Toxicity and efficacy of hepatic arterial infusion chemotherapy for advanced hepatocellular carcinoma (Review)

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Abstract. The prognosis of advanced hepatocellular carcinoma (HCC) remains poor, particularly for patients with portal vein tumor thrombosis. Chemotherapy is one of the most significant treatment options for patients with advanced HCC not indicated for hepatic resection, percutaneous ablation and transcatheter arterial chemoembolization. Systemic chemotherapy does not play a central role in the treatment of HCC due to the issue of low sensitivity for chemotherapeutic agents and the difficulties in administering a sufficient dose due to chronic liver dysfunction. Therefore, patients with advanced HCC are usually treated with hepatic arterial infusion chemotherapy (HAIC), which is increasingly used as an approach to advanced HCC in Japan. HAIC provides moderate therapeutic efficacy and survival benefit with substantially tolerable toxicity profiles in patients with advanced HCC.

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1. Introduction

Hepatocellular carcinoma (HCC) is the most common type of liver cancer and its incidence is on the increase in many coun-

tries (1-5). Several non-surgical treatment options, including transcatheter arterial chemoemobolization (TACE) and radio-frequency ablation (RFA) have been developed and are widely used in patients with unresectable HCC. However, these modalities are not indicated for patients with advanced HCC as they are not expected to survive for longer than six months (6,7). Chemotherapy is one of the few remaining options for patients with advanced HCC. Despite decades of efforts by many investigators, systemic chemotherapy has failed to demonstrate improved survival in patients with advanced HCC (8-14). HCC is resistant to chemotherapy and therefore no significant tumor regression effects can be expected. In addition, tolerability towards chemotherapy is low due to the decreased liver function as shown by the Child-Pugh class or CLIP score (15). Moreover, when HCC is accompanied by hepatic cirrhosis, pancytopenia has already occurred, thus making highly myelosuppressive chemotherapy more difficult to perform. However, one characteristic of HCC is that it does not easily metastasize to areas outside the liver; although metastasis occurs outside the liver, in most cases, intrahepatic lesions control the prognosis.

In hepatic arterial infusion chemotherapy (HAIC), an increase in the anti-tumor effect against malignant tumors may be expected in the liver by injecting a highly concentrated chemotherapeutic agent directly into the liver, via the hepatic artery, in order to topically increase the concentration of the chemotherapeutic agent at the tumor site. Furthermore, since the agent first passes through the liver, which is the organ involved in metabolizing the chemotherapeutic agent, a reduction of whole-body side effects is to be expected. Consequently, in Japan, HAIC is generally performed for advanced HCC, as well as TACE. Excision, RFA (16) and TACE are well established as therapies, and their efficacies have already been proven. However, since the therapeutic efficacy of HAIC is lower than that of the aforementioned therapies, it is generally used in cases of advanced HCC in which excision, RFA and TACE cannot be performed or in cases where no therapeutic efficacy is expected, as well as in multiple tumor cases that demonstrate resistance to TACE. In addition, with respect to liver function, since class C cases of the Child-Pugh classification demonstrate a low tolerance level, this therapy is considered to be targeted towards cases of either class A or B. For the previously described algorithm in HCC, class A or B is considered.

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When performing HAIC, the insertion of a catheter into the hepatic artery is required. There are two methods by which a catheter is inserted: the one-shot intra-arterial injection, in which a catheter is inserted for a single application of the chemotherapeutic agent every time chemotherapy is administered; and the reservoir intra-arterial injection, in which a reservoir system is embedded under the skin for continuous infusion or repetitive administration. When using a regimen in which the time required for an intra-arterial injection is short and where administration is required only at a frequency of approximately once a month (for example, epirubicin hydrochloride, cisplatin and other similar agents), the one-shot intra-arterial injection is possible. However, when a long period of time is required for each administration, or when the administration is required at a high frequency such as once or twice a week (as in the case of fluorouracil plus cisplatin, fluorouracil plus interferon or other similar therapies), the reservoir intra-arterial injection is necessary. Moreover, while hospitalization is required for each angiography to be performed for the one-shot intra-arterial injection, the patient may receive injections as an outpatient for the intra-arterial injection method using the reservoir system, with the exception of the initial embedding of the system. The methods for indwelling the reservoir system include i) the gastroduodenal artery coil method, by which the tip of a side-hole catheter is fixed and indwelled to the gastroduodenal artery via the femoral artery or the left subclavian artery; and ii) the hepatic periphery fixation method, by which the catheter is fixed to the peripheral of the hepatic artery. Reservoir indwelling procedures which enable a safe, favorable drug distribution under the use of angiography are performed.

2. Intra-arterial injection using epirubicin hydrochloride alone

Epirubicin hydrochloride (EPI) is a stereoisomer in which the 4'-hydroxy of doxorubicin hydrochloride (DXR) is reversed. It is an anthracycline chemotherapeutic agent whose cardiac toxicity is milder than that of DXR. The maximum dose for myocardial damage is 25 mg/kg, thus enabling administration of the drug at twice the volume of the DXR conversion. Therefore, EPI is used instead of DXR due to its reduced cardiac toxicity. The response rate of the intra-arterial injection using EPI alone against non-resectable HCC is reported to be 15.1% (17). Moreover, the response rate of the intra-arterial injection using EPI alone against HCC with portal vein tumor embolism is 9%, and progression-free survival (PFS) is only 1.1 months (18). Therefore, therapeutic efficacy should not be expected while using EPI alone. Its major side effects include leukopenia (34%), vomiting/anorexia (25%) and loss of hair (24%); it can severely aggravate myocardial damage, hepatobiliary disorders and gastroduodenal ulcers (3).

3. Intra-arterial injection using cisplatin alone

Cisplatin (IA-call®) is a powdered cisplatin (cis-diamminedichloroplatinum, CDDP) chemotherapeutic agent suitable for hepatic intra-arterial administration. IA-call demonstrates an anti-tumor effect (cytotoxic reaction) by binding to the DNA strands in cancer cells and inhibiting DNA synthesis and subsequently, the cancer cell. The dose-limiting toxicity of IA-call causes neutropenia, which limits the maximum tolerated dose to 80 mg/m^2, with an optimal dose of 65 mg/m^2. Using the optimal dose, a response rate of 26.7% was obtained. In the phase II study, the optimal dose of 65 mg/m^2 was dissolved in 70 ml isotonic sodium chloride solution. This solution was administered for 20-40 min and repeated every 4-6 weeks. As a result, a response rate of 33.8% (19) and a favorable anti-tumor effect were demonstrated with a single-drug administration. Kondo *et al* also performed the treatment on 24 patients with HCC, and reported favorable results with a response rate of 20.8% and a median survival time (MST) of 7.0 months (20). In addition, IA-call is generally used as a chemotherapeutic agent in the use of the one-shot intra-arterial injection. The key side effects include leukopenia (79%) and thrombocytopenia (77%), as well as renal dysfunction (21%) and vomiting (76%). Renal dysfunction occurs mainly on the renal tubule. Therefore, reductions in the contact time between platinum and the renal tubule are attempted through large-volume infusion. When the total injected dose exceeds 300 mg/m^2, the expression of neuropathy and auditory disorders increases.

4. Chemolipiodolization

It has been reported that the tumor-clustering property of ethiodised oil (Lipiodol®) remains in HCC at a high level of concentration when it is injected into the hepatic artery (21). Currently, Lipiodol is used in combination with chemolipiodolization and TACE as a carrier of a chemotherapeutic agent in order to enhance various effects, including tumor selectivity, as well as to maintain the drug concentration. It is known that by suspending Lipiodol and EPI (22) or CDDP (23) and then injecting the suspending agent into the artery, an efficacy higher than that of a single use of EPI or CDDP alone is achieved. Moreover, 131I-Lipiodol containing radioiodine demonstrated favorable effects against hepatocellular carcinoma with a response rate of 48% and a MST of 27 months (24). Miliplatin, a lipophilic platinum complex developed as a hepatic intra-arterial injection and is suspended in Lipiodol for use, is garnering attention. In the phase II study, it demonstrated a high anti-tumor effect, with a response rate of 56%. In the randomized phase II study, miliplatin was compared with Smancs®; its effectiveness was equal to that of Smancs, but the incidence of adverse events, including angiopathy and hepatobiliary disorders, was minimal (25). Thus, miliplatin may be a highly prospective agent for TACE.

5. Fluorouracil plus low-dose cisplatin therapy (low-dose FP)

This therapy is an intra-arterial injection regimen in which a small amount of CDDP (10 mg/body/day or 10 mg/m^2/day, days 1 to 5) is administered as a modulator in combination with the continuous infusion of fluorouracil (5-FU; 250 mg/m^2/day, days 1 to 5). The regimen, which is also called low-dose FP (fluorouracil and platinum) therapy, is commonly used in Japan. 5-FU inhibits DNA synthesis through the inhibitory action of the intracellular metabolite FdUMP against thymidylate synthase (TS) and interferes with the ribonucleic acid (RNA) metabolism by blocking the uptake of phosphated 5-fluorouridine 5'-triphosphate into RNA (26), while CDDP

Table I. Comparison between efficacy of each regimen.

	CDDP (IA-call)	Low-dose FP	FAIT
RR (%)	21-34[a]	39-71	44-63
MST (M)	7-30[a]	6.2-15.9	7-11.8

RR, response rate; MST, median survival time; CDDP, cis-diammin-edichloro-platinum; FP, fluorouracil and platinum (cisplatin); FAIT, fluorouracil arterial infusion and interferon therapy. [a]Includes data on lipiodolized CDDP.

Table II. Comparison between toxicity of each regimen.

	CDDP (IA-call)	Low-dose FP	FAIT
Leukopenia	+++	++	+++
Thrombocytopenia	+++	++	+++
Vomiting/nausea	+++	++	+
Fever	++	+	+++
Stomatitis	+	++	++
Diarrhea	+	++	++
Liver dysfunction	++	+	++
Renal dysfunction	+++	+	+

+++, high frequency; ++, moderate frequency; +, low frequency; CDDP, cis-diamminedichloro-platinum; FP, fluorouracil and platinum (cisplatin); FAIT, fluorouracil arterial infusion and interferon therapy.

acts on the tumor cell membrane and prevents transfection of methionine into the cells. This process reduces the intracellular methionine pool, whereby it induces methionine synthase activity within the cells, thereby facilitating folate metabolism, which combines with the methionine synthase, thus increasing 5,10-methylene tetrahydrofolate (5,10-CH2FH4) and enhancing the effects of 5-FU. Ando et al performed this intra-arterial injection on 48 patients with HCC accompanied by portal vein tumor thrombosis (27). As a result, favorable therapeutic results (response rate, 48%; MST, 10.2 months) were reported. Moreover, Okuda et al performed the same regimen on 31 patients with post-resection recurrent HCC and reported extremely favorable remote results, with a response rate of 71% and a 5-year survival rate of 45.7% (28). Tanioka et al also performed low-dose FP on 38 patients with HCC with no adaptive response to topical therapies, and reported favorable results with a response rate of 47.4% and a MST of 187 days (29). Ueshima et al performed low-dose FP on 52 patients with HCC with no adaptive response to topical therapies, and reported favorable results with a response rate of 39% and a MST of 15.9 months (30). On the basis of these results, low-dose FP therapy has become one of the most prospective HAIC regimens against advanced HCC. The major side effects of 5-FU include leukopenia (8%), thrombocytopenia (2%), nausea/vomiting (9%), loss of hair (2%), diarrhea (20%) and stomatitis (6%) (30). When used with cisplatin, although the incidence of leukopenia and nausea/vomiting increased to 13% and approximately 35%, respectively, the tolerance level remained unchanged (27).

6. 5-FU plus IFN therapy (FAIT)

Fluorouracil arterial infusion and interferon therapy (FAIT) is another intra-arterial injection regimen. One cycle of treatment continues for 4 weeks, with interferon (IFN)-α (5 MU) being administered intramuscularly on days 1, 3 and 5 of each week, resulting in a total dose of 60 MU in a cycle. 5-FU (500 mg/day) is administered into the hepatic artery for over 5 h using a portable infusion pump on days 1-5 of the first and second weeks through the intra-arterial catheter. This regimen is also commonly performed in Japan, as well as low-dose FP.

It has been reported that the anti-tumor effect of IFN increases when it is administered as a biochemical modulator of 5-FU. Its mechanism of action includes direct anti-proliferative activity via IFN receptors and indirect action via its anti-angiogenic effect (31). Sakon et al administered 5-FU to 8 HCC patients with advanced portal vein tumor thrombosis (32). Subsequently, they reported an extremely favorable anti-tumor effect, with a response rate of 63%. Additionally, according to the report of a similar study on 55 cases by Ota et al, favorable therapy results with a response rate of 44% and a MST of 11.8 months were obtained (33). Another study performed on 116 HCC patients with portal vein tumor thrombosis by Obi et al showed the results to be favorable: the response rate was 52% and the 1-year survival rate was 34% (34). With regard to the above results, IFN-combined 5-FU hepatic intra-arterial injection chemotherapy is also considered a highly prospective and effective regimen. The major side effects associated with IFN (34) include leukopenia/thrombocytopenia (40-60%), chills/fever (approximately 100%), nausea/vomiting (5-50%), and a skin rash (5%). Although the side effects of cytopenia and fever occurred at a rate of almost 100%, they were not serious and the tolerance level was high. However, since the expression of IFN receptors in HCC tissues serves as an efficacy index, it is crucial to confirm the expression prior to therapy. Furthermore, certain studies have shown that FAIT should be carefully performed in the case of HCC patients with liver dysfunction (35,36).

7. Discussion and Conclusions

In Japan, HAIC has been frequently administered as a method of treatment for advanced HCC. The representative regimens are CDDP, low-dose FP and FAIT, as described above. According to these studies, a high anti-tumor effect and survival benefit are exhibited in advanced HCC treated with HAIC although the physical condition of patients with HCC is unsuitable for chemotherapy as compared to patients with other types of cancer. However, the evidence of its efficacy is not high, and HAIC has not yet been established as a standard therapy as no large-scale study has been conducted. A large-scale randomized study is necessary to obtain the required level of evidence.

Tolerability is another significant indicator in determining the standard therapy. Almost all cases of HCC that are complicated with hepatic cirrhosis demonstrate pancytopenia

derived from hypersplenism. Thus, attention should be paid to myelosuppression in the case of chemotherapy, including HAIC. According to the Common Terminology Criteria for Adverse Events (CTCAE) version 4, white blood cells, neutrophils and platelets are required at a level of at least 2000, 1000 and 50000/mm^3, respectively. In addition, mucous membrane disorders such as stomatitis, which is a major complication with 5-FU, easily cause anorexia and hypoalbuminemia in patients with hepatic cirrhosis, and ascites derived from hypoalbuminemia may cause further anorectic aggravation. Therefore, the prevention of stomatitis is essential to maintain the performance status and administer HAIC.

A first-line regimen in HAIC has not yet been established. According to the clinical studies described, the efficacy of low-dose FP and FAIT is better than that of CDDP (Table I), although complications of the reservoir may occur. On the other hand, HAIC using CDDP alone has the advantage of the embolus effect when CDDP is lipiodolized. Major adverse events should also be taken into account when the regimen is selected (Table II). Furthermore, a recent study shows that the efficacy of low-dose FP is greater than that of FAIT. The median OS times using low-dose FP and FAIT were 13.2 and 7.8 months, respectively (Ikai *et al*; ASCO-GI, 2010). Several randomized phase III studies are required to determine a first-line regimen.

To further improve the outcome with HAIC, it may be worth considering FAIT using IFN-β. A previous *in vitro* study revealed that IFN-β suppressed the proliferation of HCC more strongly than IFN-α both alone or in combination with anticancer agents (37). In addition, our study also shows that arterial infusion chemotherapy with IFN-β may be a promising treatment modality for advanced HCC (38).

Moreover, sorafenib, a multikinase inhibitor, has been shown to significantly increase overall survival (OS) in a randomized, placebo-controlled, phase III trial of patients with HCC (SHARP trial) (39). Recently, Guan *et al* reported that the systemic treatment of HCC was no longer regarded as ineffective, with the approval of sorafenib being given milestone significance (40). In addition, a meta-analysis suggests that sorafenib-based chemotherapy is superior to placebo-based chemotherapy in terms of TPP and OS without increasing the severe toxic effects (41). In the future, a combination of HAIC with sorafenib may lead to improved therapeutic effects.

We reviewed the toxicity and efficacy of HAIC treatment in patients with advanced HCC, whereby CDDP, low-dose FP and FAIT are usually administered. HAIC is a promising modality for the treatment of advanced HCC. Recent clinical studies have shown that HAIC provides moderate therapeutic efficacy with substantially tolerable toxicity profiles in patients with advanced HCC.

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