity with mild toxicity was observed.

Diamminedichloplatinum-high dose (DDP-H), a powdered form of cisplatin, may be used in combination with lipiodol, an oily contrast medium selectively retained in hepatic arterial-infused HCCs. In a phase I/II study of 35 HCC patients receiving DDP-H (dose of 35 mg/m²) and lipiodol, 46% had a complete response, 11% had a partial response, and 26% had stable disease [24]. Only one patient experienced grade 3 thrombocytopenia. These findings show that this treatment is effective and well tolerated in patients with unresectable HCC.

Low-Dose 5-FU plus Cisplatin (FP)

Low-dose FP is a HAIC regimen in which a small amount of cisplatin (10 mg/m² per day, days 1–5) modulates the effects of 5-FU (250 mg/m² per day, days 1–5), which is continuously infused. In a study of 48 patients with HCC accompanied by PVTT, low dose FP achieved a RR of 48% and a MST of 10.2 months [25]. In other studies of low-dose FP, RRs ranged from 39% to 71%, and MSTs ranged from 6.2 to 15.9 months [16, 25]. In a phase II study of low-dose FP in 52 patients with advanced HCC, the RR was 38.5%, the median time to progression was 4.1 months, and the MST was 15.9 months [16]. The most frequent adverse event was myelosuppression (e.g., neutropenia or thrombocytopenia).

Oh et al. [26] evaluated the efficacy and safety of low-dose FP HAIC according to Child-Pugh class. The MST and PFS times for Child-Pugh A were 8.7 months and 7.1 months, respectively with 95% confidence interval (CI) of 3.8–10.4. For Child-Pugh B and C (B/C) combined, they were 3.7 months (95% CI, 2.0–5.3) and 3.6 months (95% CI, 2.0–5.2), respectively. Adverse events above grade 3 occurred frequently in both groups (83.3% for Child-Pugh A and 96.7% for Child-Pugh B/C, respectively). This study shows that low-dose FP HAIC is less effective and somewhat less safe in Child-Pugh B/C patients than in Child-Pugh A patients.

A recent Japanese nationwide survey conducted by Nouso et al. [17] supports the efficacy of low-dose FP HAIC for treatment of advanced HCC. Survival benefits were apparent after adjusting for known risk factors (hazard ratio, 0.48; 95% CI, 0.41–0.56; p<0.0001). In a propensity score-matched analysis (n=682), MST was longer in patients who received low-dose FP (14.0 months) than in patients who did not (5.2 months, p<0.0001). On the basis of those results, low-dose FP has become one of the most promising regimens for treatment of advanced HCC.

5-FU Arterial Infusion and Interferon Therapy (FAIT)

In FAIT, the antitumor effects of interferon (IFN) increase when it acts as a biochemical modulator of 5-FU. IFN directly inhibits proliferation and indirectly affects angiogenesis [27]. Sakon et al. [15] reported a very favorable RR (63%) in eight HCC patients with PVTT who received FAIT. In other reports, the RRs for FAIT has ranged from 26.7% to 63%, and MST has ranged from 7.0 to 11.8 months [12, 15, 28], respectively. The multicenter, randomized phase II study of Monden et al. [28] assessed the efficacy and safety of FAIT in HCC patients with a high degree of vascular invasion using conventional HAIC (low-dose FP or cisplatin) as a reference. RR, the primary endpoint, was similar in both groups (FAIT, 26.7%, 8 of 30 patients; conventional, 25.8%, 8 of 31 patients), as was the number of grade 3 or
higher adverse events (FAIT, 115 in 30 patients; conventional, 113 in 29 patients). None of the deaths in the study were therapy-related.

FAIT exerts modest antitumor effects, poses no particular safety concerns, and is thus considered a highly promising regimen. It may be a worthwhile strategy for treating advanced HCC with a high degree of vascular invasion.

Other Regimens

Nagamatsu et al. [29] assessed the efficacy of cisplatin (DDP-H) in a lipiodol emulsion combined with 5-FU in patients (n=51) with HCC and PVTT. The RR was 86.3%, the MST was 33 months, treatment was well tolerated, and severe toxicity was infrequent (only one case of grade 3 toxicity [thrombocytopenia]). Yamashita et al. [30] compared FAIT with or without cisplatin in a randomized phase II study of HCC patients. FAIT + cisplatin had a significantly higher RR than FAIT alone (45.6% and 24.6%, respectively; p=0.030) and a significantly higher median PFS time (6.5 vs 3.3 months, respectively; p=0.0048). MSTs were not significantly different (17.6 months for FAIT + cisplatin and 10.5 months for FAIT; p=0.522). Hematological toxicity was commonly observed, but no toxicity-related deaths occurred. These results suggest that combining FAIT with cisplatin may improve outcome.

Survival Depends on Response to Treatment

Although many studies report high RRs for HAIC in advanced HCC, median OS times are extremely short. In our study of HCC/PVTT patients treated with FAIT [12], the RR was 52.6%, but the median OS was only 6.9 months. The clinical response significantly affected survival; complete responders had the best survival rates (81% and 59% at 12 and 24 months, respectively), partial responders had intermediate rates (43% and 18% at 12 and 24 months, respectively), and patients with stable or progressive disease had the worst rates. In a multivariate analysis, a complete response predicted increased survival time (p<0.0001). Therefore, clinical response may predict survival outcome [12, 15, 16]; accordingly, a good response predicts extended survival.

Predictive Factors for Response and Survival

Survival benefits for HAIC have been reported in patients with positive antitumor responses. Because the chemosensitivity of patients with advanced HCC presumably differ, prediction of an antitumor response is important in selecting appropriate treatments. Because HCC is often accompanied by liver cirrhosis, liver function is the most important consideration. Miyaki et al. [31] examined tumor response, tolerance, and survival after HAIC according to Child-Pugh score (5/6, 7, or 8/9) [31]. The median OS time was 8.2 months, and the MSTs for scores 5/6, 7, and 8/9 were 9.7, 6.3, and 3.9 months, respectively (p<0.0001). The RR was higher for scores 5/6 (30.5%) and 7 (28.2%) than scores 8/9 (13.8%), whereas the dropout rate was significantly higher for scores 8/9 (8.0%) than scores 5/6 (33.3%) and 7 (12.8%). In patients with Child-Pugh scores of 5/6 or 7, survival rates were significantly better in complete and partial responders than non-responders. A Child-Pugh score of 8/9 was an independent negative prognostic factor for response and survival; thus, HAIC may only improve survival in patients with a Child-Pugh score of 7 or less.

Niizeki et al. [32] reported that serum VEGF levels > 100 pg/ml independently predicted therapeutic effects in HCC patients undergoing HAIC (p=0.026). VEGF level positively correlated with platelet count (r=0.569, p<0.001) and tumor size (r=0.543, p<0.001). VEGF
was identified as an independent prognostic indicator of survival in a multivariate analysis (p=0.004), as were therapeutic effect (p=0.005) and Child-Pugh class (p=0.046).

Inflammation plays a critical role in the development and progression of various cancers [33]. Inflammation-related markers, such as the absolute leukocyte count, C-reactive protein level, neutrophil to lymphocyte ratio (NLR), and cytokine level, have been linked to clinical outcomes in patients with various malignancies, including HCC [34]. In a study by Tajiri et al. [35], NLRs of 4 or more (odds ratio, 0.49; p=0.04) correlated with low RRs, whereas NLRs less than 4 correlated with prolonged OS, as did treatment response. In a study by Terashima et al. [36], patients with high NLRs (cut-off value=2.87) had significantly shorter MSTs (5.6 and 20.7 months, respectively; p<0.01) and significantly worse RRs (21.1% and 37.7%, respectively; p<0.01) than patients with low NLRs. In a multivariate analysis, the NLR was also associated with response to HAIC (p=0.024), and high NLR was identified as an independent negative prognostic indicator [34].

Yamasaki et al. [37] recently reported the effectiveness of the iron chelator deferoxamine for advanced HCC, suggesting that regulation of iron levels may significantly impact HCC therapy. Transferrin, a native chelator involved in iron homeostasis, may act as an anticancer agent in a similar manner as deferoxamine. In a study by Zaitsu et al. [38], transferrin levels significantly correlated with MSTs in HCC patients undergoing HAIC (MSTs were 12.0 and 4.9 months for ≥190 mg/dL and ≤190 mg/dL transferrin, respectively). A serum transferrin level ≥190 mg/dL (hazard ratio, 0.282; 95% CI, 0.132–0.603; p=0.001) was identified as an independent prognostic indicator in a multivariate analysis, as was Child-Pugh B (hazard ratio, 1.956; 95% CI, 1.034–3.700; p=0.039). The serum transferrin level also correlated significantly with therapeutic response (p<0.001).

Miyaki et al. [39] assessed early responses to one course of HAIC treatment using Response Evaluation Criteria in Solid Tumors (RECST), alpha-fetoprotein (AFP) ratio, and the des gummer carboxyprothrombin (DCP) ratio. Early imaging response correlated with survival (MSTs were 20.6, 11.4, and 5.0 months for a partial response, stable disease, and progressive disease, as defined by RECST; p=0.0001). AFP and DCP ratios also correlated with MST; MSTs were lowest (6.55 months) in patients with an AFP ratio >1 and a DCP ratio >1.

In practice, responders and non-responders can be distinguished after the first session of HAIC by changes in tumor size, as determined via various imaging modalities, and tumor marker changes. In early non-responders, the therapeutic strategy should be altered accordingly.

The studies described in this section identify several prognostic factors in advanced HCC. These include VEGF levels, which predict therapeutic effects and survival times, and AFP and DCP ratios, which are independent predictors of early responses. Additional useful indicators include serum transferrin levels, NLRs, and Child-Pugh scores.

### Timing of HAIC

#### Sequential Therapy

Sorafenib is the standard treatment for advanced HCC; however, therapeutic procedures after termination of sorafenib remain to be established. HAIC is a potential option previously evaluated by Terashima et al. [40] in patients with advanced HCC (n=27). In their study, a partial response was obtained in 29.6% of the patients, and stable disease was achieved in 33.3%, respectively. Median PFS times and MSTs from the initiation of HAIC were 4.0 and 7.6 months, respectively. No unexpected adverse reactions or treatment-related deaths were
observed. HAIC was well tolerated and it exhibited moderate antitumor activity. Therefore, it is a potentially useful treatment in patients with advanced HCC, even after sorafenib failure.

Miyaki et al. [41] examined the opposite sequence in patients with advanced HCC with the use of sorafenib after HAIC versus best supportive care (BSC) after HAIC, as the reference. MST was significantly higher for HAIC/sorafenib than HAIC/BSC (22.2 and 8.7 months, respectively; p=0.0017). The disease control rate after administration of sorafenib was 51.8%, and the MST was 10.4 months. Sorafenib was a significant and independent determinant of OS in both HAIC responders and non-responders.

**Adjuvant Therapy**

Several investigators have examined the efficacy of HAIC as postoperative adjuvant treatment for advanced HCC. All studies showed better outcomes with adjuvant HAIC than control: 1) 1-year OS rates were 100% and 30%, respectively (p<0.0001) [42]; 2) 5-year disease-free survival rates were 33.1% and 11.8%, respectively (p=0.029) [43]; 3) 5-year cumulative survival rates were 71.1% and 44.0%, respectively (p=0.023) [44]; 4) the percentages of patients with multiple (≥4) recurrent intrahepatic nodules were 44.4% and 100%, respectively (p=0.040); and 5) the percentages of patients with intrahepatic recurrence within 12 months were 33.3% and 80.0%, respectively (p=0.040). Five-year OS rates were also higher in the adjuvant group than in the historical group, but the difference was not significant (46.7% and 32.7%, respectively; p=0.318). In a Cox proportional multivariate analysis of disease-free survival rates, adjuvant therapy was an independent favorable prognostic factor in all patients in the study (n=73; hazard ratio 0.536; p=0.029) [43]. Of note, the improved OS times noted above were shown in patients with advanced HCC invading the portal vein [42]; in such cases, prognosis is extremely poor even after hepatic resection.

**Neo-Adjuvant Therapy**

Nishikawa et al. [45] investigated the effectiveness of transcatheter arterial infusion (TAI) of the whole liver using an epirubicin-mitomycin-lipiodol emulsion; TAI was administered before radiofrequency thermal ablation (RFA), and distant intrahepatic recurrence from a single HCC was examined. The cumulative recurrence-free survival rates for lipiodol alone at 1, 2 and 3 years were 74.0, 50.8, and 34.9%, respectively. Rates for TAI performed as described above were 90.8, 74.8, and 70.0%, respectively (p<0.0001). There was a significant difference in OS (p=0.048), but not local tumor progression (p=0.145), between the two groups.

Ishikawa et al. [46] compared the survival rates of patients who received RFA with or without prior HAIC (DDP-H). Cumulative survival rates at 1, 3, and 5 years were 77.4%, 69.2%, and 55.3% for RFA alone, respectively, and 97.4%, 87.0%, and 84.4% for prior HAIC + RFA, respectively. Survival time was significantly longer for prior HAIC + RFA than RFA alone (log-rank test, p=0.023; generalized Wilcoxon test, p=0.012). Multivariate analysis using the Cox proportional hazards model identified prior HAIC + RFA as the most important factor affecting survival.

Collectively, the studies described in this section illustrate the value of sequential treatments in advanced HCC. They suggest that sorafenib administration before or after HAIC improves prognosis, as does TAI. Adjuvant HAIC may increase the survival time by reducing distant intrahepatic recurrence, as may HAIC before RFA.
Comparative Studies

HAIC has a chemotherapeutic effect and a favorable toxicity profile in patients with advanced HCC. However, convincing clinical evidence of HAIC efficacy is lacking because there have been no large randomized studies.

HAIC versus BSC

Nouso et al. [17] assessed the efficacy of HAIC for treatment of advanced HCC in a nationwide survey. A comparison of 476 HCC patients who underwent HAIC versus 1466 HCC patients receiving BSC (active treatment) demonstrated survival benefits for the former after adjusting for known risk factors (hazard ratio, 0.48; 95% CI, 0.41–0.56; p<0.0001). In a propensity score-matched analysis (n=682), MST was longer for HAIC (14.0 months) than BSC (5.2 months, p<0.0001).

We examined consecutive HCC/PTVV patients who received HAIC (n=116) or alternative treatments, which were mostly BSC (historical control group, n=40) [12]. There were no differences in the tumor characteristics or liver function between the two groups. The survival rates at 6, 12, and 24 months were 53%, 34%, and 18% in the HAIC group, respectively, and 40%, 15%, and 5% in the historical control group, respectively (p<0.01, log-rank test).

Tsai et al. [47] compared the effects of HAIC and BSC in patients with large (>8 cm diameter) unresectable HCCs and similar baseline characteristics and tumor stages. The OS rates at 1 and 2 years were 29% and 14% in the HAIC group, and 7% and 5% in the BSC group, respectively (p<0.0001). HAIC significantly correlated with OS in a multivariate analysis (relative risk, 0.321; 95% CI, 0.200–0.515; p<0.001). These results indicate that HAIC is a safe procedure that provides better survival than BSC in patients with advanced HCC.

HAIC versus Sorafenib

Hiramine et al. [48] attempted to determine whether sorafenib (n=20) was more effective than HAIC (n=45) for treating HCC. However, sorafenib treatment was discontinued in 19 patients (95%), including 12 who experienced side effects. In a study by Jeong et al. [49], median OS times were 4.9 months for sorafenib (95% CI, 3.4–6.4) and 7.3 months for HAIC (95% CI, 4.5–10.2; p=0.599). Median PFS times were 2.0 months for sorafenib (95% CI, 1.96–2.05) and 3.0 months for HAIC (95% CI, 1.98–4.02; p=0.303). Overall RRs for sorafenib and HAIC were 10.0% and 19.0%, respectively (p=0.413); disease control rates were 35% and 38%, respectively (p=0.837). Patients receiving HAIC more frequently exhibited grade 3/4 neutropenia (23.8 versus 0% for sorafenib), but sorafenib exhibited grade 3/4 hand-foot skin reactions in 10% of the patients.

Song et al. [50] found that the OS times were comparable for HAIC and sorafenib (7.1 and 5.5 months, respectively; p=0.011), as were the times to progression (3.3 and 2.1 months, respectively; p=0.034), in advanced HCC patients with PVTT. These results suggest that both HAIC and sorafenib are effective treatments for advanced HCC, especially when accompanied by PVTT.

Discussion

HAIC is often used to treat advanced HCC. Typical regimens are cisplatin, low-dose FP, and FAIT, as described above. However, the optimal regimen remains unknown. High RRs for HAIC in advanced HCC have been reported, and clinical responses translate to survival
benefits. Because of probable differences in the chemosensitivity of HCC patients, prediction of an antitumor response is important in selecting treatment options.

HAIC has a favorable chemotherapeutic efficacy and toxicity profile in patients with advanced HCC. Sorafenib is the first systemic chemotherapeutic agent that has improved the survival times of patients with advanced HCC. However, there is no proven therapeutic procedure for post-sorafenib patients or patients with poor liver function. HAIC is one of the few remaining options for advanced HCC patients in these predicaments.

In this era of molecularly targeted anticancer therapies, HAIC treatment for advanced HCC is an unresolved issue. According to the AASLD practice guidelines for the management of HCC, sorafenib is now considered the first-line treatment for advanced HCC in patients with good liver function (Child-Pugh A). Sorafenib delays the time to progression, it prolongs survival in a clinically relevant manner, and its associated toxicity is easily managed without treatment-related mortality. HAIC, on the other hand, is not recommended and should not be used as a standard of care; there have been no large randomized studies of HAIC in advanced HCC patients and hence, no convincing clinical evidence. Furthermore, HAIC includes multiple technical procedures and is associated with the risk of vascular disorders stemming from catheter placement and reservoir management. Consequently, it is not commonly used to treat HCC in North America or Europe.

At present, HAIC is not a well-established treatment for advanced HCC, and further investigation is required. For HAIC to become a standard treatment for HCC, clinical studies that establish its efficacy relative to other therapies for HCC are required, as is optimization of treatment protocols and regimens. A multi-center, open-labelled, randomized control trial of HAIC in patients with advanced HCC is ongoing (SILIUS trial; Sorafenib vs. Sorafenib plus HAIC; ClinicalTrials.gov identifier, NCT01214343; UMIN clinical trials registry identifier, UMIN000004315).

To review previous studies and to establish future trials may improve on the current situation of HAIC. In designing clinical chemotherapy trials, prediction of the antitumor response is important. The findings presented here may be useful for designing treatment strategies and clinical chemotherapy trials in the future.

**Conclusion**

We believe that both HAIC and sorafenib are effective treatments for advanced HCC. Clinical studies that convincingly establish the efficacy of these therapies in comparison with other HCC therapies are required, as is the optimization of treatment protocols and regimens.

**References**


