Future perspectives on the treatment of hepatocellular carcinoma with cisplatin

Toru Ishikawa

Toru Ishikawa, Department of Gastroenterology and Hepatology, Saiseikai Niigata Second Hospital, Niigata 950-1104, Japan
Author contributions: Ishikawa T solely contributed to this paper.
Correspondence to: Toru Ishikawa, MD, Department of Gastroenterology and Hepatology, Saiseikai Niigata Second Hospital, Teraji 280-7, Niigata 950-1104, Japan. toruishi@ngt.saiseikai.or.jp
Telephone: +81-25-2336161 Fax: +81-25-2338880
Received: August 4, 2009 Revised: September 9, 2009
Accepted: September 16, 2009
Published online: October 31, 2009

Abstract
Hepatocellular carcinoma (HCC) is the commonest primary liver malignancy. Its incidence is increasing worldwide. Surgery, including transplantation resection, is currently the most effective treatment for HCC. However, recurrence rates are high and long-term survival is poor. Conventional cytotoxic chemotherapy has not provided clinical benefit or prolonged survival for patients with advanced HCC. Cisplatin (CDDP) is a key drug for the standard regimens of various cancers in the respiratory, digestive and genitourinary organs. Recently, several encouraging results have been shown in using CDDP in the treatment of advanced HCC patients. This review examines current knowledge regarding the chemotherapeutic potential of CDDP.

© 2009 Baishideng. All rights reserved.

Key words: Hepatocellular carcinoma; Hepatic arterial infusion; Cisplatin

Peer reviewer: Atsushi Nakajima, MD, Professor, Gastroenterology Division, Yokohama City University Hospital, 3-9 Fukuura, Kanazawaku, Yokohama 236 Kanagawa, Japan

Ishikawa T. Future perspectives on the treatment of hepatocellular carcinoma with cisplatin. World J Hepatol 2009; 1(1): 8-16 Available from: URL: http://www.wjgnet.com/wjh/full/v1/i1/8.htm DOI: http://dx.doi.org/10.4254/wjh.v1.i1.8

INTRODUCTION
It has become possible to identify a group of patients with chronic liver disease who are at a high risk of developing hepatocellular carcinoma (HCC)\(^\text{[1]}\). In addition, advances in diagnostic imaging have allowed relatively early diagnosis of HCC. However, it is still not rare to find patients in whom HCC is diagnosed at an advanced stage of the disease. For the treatment of hepatocellular carcinoma, various treatments, including hepatectomy, transcatheter hepatic arterial embolization (TAE), transcatheter hepatic arterial chemoembolization (TACE), percutaneous ethanol injection therapy (PEIT), percutaneous microwave coagulation therapy (PMCT) and percutaneous radiofrequency ablation (PRFA), were performed either singly or in combination. Thus, local control has been attempted taking into account the localization of the tumor, location of the lesion, and the hepatic reserve. On the other hand, it is necessary to apply effective chemotherapy to patients who develop recurrence after these treatments for local control of the disease, as also those with highly advanced disease. In most previous studies, either only a small number of patients were included or there was no control group, resulting in the difficulty of reaching a consensus in the establishment of a standard treatment. A group, led by Dr Makuuchi, was formed with the purpose of issuing guidelines for the diagnosis and treatment of liver cancer by “Development of Evidence-based Guideline Diagnosis and Treatment” of Ministry of Health, Labor and Welfare. “Evidence-based Guidelines for the Diagnosis and Treatment of Hepatocellular Carcinoma, version 2005”\(^\text{[2]}\) were published in March 2005. These are the first established guidelines for the diagnosis and treatment of HCC based on the principle of evidence-based medicine. According to the guidelines, currently, and based on scientific evidence, there are no chemotherapies that can be recommended. HCC is resistant and relatively insensitive to chemotherapy, rarely showing response to treatment. Therefore, no standard regimens have been established yet.
This study is focused on cisplatin, which is now attracting much attention among anticancer drugs, used for solid cancers, as a powerful agent that can be used for the treatment of HCC by arterial infusion. Future perspectives in relation to the use of this agent are outlined, based on a review of all the studies reported to date in the literature.

OVERVIEW OF CISPLATIN

In 1965, a bacteriologist, Barnett Rosenberg, found that a platinum compound, eluted from platinum electrodes used in his experiments, had an inhibitory effect on the growth of *Escherichia coli*. Later, various platinum compounds were examined for their antitumor activity, hoping to find a drug that would inhibit the division of cancer cells, characterized by rapid proliferation. Subsequently, cisplatin (cis-diaminedichloroplatinum; CDDP) was identified as a compound with high antitumor activity.

In 1972, clinical research on CDDP was started at the US National Cancer Institute (NCI), and the usefulness of CDDP as an antineoplastic agent was first confirmed in the treatment of malignant tumors of the urinary system. Currently, CDDP is a key drug in standard regimens for the treatment of various cancers, including of the respiratory, digestive and genitourinary systems.

CDDP exerts its action through the following mechanism. After entering the target cells, CDDP binds to the cellular DNA to form a covalent complex. The drug causes reversible alkylation of guanine and adenine, and forms intra- and interstrand cross-links in the DNA, thereby inhibiting elongation of DNA by DNA polymerase (inhibition of DNA transcription and replication). In addition, the formation of intrastrand cross-links results in changes in the conformation of the cells. These changes induce apoptosis and necrosis of the cancer cells, and underlie the antitumor effect of the drug. The anticancer effect of CDDP is characterized by both concentration-dependent and time-dependent features.

CDDP is mainly excreted via the kidney. The percentage of cumulative 24-h urinary excretion relative to the dose administered has been reported to be 30%-40%. Pharmacokinetic studies have revealed that the CDDP in the plasma rapidly binds to plasma proteins practically irreversibly, to become inactivated. Free CDDP (unbound to proteins) has been found at a minimally detectable levels 2 h after the end of administration, to fall below the detection limit 2-4 h later. Free CDDP exerts antitumor activity and, at the same time, accumulates in the proximal renal tubules to cause tubular impairment. Therefore, it is important to take measures against potential acute renal damage occurring in the presence of free CDDP in the blood within 2 h of the end of administration. Prophylactic measures against renal damage include hydration and forced diuresis to decrease the urinary CDDP concentration, aimed at minimizing the period of contact between CDDP and the renal tubules. Furosemide and/or mannitol are the commonly used diuretics to induce forced diuresis. Premedication with an antiemetic, such as a 5HT3 receptor inhibitor, is necessary, because CDDP has a strong emetic action.

CDDP is also known as a modulator of 5-fluorouracil (5-FU). It is well-known that 5-FU forms a covalent ternary complex with thymidylate synthase (TS). FdUMP is converted into the active form inside the cell in the presence of tetrahydrofolate, and inhibits the catalytic function of TS, thereby inhibiting DNA synthesis, which underlies the antitumor effect of 5-FU. CDDP acts on the cell membrane and inhibits the entry of methionine into the cells, leading to a reduction of the intracellular methionine pool. It has been postulated that this results in homocysteine methylation for the synthesis of methionine inside the cells. In relation to this synthetic reaction, the tetrahydrofolate pool increases to promote the formation of the covalent ternary complex and enhances DNA synthesis inhibition by 5-FU. CDDP exerts this effect, regardless of whether it is bound or unbound to plasma proteins.

SYSTEMIC CHEMOTHERAPY

Advanced HCC patients who are candidates to chemotherapy are those who are unlikely to respond to hepatectomy; RFA and/or TACE, have well-maintained liver function (Child-Pugh A, B) and a stable general condition (PS 0-2). Such patients would include those with (1) severe vascular invasion, (2) multiple intrahepatic lesions, and (3) distant metastases. No chemotherapeutic agent has been shown to exert consistently satisfactory antitumor effect against HCC, and most potentially effective drugs have been examined in pilot studies conducted on only limited numbers of patients. Among such drugs, the response rate to CDDP, given as systemic monotherapy, has been reported to be 15%, and multidrug regimens containing this agent may be expected to yield higher response rates. Arterial infusion chemotherapy, which allows higher concentrations of the drug to be achieved inside the tumor and thereby higher antitumor effect, has been reported to yield higher antitumor efficacy than systemic administration, and the reported response rates to arterial infusion regimens containing CDDP range from 41%-61%.[4,8] High efficacy of systemic chemotherapy with CDDP for HCC has not been reported, similarly to various other anticancer drugs. According to the available results, the response rate is 9.3%-17% for the intravenous administration of CDDP alone, and 10%-20% for the combined therapy. Thus, no satisfactory survival effect has been shown for any of the various regimens[6-17] (Table 1). However, Ikeda et al.[12,13], who used three drugs (5-FU, mitoxantrone, CDDP), achieved relatively favorable results: a response rate of 27% (14/51), median survival time (MST) of 11.6 mo, and median progression-free survival of 4.0 mo. This seems to be a promising treatment regimen for patients of HCC with extrahepatic metastases.
HEPATIC ARTERIAL INFUSION CHEMOTHERAPY WITH CISPLATIN

Although systemic chemotherapy is technically simpler than hepatic arterial infusion (HAI) chemotherapy, it has the disadvantages that the proportion of the drug reaching the intrahepatic lesion is low, and that the incidence of systemic adverse reactions is higher. Patients with HCC show lower tolerance to anticancer drug therapy because of impaired liver function. Pancyclopenias may already be present due to concomitant cirrhosis, and marrow suppression is likely to occur with chemotherapy. Because of these features, hepatic arterial infusion chemotherapy is not commonly used in Europe and North America for HCC. However, in cases where the vital prognosis is determined by the intrahepatic lesion, control of the intrahepatic lesion may improve the prognosis, even if there are extrahepatic metastases. Therefore, hepatic arterial infusion chemotherapy is used for these cases in Japan. Hepatic arterial infusion chemotherapy requires certain skilled procedures, including catheterization, and is associated with a risk of vascular disorders related to catheter placement and reservoir management. On the other hand, it is a useful therapeutic modality, because it allows higher concentrations of the anticancer drug to be achieved in the target lesion. In fact, the drug is administered directly into the liver, allowing enhanced antitumor effect while being associated with a lower incidence of systemic adverse reactions. The proportion of CDDP into the hepatic tumor by first-pass kinetics was reported to be less than 5% after intravenous administration, but that of HAI administration was reported to be 48.4% (34%-55%) [18]. The response rate of CDDP monotherapy administered by HAI ranges from 14% to 42% [19-21] (Table 2). The dose-limiting toxicities (DLT) of CDDP are hematologic toxicity and nephrotoxicity, while hepatotoxicity is less significant. Therefore, it seems that a high therapeutic efficacy can be expected from selective HAI using a high concentration of CDDP.

In Japan, CDDP preparations for arterial infusion were approved in 2004. At variance with the conventional CDDP injection solutions (CDDP concentration, 0.5 mg/mL), the microfine powder CDDP preparation, whose average particle size lies between about 20 and 30 μm (IA-call®; NIPPON KAYAKU CO., LTD), is able to dispense an approximately 3-fold more concentrated CDDP solution than used in arterial infusion.

A multi-center phase-II study of patients with unresectable advanced HCC was carried out in Japan [21]. In this study, where a highly concentrated CDDP solution (1.43 mg/mL) in warmed saline was used, the drug was administered by HAI. The dose was 65 mg/m² every 4-6 wk at each course, and 80 patients were given two courses.

Among the treated patients, 87.5% had underlying cirrhosis, and 48 patients had recurrent disease (46 of...
Ishikawa T. Cisplatin administration for HCC

Table 2 Hepatic arterial infusion chemotherapy

| Author | Country and region | Publication year | Treatment schedule | n   | RR (%) | PFS (M) | MST (M) | 1yrs (%) | 2yrs (%) | 3yrs (%) | 5yrs (%) |
|--------|--------------------|-----------------|--------------------|-----|--------|---------|---------|----------|----------|----------|----------|
| Court et al[20] | USA | 2002 | CDDP 50 mg/sq (+Radiation) q4w | 67 | 37.0 | - | 10.7 | - | - | - | - |
| Yoshikawa et al[21] | Japan | 2008 | CDDP 65 mg/sq q6-8w | 80 | 33.8 | - | - | 67.5 | 50.8 | - | - |
| Carr[22] | USA | 2000 | CDDP 125-200 mg/sq q4-8w | 26 | 42.3 | - | 19.5 | - | - | - | - |
| Chung et al[23] | Korea | 2000 | CDDP 2 mg/kg q8w | 23 | 14.0 | - | 2.5 | 9 | - | - | - |
| | | | CDDP 2 mg/kg q8w | 19 | 33.0 | - | 4.4 | 27 | - | - | - |
| Patt et al[24] | USA | 1994 | CDDP 100 mg/sq, d1 | 29 | 41.0 | - | 15.0 | - | - | - | - |
| | | | DXR 30-35 mg/sq, d1 | FUDR 60 mg/sq, d1-4 | - | - | - | - | - | - |
| Toyoda et al[25] | Japan | 1995 | CDDP 5-10 mg/sq, d1-4 | 21 | 14.0 | - | 61.1 | - | - | - | - |
| Okuda et al[26] | Japan | 1999 | CDDP 10 mg/h d1-5 | 31 | 70.9 | - | - | 45.7 | 45.7 | - | - |
| Takayasu et al[27] | Japan | 2000 | CDDP 30 mg/sq, d1, 4, 5 | 30 | 42.9 | - | - | - | - | - | - |
| Tanaka et al[28] | Japan | 2000 | CDDP 7 mg/sq 1h, d1-5 | 77 | 45.5 | - | 55.8 | 27.6 | 18.3 | - | - |
| Ando et al[29] | Japan | 2002 | CDDP 50 mg/sq, d1-5 | 48 | 47.9 | - | 10.2 | - | - | - | - |
| Kaneko et al[30] | Japan | 2002 | Leucovorin 15 mg/sq, d1-4 | 34 | 45.0 | - | 24 | - | - | - | - |
| Sumie et al[31] | Japan | 2003 | Leucovorin 15 mg/sq, d1-4 | 16 | 56.3 | - | 32.4 | - | - | - | - |
| Tanioka et al[32] | Japan | 2003 | Leucovorin 15 mg/sq, d1-4 | 38 | 47.4 | - | 6.1 | - | - | - | - |
| Lin et al[33] | Taiwan | 2004 | CDDP 75 mg/sq, d1, 15 | 34 | 45.0 | - | 24 | - | - | - | - |
| Yamasaki et al[34] | Japan | 2005 | CDDP 10 mg/sq 0.5 h, d1-5 | 16 | 56.3 | - | 32.4 | - | - | - | - |
| Nagai et al[35] | Japan | 2007 | CDDP 50 mg/sq 0.5 h, d1-5 | 37 | 6.7 | (15 vs 31.8) | 7.4 vs 16.3 | - | - | - | - |
| Park et al[36] | Korea | 2007 | CDDP 60 mg/sq d2 | 41 | 22.0 | 7 | 12.0 | - | - | - | - |

SC: Subcutaneous injection; CDDP: Cisplatin; DXR: Doxorubicin; EPI: Epirubicin; 5-FU: 5-fluorouracil; ETP: Etoposide; MTX: Methotrexate; FUDR: 5-fluorodeoxyuridine; IFN: Interferon; RR: Response rate; PFS: Progression free survival; MST: Median survival time; 1yrs: 1 year survival rate.

these patients had a history of previous chemotherapy. The response rate was 33.8% (27/80) (95% CI: 23.6%-45.2%), and PR was achieved in these 27 patients with a median of 28.0 d (25-71 d). Multivariate analysis of the response rates revealed that the presence/absence of vascular invasion was a significant factor influencing the therapeutic effect, whereas no such relation was found for a history of previous chemotherapy. In regard to other anticancer drugs, response rates of 15.1%, 26.1% and 20.0% have been reported for arterial infusion monotherapy using epirubicin[33], mitoxantrone[34] and mitomycin C[35], respectively. Thus, CDDP showed higher antitumor efficacy than other anticancer drugs when administered by HAI. Multivariate analysis also showed that the prognosis was significantly poor in patients with vascular invasion, but the survival tended to be prolonged in patients who responded to the therapy. In regard to the incidence of grade 3 or more severe adverse events, anorexia occurred in 22.5% of the patients, vomiting in 6.3%, and abdominal pain in 1.3%, and all of these tended to improve within 1 wk. Grade 3 or more severe laboratory abnormalities included thrombocytopenia (25.0%), neutropenia (13.0%), leukopenia (1.3%), hypochromia (1.3%), and AST elevation (32.5%).
Abnormal values were usually found within 1 wk after the drug administration, and were almost completely back to pretreatment levels 2 wk later.

In this study, the incidence of gastrointestinal symptoms, such as anorexia and vomiting, and hematologic toxicities, such as leucopenia, thrombocytopenia and hypochromia, following arterial infusion of CDDP were similar to those observed after intravenous administration. Nephropathy was milder than after intravenous infusion of CDDP. Although liver damage occurred at a rather high frequency, it never resulted in death. The higher concentrations of the drug in the non-cancerous lesions caused by HAI were at the origin of the liver toxicity.

Concerning the multidrug regimens containing CDDP for HAI therapy, low-dose CDDP combined with 5-FU (low-dose FP) has been intensively investigated in recent years [21,24,25,27,29,32,33] (Table 2). A response rate of about 40% and a median survival time of 6-12 mo have been reported for this treatment. However, the optimal administration time of 5-FU each day, the number of treatment cycles, and the modalities of the maintenance therapy, i.e. three factors constituting standard treatment, have not been established yet. In addition, low-dose FP is characterized by a problem represented by the prolonged hospitalization due to the long duration of treatment. Park et al. [34] administered FP therapy using a three-day treatment schedule, and reported favorable results with a median survival time of 12 mo. This schedule allows the treatment administration with a short-term hospitalization, and is therefore considered as cost effective.

Combined regimens containing three or more drugs, including the anticancer drug anthracycline, have also been studied. The response rates for these regimens have been reported to be in the range of 28%-45% [22,25,28,31] (Table 2).

**EXPECTATIONS FOR CDDP USE VIA TRANSCATHETER HEPATIC ARTERIAL CHEMOEMBOLIZATION**

Transcatheter hepatic arterial chemoembolization (TACE) is a therapeutic modality that comprises a combination of hepatic arterial infusion and embolization. Some recent reports concluded that TACE impacted on the survival rate of HCC patients [16,39]. Anthracyclines are commonly used for TACE, and these agents are usually mixed with lipiodol (lipiodolization).

The antitumor effect of lipiodolization has not been validated because necrotic areas in the diagnostic images have been dealt with according to different standards among the studies. However, combined regimens containing CDDP and lipiodol have been reported to yield response rates of 15%-57%, while corresponding rates of 45%-73% have been reported for the treatment combined with embolization using gelatin sponge particles. Thus, the response rates of TACE tend to be higher than other chemotherapy [5,6,20,40-57] (Table 3). Two relevant randomized controlled studies have been reported. A study, conducted by a French group and published in 1995 [41], reported that the 1-year and 2-year survival rates following this therapy were better than those following conservative treatment, while no significant difference in the overall survival was observed. However, Lo et al. [40] reported a significantly better overall survival despite using a relatively low dose of CDDP (median 10 mg/20 mL) (Table 4). This difference may be explained by the improved catheter management and other technical advances related to the vascular route of dosing.

In Japan, arterial infusion of micropulverized CDDP directly suspended in lipiodol has been investigated since the 1980s. Fundamental studies of CDDP/Lipiodol suspensions (lipiodol platinum suspension, LPS) have confirmed the extended-release nature of CDDP [42,52-56]. It is also considered that the lipiodol suspension prevents inactivation by protein binding of the drug, allowing a higher concentration of the drug to be maintained inside the tumor. LPS can be prepared conveniently if micropulverized preparations are used. LPS is prepared by directly mixing micropulverized CDDP with lipiodol (10-20 mg/mL), followed by adequate stirring until the powder is evenly dispersed. In regard to the precautions that must be followed for administration, LPS should be infused slowly into the hepatic artery via a microcatheter, without mixing with physiological saline. Since a fine powder is infused directly, occlusion is likely to occur in the infused blood vessels, and caution related to the infusion volume is necessary whenever TACE is employed. Similarly to the usual intravenous administration, hydration is necessary as a prophylaxis against nephropathy. Adverse reactions may be tolerable when pretreatment fluid infusion is employed. Therefore, TACE with LPS is considered to improve therapeutic results in advanced HCC patients. As for the usefulness of TACE using LPS, randomized controlled studies are warranted to compare with anthracyclines.

**FUTURE PERSPECTIVES OF HEPATIC ARTERIAL INFUSION CHEMOTHERAPY**

The advent of CDDP has resulted in a certain level of therapeutic efficacy of HAI. However, the response rate is still inadequate. Further studies of the optimal dosing schedule and optimal combinations, including new drugs, are awaited.

The treatment modality for HCC is determined by the stage of cancer and the hepatic functional reserve. It is also important not to cause reduction of the hepatic reserve during treatment, because this is a critical prognostic factor. Therefore, combined use of supportive treatment with liver-protective drugs, ramified amino acids, or other agents that improve or maintain hepatic function should also be considered.

In Asian countries, it has been speculated that HCC...
mostly arises from mutations induced by hepatitis B virus and cirrhosis due to persistent infection with hepatitis C virus. Therefore, when these viruses are present, most patients will have recurrent disease within several years.

Ishikawa T. Cisplatin administration for HCC

Table 3  Transcatheter arterial chemoembolization (inc. transcatheter arterial infusion with lipiodol)

| Author            | Country | Publication year | Treatment schedule                                                                 | Root            | n   | RR (%) | MST (M) | 1yrs (%) | 2yrs (%) | 3yrs (%) |
|-------------------|---------|-----------------|-------------------------------------------------------------------------------------|-----------------|-----|--------|--------|--------|---------|---------|
| Ikeda et al[44]   | Japan   | 1992            | DXR/Lip 10.5 mg/Lipiodol + GS 3.7 mL                                                          | Lip-TAI       | 76  | 23.7   | 68.0   | 41.0   | 24.0   |        |
| Yodono et al[45]  | Japan   | 1992            | CDDP 20 mg/Lipiodol + GS 30-40 mg/Lipiodol + GS 135.7 mg/Lipiodol + GS 5-FU 250 mg/Lipiodol + GS 25 1.3 56. | Lip-TAI       | 14  | 46.2   | 27.6   | 50.0   | 43.0   | 34.0   |
| Hatanaka et al[42] | Japan   | 1995            | CDDP 50-100 mg/Lipiodol 20 mg + CDDP 50 mg/Lipiodol 4.0 29.6 73.0 13 | Lip-TACE | 31  48.4 | 21.7   | 77.0   | 42.0   |        |
| Raoul et al[46]   | France  | 1997            | CDDP 70 mg/Lipiodol 50 mg + DXR 20-40 mg/Lipiodol + GS 4.0 20-50 mg/Lipiodol + GS 5.0 57.2  7. | Lip-TACE | 60  -     | -     | 80.4   | 65.2   | 48.6   |        |
| Uyama et al[49]   | Japan   | 1999            | CDDP 50 mg/Lipiodol 150-200 mg/Lipiodol 4.0 20-30 mg/Lipiodol + GS 4.5 39.3 1.3 45.0 | Lip-TACE | 46  38.0 | -     | -     | 31.0   | 6.0    |        |
| Maeda et al[49]   | Japan   | 2003            | CDDP 70.5 mg/Lipiodol 50 mg/Lipiodol 4.0 20-50 mg/Lipiodol + GS 30-150 mg/Lipiodol + GS 4.0 24.1  4. | Lip-TAI | 26  4.0    | 17.0  | 67.0   | 18.0   | 0.0    |        |
| Ikeda et al[44]   | Japan   | 2009-2004       | CDDP 50 mg/Lipiodol 20-150 mg/Lipiodol 4.0 20-50 mg/Lipiodol + GS 32.0 5.0  3.6 45.0 | Lip-TAI | 143  57.3 | -     | 89.2   | 65.3   | 48.8   | 29.6   |
| Uyama et al[49]   | Japan   | 2008            | CDDP 70 mg/Lipiodol 30-200 mg/Lipiodol 4.0 20-50 mg/Lipiodol + GS 37.0 5.0  5.0 45.0 | Lip-TAI | 24  45.8 | -     | -     | -     | -     |        |
| Yamashita et al[48] | Japan   | 2009            | CDDP 35 mg/Lipiodol 20-100 mg/Lipiodol 4.0 20-50 mg/Lipiodol + GS 35.7 5.0  5.0 45.0 | Lip-TAI | 35  57.1 | -     | -     | -     | -     |        |

CDDP: Cisplatin; DXR: Doxorubicin; EPI: Epirubicin; ETP: Etoposide; 5-FU: 5-fluorouracil; FUDR: Floxuridine; MMC: Mitomycin C; GS: Gelatin sponge; Lip: Lipiodol; TAI: Traschteter arterial infusion; TACE: Traschteter arterial chemoembolization; RR: Response rate; MST: Median survival time; 1yrs: 1 year survival rate. 

Table 4  Randomized control trial (TACE)

| Author                              | Country and region     | Publication year | Treatment schedule                                                                 | Root                 | n   | RR (%) | 1yrs (%) | 2yrs (%) | 3yrs (%) |
|-------------------------------------|------------------------|-----------------|-------------------------------------------------------------------------------------|----------------------|-----|--------|----------|----------|----------|
| Group d'Etude et de Traitement      | France                 | 1995            | CDDP/Lipiodol 70 mg/Lipiodol 50 mg + GS 135.7 mg/Lipiodol + GS 3.7 mL + GS            | TACE                 | 50  | 16.3   | 62.0   | 37.8     |          |
| du Carcime Hepatocellulaire        |                        |                 | Conservative management CDDP/saline + Lipiodol 1:1 (median: 10 mg/20 mL/bd max: 30 mg/60 mL/bd) + GS conservative management | TACE                 | 46  | 5.0    | 43.5   | 26.0     |          |
| Lo et al[51]                       | Hong Kong              | 2002            | CDDP/Lipiodol 50 mg/Lipiodol 150-200 mg/Lipiodol + GS 30-150 mg/Lipiodol + GS 70 mg/Lipiodol + GS 50 mg/Lipiodol 10-50 mg/Lipiodol + GS 35 mg/Lipiodol 10-20 mg/Lipiodol + GS | TACE                 | 40  | 39.0   | 57.0   | 31.0     | 26.0     |

CDDP: Cisplatin; GS: Gelatin sponge; Lip: Lipiodol; TAI: Traschteter arterial infusion; TACE: Traschteter arterial chemoembolization; RR: Response rate; MST: Median survival time; 1yrs: 1 year survival rate.
years, even if the disease is detected at an early stage and treated by resection or radical local treatment (e.g. RFA). In cases of early recurrence, i.e. within 2 years from radical treatment, it is highly likely that minute cancer cells were already present at the time of the previous treatment, leading to intrahepatic metastases or multinodular disease [15]. Therefore, to prevent early recurrence after hepatectomy or radical local treatment, we can anticipate a role of hepatic arterial infusion chemotherapy as adjuvant therapy. In addition, control of the hepatitis viral infection and prevention of carcinogenesis by interferon therapy are considered important factors to prevent recurrence occurring more than two years after the radical treatment [16].

Currently, the efficacy of anti-cancer drugs, as evaluated by the sensitivity of individual cancers, is being evaluated. Subsequently, tailor-made treatments for HCC will rapidly become available.

REFERENCES

1 Ishikawa T, Ichida T, Yamagazi S, Sugahara S, Uehara K, Okoshi S, Asakura H. High viral loads, serum alanine aminotransferase and gender are predictive factors for the development of hepatocellular carcinoma from viral compensated liver cirrhosis. J Gastroenterol Hepatol 2001; 16: 1274-1281
2 Makuuchi M, Kokudo N. Clinical practice guidelines for hepatocellular carcinoma: the first evidence based guidelines from Japan. World J Gastroenterol 2006; 12: 828-829
3 Go RS, Adjei AA. Review of the comparative pharmacology and clinical activity of cisplatin and carboplatin. J Clin Oncol 1999; 17: 409-422
4 Okada S, Okazaki N, Nose H, Shimada Y, Yoshimori M, Aoki K. A phase 2 study of cisplatin in patients with hepatocellular carcinoma. Oncology 1993; 50: 22-26
5 Ikeda M, Maeda S, Shibata J, Muta R, Ashihara H, Tanaka M, Fujiyama S, Tomita K. Transcatheter arterial chemotherapy with and without embolization in patients with hepatocellular carcinoma. Oncology 2004; 66: 24-31
6 Ikeda M, Maeda S, Ashihara H, Nagahama H, Tanaka M, Sasaki Y. Transcatheter arterial infusion chemotherapy with cisplatin, doxorubicin, and cytosine arabinoside in patients with hepatocellular carcinoma. J Gastroenterol 2009; Epub ahead of print [PMID: 19655801]
7 Falkson G, Ryan LM, Johnson LA, Simson IW, Coetzter BJ, Carbone PP, Creech RH, Schutt AJ. A random phase II study of mitoxantrone and cisplatin in patients with hepatocellular carcinoma. An ECOG study. Cancer 1987; 60: 2141-2145
8 Nagahama H, Okada S, Okusaka T, Ishii H, Ikeda M, Nakasuka H, Yoshimori M. Predictive factors for tumor response to systemic chemotherapy in patients with hepatocellular carcinoma. Jpn J Clin Oncol 1997; 27: 321-327
9 Ji SK, Park NH, Choi HM, Kim YW, Lee SH, Lee KH, Ahn SY, Lee SU, Han BH, Park BC. Combined cis-platinum and interferon therapy of advanced hepatocellular carcinoma. Korean J Intern Med 1996; 11: 58-68
10 Leung TW, Tang AM, Zee B, Yu SC, Lai PB, Lau WY, Johnson PJ. Factors predicting response and survival in 149 patients with unresectable hepatocellular carcinoma treated by combination cisplatin, interferon-alpha, doxorubicin and 5-fluorouracil chemotherapy. Cancer 2002; 94: 421-427
11 Yang TS, Chang HK, Chen JS, Lin YC, Liau CT, Chang WC. Chemotherapy using 5-fluorouracil, mitoxantrone, and cisplatin for patients with advanced hepatocellular carcinoma: an analysis of 63 cases. J Gastroenterol 2004; 39: 362-369
12 Ikeda M, Okusaka T, Ueno H, Takezako Y, Morizane C. A phase II trial of continuous infusion of 5-fluorouracil, mitoxantrone, and cisplatin for metastatic hepatocellular carcinoma. Cancer 2005; 103: 756-762
13 Ikeda M, Okusaka T, Ueno H, Morizane C, Kojima Y, Iwasa S, Hagihara A. Predictive factors of outcome and tumor response to systemic chemotherapy in patients with metastatic hepatocellular carcinoma. Jpn J Clin Oncol 2008; 38: 675-682
14 Parikh PM, Fuloria J, Babu G, Doval DC, Awasthy BS, Pai VR, Prabhakaran PS, Benson AB. A phase II study of gemcitabine and cisplatin in patients with advanced hepatocellular carcinoma. Trop Gastroenterol 2005; 26: 115-118
15 Yeow W, Mok TS, Zee B, Leung TW, Lai PB, Lai WW, Koh J, Mo FK, Yu SC, Chan AT, Hui P, Ma B, Lam KC, Ho WM, Wong HT, Tang A, Johnson PJ. A randomized phase III study of doxorubicin versus cisplatin/interferon-alpha2b/doxorubicin/fluorouracil (PIAF) combination chemotherapy for unresectable hepatocellular carcinoma. J Natl Cancer Inst 2005; 97: 1532-1538
16 Kim SJ, Seo HY, Choi JG, Sul HR, Sung HJ, Park KH, Choi IK, Oh SC, Yoon SY, Seo JH, Choi CW, Kim BS, Shin SW, Kim YH, Kim JS. Phase II study with a combination of epirubicin, cisplatin, UFT, and leucovorin in advanced hepatocellular carcinoma. Cancer Chemother Pharmacol 2006; 57: 436-442
17 Park SH, Lee Y, Han SH, Kwon SY, Kwon OS, Kim SS, Kim JH, Park YH, Lee JN, Bang SM, Cho EK, Shin DB, Lee JH. Systemic chemotherapy with doxorubicin, cisplatin and capecitabine for metastatic hepatocellular carcinoma. BMC Cancer 2006; 6: 3
18 Court WS, Order SE, Siegel JA, Johnson E, DeNittis AS, Principato R, Mertz K, Zeiger LS. Remission and survival following monthly intraarterial cisplatinum in nonresectable hepatoma. Cancer Invest 2002; 20: 613-625
19 Yoshikawa M, Ono N, Yodono H, Ichida T, Nakamura H. Phase II study of hepatic arterial infusion of a fine-powder formulation of cisplatin for advanced hepatocellular carcinoma. Hepatol Res 2008; 38: 474-483
20 Carr BI. Hepatic artery chemoembolization for advanced stage HCC: experience of 650 patients. Hepatogastroenterology 2002; 49: 79-86
21 Chung YH, Song IH, Song BC, Lee GC, Koh MS, Yoon HK, Lee YS, Sung KB, Suh DJ. Combined therapy consisting of intraarterial cisplatin infusion in hepatocellular carcinoma patients with major portal vein thrombosis or distant metastasis. Cancer 2000; 88: 1986-1991
22 Patt YZ, Charnsangavej C, Yoffe B, Smith R, Lawrence D, Chuang V, Carrasco H, Roh M, Chase J, Fischer H. Hepatic arterial infusion of fluorouridine, leucovorin, doxorubicin, and cisplatin for hepatocellular carcinoma: effects of hepatitis B and C viral infection on drug toxicity and patient survival. J Clin Oncol 1994; 12: 1204-1211
23 Toyoda H, Nakano S, Kumada T, Takeda I, Sugiyama K, Osada T, Kiriyama S, Suga T, Takahashi M. The efficacy of continuous local arterial infusion of 5-fluorouracil and cisplatin through an implanted reservoir for severe advanced hepatocellular carcinoma. Oncology 1995; 52: 295-299
24 Okuda K, Tanaka M, Shibata J, Ando E, Ogata T, Kinoshita H, Eriuchi N, Aoyagi S, Tanikawa S. Hepatic arterial infusion chemotherapy with continuous low dose administration of cisplatin and 5-fluorouracil for multiple recurrence of hepatocellular carcinoma after surgical treatment. Oncol Rep 1999; 6: 587-591
25 Takayasu Y, Yamamoto S, Ikeda J. [Hepatic arterial infusion chemotherapy using totally implantable port system] Gan To Kagaku Ryoho 2000; 27: 1516-1520
26 Tanaka M, Ando E, Yutani S, Fukumori K, Kuromatsu R,
Shimauchi Y, Nagamatsu H, Matsuaki S, Itano S, Ono N, Sakisaka S, Sata M. Phase II trial of hepatic arterial infusion chemotherapy using cisplatin and 5-fluorouracil in patients with advanced hepatocellular carcinoma. Progress in hepatocellular carcinoma treatment, 2000: 49-55

Ando E, Tanaka M, Yamashita F, Kuromatsu R, Yutani S, Fukumori K, Sumie S, Yano Y, Okuda K, Sata M. Hepatic arterial infusion chemotherapy for advanced hepatocellular carcinoma with portal vein tumor thrombosis: analysis of 48 cases. Cancer 2002; 95: 588-595

Kaneko S, Urabe T, Kobayashi K. Combination chemotherapy for advanced hepatocellular carcinoma complicated by major portal vein thrombosis. Oncology 2002; 62 Suppl 1: 69-73

Sumie S, Yamashita F, Ando E, Tanaka M, Yano Y, Fukumori K, Sata M. Interventional radiology for advanced hepatocellular carcinoma: comparison of hepatic artery infusion chemotherapy and transcatheter arterial lipidol chemoembolization. AJR Am J Roentgenol 2003; 181: 1327-1334

Tanioka H, Tsuji A, Morita S, Horimi T, Takamatsu M, Shirasaka T, Mizushima O, Ochi K, Kiura K, Tanimoto M. Combination chemotherapy with continuous 5-fluorouracil and low-dose cisplatin infusion for advanced hepatocellular carcinoma. Anticancer Res 2003; 23: 1891-1897

Lin CP, Yu HC, Cheng JS, Lai KH, Lo GH, Hsu PI, Lin CK, Chen HH, Lo CC, Liang HL, Tseng HH. Clinical effects of intra-arterial infusion chemotherapy with cisplatin, mitomycin C, leucovorin and 5-fluorouracil for unresectable advanced hepatocellular carcinoma. J Clin Med Assoc 2004; 67: 602-610

Yamasaki T, Kimura T, Kurokawa F, Aoyama K, Ishikawa T, Tajima K, Yokoyama Y, Takami T, Omori K, Kawaguchi K, Tsuchiya M, Terai S, Sakaia I, Okita K. Prognostic factors in patients with advanced hepatocellular carcinoma receiving hepatic arterial infusion chemotherapy. J Gastroenterol 2005; 40: 70-78

Nagai H, Kanayama M, Higami K, Momiyama K, Ikoma A, Okano N, Matsumaru K, Watanabe M, Ishii K, Sumino Y, Miki K. Twenty-four hour intra-arterial infusion of 5-fluorouracil, cisplatin, and leucovorin is more effective than 6-hour infusion for advanced hepatocellular carcinoma. World J Gastroenterol 2007; 13: 280-284

Park JY, Ahn SH, Yoon YJ, Kim JK, Lee HW, Lee do Y, Chon CY, Moon YM, Han KH. Repetitive short-course hepatic arterial infusion chemotherapy with high-dose 5-fluorouracil and cisplatin in patients with advanced hepatocellular carcinoma. Cancer 2007; 110: 129-137

Nagase N, Yukaya H, Okamura J, Kuroda C, Kubo Y, Hirai K, Tanikawa K, Okita K, Ando K, Tamura K. [Intra-arterial administration of epirubicin in the treatment of non-resectable hepatocellular carcinoma]. Epirubicin Study Group for Hepatocellular Carcinoma. Gan To Kagaku Ryoho 1986; 13: 2786-2792

Shepherd FA, Evans WK, Blackstein ME, Fine S, Heathcote J, Langer B, Taylor B, Habal F, Kutas G, Pritchard KI. Hepatic arterial infusion of mitoxantrone in the treatment of primary hepatocellular carcinoma. J Clin Oncol 1987; 5: 635-640

Makela J, Tikkakoski T, Leinonen A, Siniluoto T, Karttunen A, Tikkakoski T, Leinonen A, Siniluoto T, Karttunen A, Kairauloma MI. Superselective intra-arterial chemotherapy with mitomycin C in hepatic neoplasms. Eur J Surg Oncol 1993; 19: 348-354

Ilovet JM, Real MI, Montano X, Planas R, Coll S, Aponte J, Ayuso C, Sala M, Muchart J, Sola R, Rodes J, Bruix J. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. Lancet 2002; 359: 1734-1739

Lo CM, Ngan H, Tso WK, Lui CL, Lam CM, Poon RT, Fan ST, Wong J. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. Hepatology 2002; 35: 1164-1171

Ikeda K, Inoue H, Yano T, Kobayashi H, Nakajo M. Comparison of the anticancer effect of ADMO5 alone and ADMO5 with CDDP in the treatment of hepatocellular carcinoma by intra-arterial injection. Cancer Chemother Pharmacol 1992; 31: Suppl: S565-S568

Yodono H, Sasaki T, Tarusawa K, Midoriwaka H, Saito Y, Takekawa SD. Arterial infusion chemotherapy for advanced hepatocellular carcinoma using EFP and EAP therapies. Cancer Chemother Pharmacol 1992; 31 Suppl: S589-S592

Hatana Ka, Yamashita Y, Takahashi M, Koga Y, Saito R, Nakashima K, Urata J, Miyao M. Unresectable hepatocellular carcinoma: analysis of prognostic factors in transcatheter management. Radiology 1995; 195: 747-752

Raoul JL, Guyader D, Breugnot JF, Heautot JF, Duvaufier R, Bourguet P, Bekhechi D, Deugnier YM, Gosselin M. Prospective randomized trial of chemoembolization versus intra-arterial injection of 131I-labeled-iodized oil in the treatment of hepatocellular carcinoma. Hepatology 1997; 26: 1156-1161

Shibata J, Fujiyama S, Sato T, Kishimoto S, Fukushima S, Nakano M. Hepatic arterial injection chemotherapy with cisplatin suspended in an oily lymphographic agent for hepatocellular carcinoma. Cancer 1989; 64: 1586-1594

Kawakami A, Yoshiohi H, Ohkusa Okafuji T, Ono Y, Shindon K, Arita S, Ishida O, Yamazoe Y, Matsuoka H, Ishida S. Effects of intrahepatic arterial injection of cisplatin suspended lipiodol on hepatocellular carcinoma J Jpn Soc Cancer Ther 1993; 28: 794-803

Ono Y, Yoshimasu T, Ashikaga R, Inoue M, Shindou H, Fuji K, Araki Y, Nishimura Y. Long-term results of lipiodol-transcatheter arterial embolisation with cisplatin or doxorubicin for unresectable hepatocellular carcinoma. Ant J Clin Oncol 2000; 23: 564-568

Kamada K, Nakanishi T, Kitamoto M, Aikata H, Kawakami Y, Ito K, Asahara T, Kajiyama G. Long-term prognosis of patients undergoing transcatheter arterial chemoembolization for unresectable hepatocellular carcinoma: comparison of cisplatin lipiodol suspension and doxorubicin hydrochloride emulsion. J Vasc Interv Radiol 2001; 12: 847-854

Maeda S, Shitaba J, Fujiyama S, Tanaka M, Nomura S, Sato K, Tomita K. Long-term follow-up of hepatic arterial chemoembolization with cisplatin suspended in iodized oil for hepatocellular carcinoma. Hepatogastroenterology 2003; 50: 809-813

Uyama N, Hatano E, Maetani Y, Isoda H, Shibata T, Taura K, Oe S, Naito M, Yasukihia K, Fujii H, Ikai I, Uemoto S. [Efficacy and toxicity of transcatheter arterial chemoembolization with cisplatin suspended in lipiodol for unresectable hepatocellular carcinoma] Gan To Kagaku Ryoho 2008; 35: 775-780

Yamashita YI, Taketomi A, Itoh S, Harimoto N, Morita K, Fukuhara T, Ueda S, Sanefuji K, Sugimachi K, Tajima T, Maehara Y. Phase I/II study of the lipiodolization using DDP-H (CDDP powder; IA-call((R))) in patients with unresectable hepatocellular carcinoma. Cancer Chemother Pharmacol 2009; Epub ahead of print [PMID: 19495755]

A comparison of lipiodol chemoembolization and conservative treatment for unresectable hepatocellular carcinoma. Groupe d’Etude et de Traitement du Carcinome Hepatocellulaire. N Engl J Med 1995; 332: 1256-1261

Fukushima S, Kishimoto S, Hayashi Y, Kaneko M, Nakano M, Shibata J, Fujiyama S, Sato T. [Intra-hepatic artery infusion chemotherapy with cisplatin suspension in lipiodol (LPS) of hepatocellular carcinoma (I)–Preparation of LPS and its anticancer effect on a rabbit liver cancer model after injection into the hepatic artery] Nippon Gan Chiryo Gakkai Shi 1988; 23: 2743-2749

Sonoda A, Nitta N, Obta S, Ichihashi M, Murata K, Ishikawa T. Cisplatin administration for HCC.
Morikawa S, Inubushi T, Miyagawa Y, Takamori M, Oonaka Y. [Plasma platinum concentration and anti-tumor effects after intra-arterial infusion of lipiodol-CDDP suspension evaluation with VX 2 rabbit liver cancer model and 7.0 Tesla MRI system] Gan To Kagaku Ryoho 2006; 33: 951-957

Morimoto K, Sakaguchi H, Tanaka T, Yamamoto K, Anai H, Hayashi T, Satake M, Kichikawa K. Transarterial chemoembolization using cisplatin powder in a rabbit model of liver cancer. Cardiovasc Intervent Radiol 2008; 31: 981-985

Sahara S, Tanihata H, Sato M, Kawai N, Takasaka I, Minamiguchi H, Nakai M, Sonomura T. Effects of hepatic artery chemoembolization using cisplatin-lipiodol suspension with gelatin sponge particles on swine liver. J Vasc Interv Radiol 2009; 20: 1359-1364

Sakon M, Umeshita K, Nagano H, Eguchi H, Kishimoto S, Miyamoto A, Ohshima S, Dono K, Nakamori S, Gotoh M, Monden M. Clinical significance of hepatic resection in hepatocellular carcinoma: analysis by disease-free survival curves. Arch Surg 2000; 135: 1456-1459

Ishikawa T. Secondary prevention of recurrence by interferon therapy after ablation therapy for hepatocellular carcinoma in chronic hepatitis C patients. World J Gastroenterol 2008; 14: 6140-6144

Ishikawa T. Cisplatin administration for HCC

Takaki Y, Kaminou T, Shabana M, Ihaya T, Otsubo K, Ogawa T. Suitable blending method of lipiodol-cisplatin in transcatheter arterial embolization for hepatocellular carcinoma: evaluation of sustained release and accumulation nature. Hepatogastroenterology 2008; 55: 202-206

S- Editor Zhang HN  L- Editor Negro F  E- Editor Ma WH