

Current Status of Hepatocellular Carcinoma Treatment in Japan

Hepatic Arterial Infusion Chemotherapy

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Abstract

Hepatic arterial infusion chemotherapy (HAIC) allows the long-term administration of cytotoxic drugs to the liver. In Japan, HAIC has traditionally been used to treat patients with advanced hepatocellular carcinoma (HCC) with vascular invasion or multiple intrahepatic lesions, or both. The most common chemotherapy drugs used for HAIC in Japan are 5-fluorouracil and cisplatin.

Although HAIC is associated with a high rate of response in some studies, it is not associated with a survival benefit. Furthermore, HAIC is associated with complications that are not observed with systemic chemotherapy, including peptic ulcer, arterial occlusion and port infection.

A molecular targeted agent, sorafenib, recently became the standard therapy for advanced HCC on the basis of data from two randomized controlled trials. For this reason, the position of HAIC in the treatment of advanced HCC in Japan is under discussion. Clinical trials must be undertaken to establish standardized protocols and regimens for HAIC, and to determine the efficacy of HAIC in comparison with other therapies for HCC. Without evidence from such trials, HAIC may not find an established role in the treatment of HCC, and may even fall out of use.

Recent evidence suggests that HAIC may be useful in combination with molecular targeted therapy; this is currently being investigated in a number of clinical trials.

1. Introduction

Conventional chemotherapy for advanced hepatocellular carcinoma (HCC) comprises systemic chemotherapy (administered intravenously or orally) or hepatic arterial infusion chemotherapy (HAIC). Both systemic chemotherapy and HAIC have been shown to be effective in patients with advanced HCC in Japan.^[1]

HAIC allows the long-term administration of cytotoxic drugs to the liver through the use of an indwelling catheter-port system. Compared with systemic chemotherapy, HAIC delivers a higher local drug concentration directly to liver tumours and is associated with fewer significant systemic side effects.^[2] In the past, catheters were placed surgically under general anaesthesia; however, as a result of recent advances in interventional

radiological techniques, it is now possible to insert catheter-port systems percutaneously under local anaesthesia.^[2]

In Japan, HCC is a common malignancy,^[3] and is one of the leading causes of cancer mortality.^[4] HAIC is a treatment for HCC that is used primarily in Japan and some other Asian countries, including Korea. Data from some studies indicate that HAIC is associated with a high response rate; however, treatment response has not been consistent across studies and there is little evidence of a survival benefit with HAIC.

Molecular targeted therapy recently became a new field of cancer chemotherapy for patients with HCC. The introduction of such agents has meant that the role of HAIC in patients with advanced HCC is under discussion. This review discusses the current status of HAIC for the treatment of HCC in Japan and the role that this form of treatment may play in the future. The contents of this review are based on a Medline literature search (from 2000 to 2010) using the following search terms: ‘hepatocellular carcinoma’ and ‘hepatic arterial infusion chemotherapy’.

2. Current Status of Chemotherapy for Hepatocellular Carcinoma in Japan

According to data from the 14th to the 18th Nationwide Follow-up Survey of Primary Liver Cancer conducted in Japan between 1996 and 2005,^[3,5-8] chemotherapy was used as initial therapy in 3.4% of newly diagnosed patients with HCC in 1996–1997, increasing to 5.5% of patients in 2004–2005 (figure 1a). Of those patients who were initially treated with chemotherapy, HAIC was the most common administration method (figure 1b). Between 2000 and 2005, the proportion of chemotherapy patients who received treatment in the form of HAIC was approximately 90%.^[3,5-8] In the same time period, the proportion of patients with HCC who had a complete response to chemotherapy (assessed according to various criteria) ranged from 13.5% to 19.9%. During the same time period, 25.5–30.2% of patients had a partial response to chemotherapy (figure 1c).^[3,5-8]

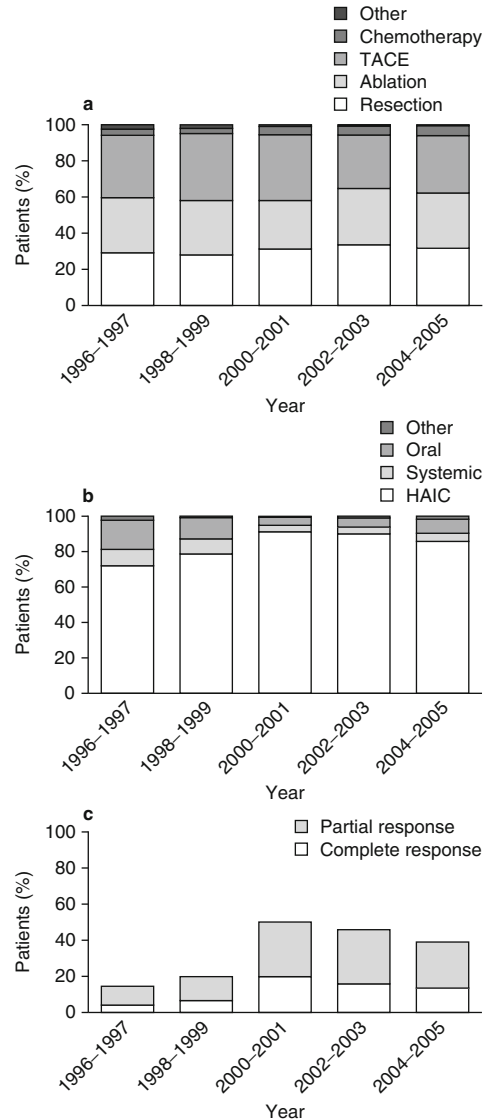


Fig. 1. (a) Treatment modality in newly diagnosed patients with hepatocellular carcinoma (HCC) from 1996 to 2005 according to data from the 14th to 18th Nationwide Follow-up Survey of Primary Liver Cancer in Japan (percentages for 1996–1997 and 1998–1999 were calculated from the original Japanese version of the data).^[3,5-8] TACE = transcatheter arterial embolization. (b) Method of chemotherapy administration in newly diagnosed patients with HCC from 1996 to 2005 according to data from the 14th to the 18th Nationwide Follow-up Survey of Primary Liver Cancer in Japan (percentages for 1996–1997, 2000–2001 and 2002–2003 were calculated from the original Japanese version of the data).^[3,5-8] HAIC = hepatic arterial infusion chemotherapy. (c). Response rates to chemotherapy for newly diagnosed patients with HCC from 1996 to 2005 according to data from the 14th to the 18th Nationwide Follow-up Survey of Primary Liver Cancer in Japan.^[3,5-8]

3. Guideline Recommendations for the Use of Hepatic Artery Infusion Chemotherapy in Patients with Hepatocellular Carcinoma

3.1 Japan

The clinical practice guidelines for hepatocellular carcinoma (J-HCC) were the first evidence-based guidelines for the treatment of HCC in Japan. The J-HCC guidelines were compiled by an expert panel supported by the Japanese Ministry of Health, Labour, and Welfare, and encompass the prevention, diagnosis, surveillance and treatment of HCC. They were first developed in 2005, and were subsequently revised in 2009. The most recent version of the J-HCC guidelines recommends the use of HAIC or transcatheter arterial embolization (TACE) in patients with multifocal HCC (four or more tumours) who have Child–Pugh class A or B liver disease. HAIC (or hepatectomy or TACE) is also recommended for those patients with Child–Pugh class A liver disease accompanied by vascular invasion.^[9] An English translation of the guidelines is available at the following URL: <http://www.jsh.or.jp/english/examination.html>.

3.2 Other Countries

Although HAIC is recommended for the treatment of HCC in certain situations in Japan, as described previously, a number of international practice guidelines do not endorse the use of HAIC in patients with HCC. The Barcelona Clinic Liver Cancer staging classification and treatment schedule^[10] does not include HAIC in its list of treatment options for HCC, while the American Association for the Study of Liver Disease practice guidelines^[11] state that ‘systemic or selective intra-arterial chemotherapy is not recommended and should not be used as standard of care’. Although the 2010 version of the practice guidelines for hepatobiliary cancers developed by the National Comprehensive Cancer Network recommends the use of systemic single-agent or multiple-agent chemotherapy or intra-arterial chemotherapy in patients with unresectable HCC, this is restricted to those patients participating in a clinical trial.^[12]

4. Hepatic Artery Infusion Chemotherapy versus Systemic Chemotherapy

There are almost no well-designed, controlled studies that have directly compared systemic chemotherapy and HAIC for the treatment of HCC, and there are insufficient data to show that one treatment is better than the other. Indeed, in the 2009 version of the J-HCC guidelines it is noted that there is ‘no sufficient scientific evidence that hepatic arterial infusion chemotherapy is more beneficial than systemic chemotherapy’.^[13] In developing the guidelines, an analysis of response rates in trials that investigated each type of chemotherapy in 30 or more patients was undertaken. Data from these trials showed that the rate of response was 22–71% with HAIC compared with 0–28% with single-agent systemic chemotherapy and 2.5–39% with multiple-agent systemic chemotherapy; the median survival time (MST) with these treatment modalities was 4.4–32.4, 1.9–13.7, and 3.0–30.9 months, respectively.^[13] These data suggested that HAIC was more beneficial than systemic chemotherapy; however, there was great variability in the outcomes assessed, most likely as a result of the different sample sizes and selection criteria of the individual studies. The final recommendation that HAIC was no better than systemic chemotherapy was based on the results of a randomized trial that directly compared the effects of doxorubicin administered as HAIC or as systemic chemotherapy in 64 patients with unresectable HCC.^[14] Although the proportion of patients who experienced a complete response or a partial response was numerically higher in the HAIC group compared with the systemic chemotherapy group (60.0% vs 44.1% of patients), MST was not significantly different in the two treatment groups (7.0 vs 6.5 months).

5. Standard Hepatic Artery Infusion Chemotherapy Protocols

In contrast to what has been observed for other malignant tumours, there are relatively few large-scale, randomized controlled studies that have investigated the efficacy of chemotherapy

for the treatment of HCC.^[13] As such, according to the expert panel that developed the 2009 J-HCC guidelines, there is no established standard chemotherapy protocol for the treatment of advanced HCC.^[13]

Within Japan, 5-fluorouracil and cisplatin are the most common chemotherapy drugs used for HAIC; these agents account for more than 50% of those used for HAIC.^[15-18] HAIC may involve multiple agents or a single agent. In Japan, representative HAIC protocols include 5-fluorouracil plus cisplatin (primarily at low doses), interferon plus 5-fluorouracil, and cisplatin alone; however, the optimal regimens of these protocols have not been established.

5.1 Cisplatin Plus 5-Fluorouracil

HAIC with low-dose 5-fluorouracil plus cisplatin is commonly used in patients with advanced HCC, but requires careful monitoring of haematological function.^[19] In studies involving 16–97 patients,^[19-30] HAIC with 5-fluorouracil plus cisplatin was associated with a complete or partial response in 8–71% of patients and an MST of 6.0–15.9 months. There was much variation in the dose of 5-fluorouracil and cisplatin administered in these studies, as well as variation in the timing and duration of the two treatments. To establish the optimum regimen of HAIC with 5-fluorouracil plus cisplatin, the dose, infusion time and dosing interval of 5-fluorouracil as well as the dose, infusion time and dosing duration of cisplatin should be standardized in future. Further research should also focus on the combination of 5-fluorouracil and cisplatin with leucovorin/isovorin^[31,32] and lipiodol;^[33] preliminary data from small-scale studies show that these combinations may be suitable for patients with advanced HCC.

5.2 Interferon Plus 5-Fluorouracil

Combination chemotherapy with interferon and 5-fluorouracil has been shown to be effective in patients with HCC. In studies involving 10–116 patients with HCC,^[34-42] HAIC with interferon plus 5-fluorouracil was associated with a response rate of 14–85% and an MST of 6.5–31.8 months. In several of the studies, 5-fluorouracil was ad-

ministered as a continuous infusion at a dose of approximately 500 mg/day, whereas the type and the dose of interferon varied. Further research should focus on the optimum interferon species (IFN α -2b, natural IFN α , or pegylated interferon) to use, the patient groups for which HAIC with interferon plus 5-fluorouracil is indicated, and the rationale for combining interferon with a cytotoxic drug. In addition, research should assess the feasibility of combining interferon, 5-fluorouracil and cisplatin; although data suggest that HAIC with interferon, 5-fluorouracil and cisplatin may be beneficial in patients with HCC,^[43] no standard regimen for this combination has been established.

5.3 Single-Agent Cisplatin

In studies involving 10–80 patients,^[44-48] HAIC with cisplatin was associated with response rates of 14–42% and an MST of 2.6–10.7 months (mean survival time of 19.7 months in one study). Although the first cisplatin formulation (fine powder) intended for HAIC (IA call; Nippon Kayaku, Tokyo, Japan) was approved and marketed in Japan in 2004, the optimum formulation, dose and dosing interval of this drug has yet to be determined. Further research into the efficacy of cisplatin in combination with lipiodol should be undertaken; data from a phase I/II study conducted in patients with unresectable HCC has shown this combination to be effective and well tolerated.^[49]

6. Case Studies of Patients Treated with Hepatic Artery Infusion Chemotherapy

A number of patients with advanced HCC have shown a dramatic response to several cycles of HAIC at our institute, the Kanazawa University Hospital, Kanazawa, Ishikawa, Japan. Such patients were treated with curative therapy, including hepatic resection and radiofrequency ablation, following treatment with HAIC, and went on to survive for more than 5 years. Two such case studies are described here. Despite the patients showing a dramatic response to HAIC, few prospective studies have evaluated the survival of HCC patients following treatment with HAIC.

A 70-year-old man with type C liver cirrhosis (Child–Pugh score 7/class B) presented to the clinic. The patient had multifocal HCC (major lesion 11 cm) with tumour thrombus in the right portal branch (VP3) and leg veins, but he had no lymph node or distant metastases. Nine cycles of HAIC with interferon plus 5-fluorouracil were administered from November 2004, resulting in a 48% reduction in tumour size (partial response). Two subsequent cycles of HAIC with interferon, 5-fluorouracil and cisplatin were given but further tumour regression was not observed. In October 2006, the patient underwent hepatic resection as salvage therapy. As of March 2010, the patient was alive and recurrence free. As a result of the effect of salvage therapy, the survival time from the start of HAIC was more than 65 months. This experience re-emphasizes the importance of salvage therapy.

A 60-year-old man with type B liver cirrhosis (Child–Pugh score 8/class B) with multifocal HCC (major lesion 5.3 cm), tumour thrombus in the right to left portal branches (VP4) and no lymph node or distant metastases presented for treatment. Five cycles of HAIC with interferon plus 5-fluorouracil were administered from December 2004 onwards. A 47% decrease in tumour size was observed, as was regression of portal invasion. Suspected residual tumours were treated by radiofrequency ablation. The patient was subsequently treated with three cycles of radiofrequency ablation for recurrence in segment V and has survived for more than 5 years. The survival time from the start of HAIC was more than 64 months.

7. Complications of Hepatic Artery Infusion Chemotherapy

HAIC requires the precise placement of the catheter tip so as to optimize hepatic chemoinfusion and to reduce extrahepatic cytotoxic side effects.^[2] To this end, specific skills in arterial catheterization are required.

Because HAIC requires the implantation of a catheter-port system, it is considered invasive for patients. Furthermore, the process is associated with complications that are not observed with

systemic chemotherapy, including bruising and the formation of haematomas at the puncture and port pocket site. Additional complications may include dislocation of the catheter, thrombotic occlusion of the catheter and/or the hepatic artery, and stroke.^[2] Development of abdominal pain following HAIC has also been observed by the author. Further investigation with gastric endoscopy in the affected patient showed a red lesion with an ulcerated centre in the vestibule, suggesting that the cytotoxic drug used for HAIC may have leaked into the gastrointestinal tract causing a peptic ulcer.

Vascular complications of HAIC, including hepatic arterial vasculitis and occlusion, port infection and catheter occlusion, may also occasionally occur.

8. Hepatic Artery Infusion Chemotherapy Compared with Sorafenib

Within Japan, HAIC is considered an unsuitable treatment option in patients with HCC with multiple intrahepatic nodules or HCC with portal invasion, lymph node involvement or distant metastasis, or both. Therefore, HAIC is restricted to patients with HCC with extensive vascular invasion (VP3/4), HCC with very extensive portal invasion (VP4) and a massive intrahepatic lesion, or bilobar multifocal HCC with multiple intrahepatic lesions that are unresponsive to TACE.

The role of HAIC for the treatment of advanced HCC in Japan has recently been revisited. This has been prompted by the publication of the results of two randomized, controlled, phase III trials, which showed that the molecular targeted therapy, sorafenib, was effective for the treatment of advanced HCC.^[50,51] These results led to sorafenib being preferentially indicated for the treatment of HCC with distant metastasis, multiple intrahepatic lesions or vascular invasion, or both; therefore, in the author's opinion, reducing the role of HAIC in the treatment of HCC in Japan. If HAIC is to be considered a recognized treatment for HCC and not fall out of use, clinical studies that establish its efficacy in comparison with other therapies for HCC, as well as the optimal treatment protocol and regimen, should be conducted.

Sorafenib was approved for use in Japan in May 2009.^[52] In the absence of direct comparative data, a comparison of HAIC and sorafenib with regard to regional usage, advantages, disadvantages, tumour response rate, patient survival and cost of treatment is provided in table I.

9. Sequential Therapy with Sorafenib and Hepatic Artery Infusion Chemotherapy

It is the author's experience that sequential therapy with sorafenib then HAIC may be effective. Treatment with sorafenib then HAIC was trialled in a 70-year-old man with type C liver cirrhosis who was referred to the author's clinic in May 2009, 1 month after a diagnosis of HCC. The patient was alcohol dependent with a family history of HCC. Computed tomography and computed tomography hepatic arteriography showed bilobar multifocal HCC with multiple intrahepatic lesions. At baseline, the patient had Child–Pugh class A liver disease. Following treatment with sorafenib 800 mg/day, the patient experienced fever, rash and back pain. The back pain was the result of bone metastasis that was not present at the initial diagnosis; radiotherapy was directed towards the bone metastasis. Response to sorafenib was judged as progressive disease. Following two cycles of

HAIC with interferon, 5-fluorouracil and cisplatin, the liver tumour size was reduced by 34% (partial response according to version 1 of the response evaluation criteria in solid tumors)^[54] [figure 2]. The patient remains alive 13 months after the initiation of sorafenib therapy. This case study is intriguing as it highlights the possibility that previous treatment with sorafenib may render tumour cells more sensitive to cytotoxic effects. Further experience with HAIC in other patients unresponsive to sorafenib also suggests that previous treatment with sorafenib may enhance tumour response to cytotoxic drugs.

10. Concurrent Therapy with Sorafenib and Hepatic Artery Infusion Chemotherapy

Concurrent treatment with HAIC and sorafenib is now under investigation in several clinical trials in Japan, including the phase III SILIUS trial (ClinicalTrials.gov identifier, NCT01214343; UMIN clinical trials registry identifier, UMIN00004315). This randomized, open-label trial will compare the efficacy of 28-day cycles of sorafenib alone (400 mg twice a day) and sorafenib plus HAIC comprising low-dose cisplatin (20 mg/m² on days 1 and 8) and 5-fluorouracil (330 mg/m² administered

Table I. Key characteristics of HAIC and sorafenib for the treatment of HCC

	HAIC	Sorafenib
Primary country of use	Japan and Korea	USA, Europe
Advantages	Substantial tumour shrinkage possible Regression of tumour thrombi possible Long-term survival possible if treatment is effective	Survival benefit demonstrated in well-designed clinical trials Orally active
Disadvantages	No standardized treatment protocol/regimen Uncertain survival benefit Very few trials comparing HAIC with systemic chemotherapy Specific skill required for administration (e.g. arterial catheterization) Associated with unique complications	Poor rate of tumour shrinkage Restricted to patients with preserved liver function (Child–Pugh class A liver disease) May cause serious adverse reactions that necessitate treatment discontinuation Not well utilized in Japan ^a Drug withdrawal criteria not yet established
Tumour response rate	14–85% ^[35,45]	2–3.7% ^[50,53]
Survival time (months)	2.6–31.8 ^[35,45]	6.5–15.6 ^[51,53]
Cost	¥1000 000–¥2000 000 (including the cost of arterial catheterization and port implantation)	¥600 000 per month

a Although available in Japan since May 2009,^[52] sorafenib has only been used in approximately 5000 patients (personal communication, May 2010).

HAIC = hepatic artery infusion chemotherapy; **HCC** = hepatocellular carcinoma.

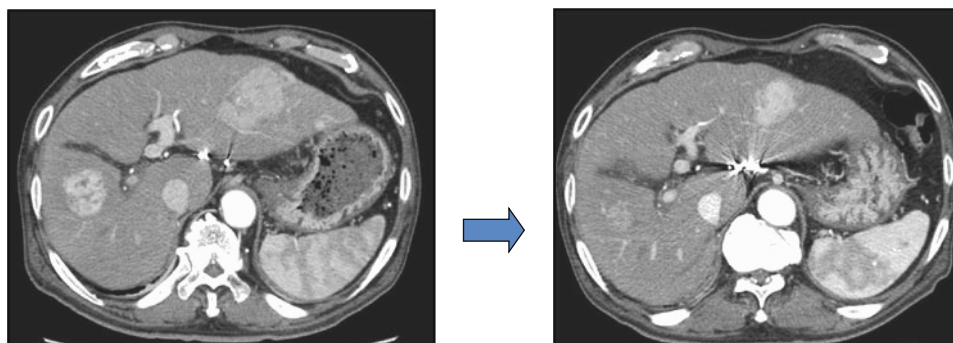


Fig. 2. Computed tomography images (a) after sorafenib therapy but before hepatic artery infusion chemotherapy (HAIC) and (b) after sorafenib treatment followed sequentially by HAIC comprising 5-fluorouracil, cisplatin and interferon in a 70-year-old man with type C liver cirrhosis diagnosed with hepatocellular carcinoma.

continuously on days 1–5 and 8–12) in 190 patients with advanced HCC aged over 20 years. Treatment will be continued until radiographic or symptomatic progression, or the development of unacceptable toxicity. The primary outcome measure is overall survival, but time to disease progression, progression-free survival, change in tumour markers and biomarkers predicting efficacy will also be evaluated. This trial started in October 2010; as of February 2012, recruitment was ongoing and completion of the study and primary outcome measure data collection was planned for September 2013.

The safety of sorafenib and cisplatin HAIC has recently been investigated in a phase I, non-randomized, dose-finding clinical trial in patients with advanced HCC (UMIN clinical trials registry identifier, UMIN00001496). Twenty-one patients aged between 20 and 79 years received sorafenib 400 mg twice a day combined with six courses of cisplatin administered every 4–6 weeks. Results from that study are anticipated as the date of first enrolment was December 2008, and as of January 2012 study recruitment had ceased.

11. Conclusion

Traditionally, HAIC has been used in Japan to treat HCC with vascular invasion and/or multiple intrahepatic lesions. Although HAIC has been associated with high response rates in some studies, the outcome of therapy has not been consistent. Furthermore, there is little evidence of a survival

benefit with HAIC. Sorafenib, a molecular targeted drug, has been established as the new standard of care in patients with HCC, based on the results of two randomized, controlled clinical trials. As such, the position of HAIC for the treatment of advanced HCC is under discussion. If HAIC is to be considered a recognized treatment for HCC, clinical studies that establish its efficacy in comparison with other therapies for HCC as well as the optimal treatment protocol and regimen must be undertaken. In the absence of such data, HAIC may fall out of use. It has recently emerged that HAIC may be useful when combined (either sequentially or concurrently) with sorafenib. The combination of HAIC with molecular targeted therapy is currently being investigated in a number of clinical trials, the results of which are awaited with interest.

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