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RESEARCH FRONTIER

Future perspectives on the treatment of hepatocellular carcinoma with cisplatin

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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.

Key words: Hepatocellular carcinoma; Hepatic arterial infusion; Cisplatin

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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)[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"[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-diamminedichloroplatinum; 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[3].

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 $5HT_3$ 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%[4], 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%[5,6]. 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[4,7-17] (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.

Table 1 Systemic chemotherapy

Author	Country and region	Publication year	Treatment schedule	*n*	RR (%)	PFS (M)	MST (M)	1yrs (%)
Falkson *et al*[7]	USA	1987	CDDP 75 mg/sq q3w	35	< 17	-	3.2	-
Okada *et al*[4]	Japan	1993	CDDP 80 mg/sq q4w	26	15.4	-	-	-
Nagahama *et al*[8]	Japan	1997	CDDP	43	9.3	-	-	-
Ji *et al*[9]	Korea	1996	CDDP 60 mg/sq q4w IFN-α 3MU im for 3 mo	30	13.3	-	7.6	23.5
Leung *et al*[10]	China	2002	CDDP 20 mg/sq, d1-4 DXR 40 mg/sq, d1 5-FU 400 mg/sq, d1-4 IFN-α 5MU SC d1-4 q3w	149	16.8	-	7.1	-
Yang *et al*[11]	Taiwan	2004	CDDP 80 mg/sq d1 Mitoxantrone 6mg/sq d1 5-FU 450 mg/sq d1-5 q4w	63	23.8	2.5	4.9	-
Ikeda *et al*[12,13]	Japan	2008 (2005)	CDDP 80 mg/sq d1 Mitoxantrone 6 mg/sq d1 5-FU 450 mg/sq d1-5 q4w	82	22.0	3.2	11.2	43.5
Parikh *et al*[14]	India	2005	CDDP 70 mg/sq d1 GEM 1250 mg/sq d1, 8 q3w	30	20.0	4.1	4.8	27.0
Yeo *et al*[15]	China	2005	CDDP 20 mg/sq, d1-4 DXR 40 mg/sq, d1 5-FU 400 mg/sq, d1-4 IFN-α 5MU. SC d1-4 q3w	94	20.9	-	8.7	39.0
Kim *et al*[16]	Korea	2006	CDDP 60 mg/sq d1 EPI 50 mg/sq d1 UFT 400-600 mg/d PO 3w leucovorin 75 mg/d PO 3w q4w	53	16.9	2.7	5.7	-
Park *et al*[17]	Korea	2006	CDDP 60 mg/sq, d1 DXR 60 mg/sq, d1 Capecitabine 2 g/sq per day 2w q3w	29	24.1	3.7	7.7	-

PO: Per os; SC: Subcutaneous injection; im: Intramuscular injection; CDDP: Cisplatin; DXR: Doxorubicin; EPI: Epirubicin; 5-FU: 5-fluorouracil; UFT: Tegaful-uracil; GEM: Gemcitabine; IFN: Interferon; RR: Response rate; PFS: Progression free survival; MST: Median survival time; 1yrs: 1 year survival rate.

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. Pancytopenia 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%[18-21] (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[19]. 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/m^2 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

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*[18]	USA	2002	CDDP 50 mg/sq (+Radiation) q4w	67	37.0	-	10.7	-	-	-	-
Yoshikawa *et al*[19]	Japan	2008	CDDP 65 mg/sq q6-8w	80	33.8	-	-	67.5	50.8	-	-
Carr[20]	USA	2000	CDDP 125-200 mg/sq q4-8w	26	42.3	-	19.5	-	-	-	-
Chung *et al*[21]	Korea	2000	CDDP 2 mg/kg q8w	23	14.0	-	2.5	9	-	-	-
			CDDP 2 mg/kg q8w IFN-α 3MU. SC. 3/w	19	33.0	-	4.4	27	-	-	-
Patt *et al*[22]	USA	1994	CDDP 100 mg/sq, d1 DXR 30-35 mg/sq, d1 FUDR 60 mg/sq, d1-4 Leucovorin 15 mg/sq, d1-4	29	41.0	-	15.0	-	-	-	-
Toyoda *et al*[23]	Japan	1995	CDDP 5-10 mg/24h, d1-7 5-FU 500 mg/24h, d1-7	21	14.0	-	-	61.1	-	-	-
Okuda *et al*[24]	Japan	1999	CDDP 10 mg/1h, d1-5 5-FU 250 mg/5h, d1-5 q3-6w	31	70.9	-	-	-	-	45.7	45.7
Takayasu *et al*[25]	Japan	2000	EPI 30 mg/sq, d1, 6 CDDP 50 mg/sq, d2,7 ETP 60 mg/sq, d3, 4, 5	30	42.9	-	-	-	-	-	-
Tanaka *et al*[26]	Japan	2000	CDDP 10 mg/1h, d1-5 5-FU 250 mg/5h, d1-5 q4w	77	45.5	-	-	55.8	27.6	18.3	-
Ando *et al*[27]	Japan	2002	CDDP 7 mg/sq 1h, d1-5 5-FU 170 mg/sq 5h, d1-5 x4w	48	47.9	-	10.2	-	-	-	-
Kaneko *et al*[28]	Japan	2002	CDDP 75 mg/sq, d1, 15 5-FU 750 mg/sq, d1, 8, 15, 22 MTX 30 mg/sq, d1, 8, 15, 22 leucovorin 30 mg/sq, d1, 8, 15, 22 IFN-α-2b 3MU. SC, 3/w q4w	34	45.0	-	-	24	-	-	-
Sumie *et al*[29]	Japan	2003	CDDP 10 mg/1h, d1-5 5-FU 250 mg/5h, d1-5 x4w	16	56.3	-	32.4	-	-	-	-
Tanioka *et al*[30]	Japan	2003	CDDP 3 mg/sq 0.5 h, d1-7 5-FU 170 mg/sq continuous d1-7 x4w q5w	38	47.4	-	6.1	-	-	-	-
Lin *et al*[31]	Taiwan	2004	CDDP 10 mg/sq d1-5 MMC 2 mg/sq d1-5 leucovorin 15 mg/sq d1-5 5-FU 100 mg/sq continuous d1-5 x2w q3-4w	53	28.3	-	13.2	-	-	-	-
Yamasaki *et al*[32]	Japan	2005	CDDP 10 mg/body d1-5 5-FU 250 mg/body d1-5 leucovorin 12 mg(or isovorin 12.5 or 6.25 mg) d1-5	29	48.3	-	11.8	-	-	-	-
Nagai *et al*[33]	Japan	2007	CDDP 10 mg/h d1-5 leucovorin 12 mg/h d1-5 5-FU 250 mg/sq (4 h *vs* 22 h) x4w	37 (15 *vs* 22)	6.7 *vs* 31.8	-	7.4 *vs* 16.3	-	-	-	-
Park *et al*[34]	Korea	2007	5-FU 500 mg/sq d1-3 q4w 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: floxuridine; 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[35], mitoxantrone[36] and mitomycin C[37], 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[23,24,26,27,29,30,32,33] (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[38,39]. 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 chemotherapies[5,6,20,40-50] (Table 3). Two relevant randomized controlled studies have been reported. A study, conducted by a French group and published in 1995[51], 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*[39] 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[44,52-56]. 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

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 (%)	5yrs (%)
Ikeda *et al*[40]	Japan	1992	DXR/Lip 10.5 mg[1] MMC/Lip 7.8 mg[1] Lip 3.7 mL[1] CDDP 135.7 mg[1]	Lip-TAI	76	23.7	-	68.0	41.0	24.0	-
Yodono *et al*[41]	Japan	1992	CDDP 20 mg/sq, d1-5 ETP 30-40 mg/sq, d1-5 5-FU 250 mg/body, d1-26 + CDDP/Lip + GS	TAI +Lip-TACE	14	46.2	27.6	50.0	43.0	34.0	-
			CDDP 50 mg/sq, d2,8 ETP 50-60 mg/sq, d4-6 DXR 20 mg/sq, d1,7 + CDDP/Lip + GS	TAI +Lip-TACE	31	48.4	21.7	77.0	42.0	-	-
Hatanaka *et al*[42]	Japan	1995	CDDP 50-100 mg DXR 20-40 mg FUDR 3-5 g + GS	TACE	60	-	-	80.4	65.2	48.6	-
			CDDP 50-100 mg DXR 20-40 mg Lip 4.8 mL[1] FUDR 3-5 g + GS	Lip-TACE	78	-	-	86.3	55.3	34.8	-
			CDDP 50-100 mg DXR 20-40 mg Lip 4.9 mL[1] FUDR 3-5 g	Lip-TAI	159	-	-	65.9	50.3	36.2	-
Raoul *et al*[43]	France	1997	CDDP 70 mg (saline 140 mL)/Lip 10 mL + GS	Lip-TACE	64	57.0	-	42.2	22.1	2.8	-
Carr[20]	USA	2002	CDDP 125-200 mg/sq q4-8w + GS	TACE	31	58.1	30.7	-	-	-	-
Shibata *et al*[44]	Japan	1989	CDDP 20-150 mg (CDDP/Lip: 20 mg/mL)	Lip-TAI	71	46.5	-	55.0	-	-	-
Kawakami *et al*[45]	Japan	1993	CDDP 50 mg (CDDP/Lip: 10 mg/mL)	Lip-TAI	12	12.5	7.0	-	-	-	-
			CDDP 50 mg (CDDP/Lip: 10 mg/mL) + GS	Lip-TACE	30	45.5	25	81.3	56.8	-	-
Ono *et al*[46]	Japan	2000	CDDP 50 mg[1] (CDDP/Lip: 10 mg/mL) + GS	Lip-TACE	38	45.0	-	-	49.0	-	19.0
			DXR 43 mg[1] (20-50 mg)/Lip + GS	Lip-TACE	46	38.0	-	-	31.0	-	6.0
Kamada *et al*[47]	Japan	2001	CDDP 41 mg[1] (15-70 mg)/Lip + GS (CDDP/Lip: 10 mg/mL)	Lip-TACE or Lip-TAI	108	15.0	24.0	81.0	-	41.0	19.0
			DXR 57mg[1] (20-100 mg)/Lip + GS	Lip-TACE or Lip-TAI	26	4.0	17.0	67.0	-	18.0	0.0
Maeda *et al*[48]	Japan	2003	CDDP 70.5 mg[1]/Lip (CDDP/Lip: 20 mg/mL)	Lip-TAI	143	57.3	-	89.2	65.3	48.8	29.6
			CDDP 78.4 mg[1]/Lip + GS (CDDP/Lip: 20 mg/mL)	Lip-TACE	96	62.5	-	85.2	67.0	48.7	24.2
Ikeda *et al*[5,6]	Japan	2009 -2004	CDDP 50 mg[1] (20-150 mg)/Lip (CDDP/Lip: 20 mg/mL)	Lip-TAI	94	51.1	30.0	81.6	65.2	39.8	18.3
			CDDP 70 mg[1] (30-150 mg)/Lip + GS (CDDP/Lip: 20mg/mL)	Lip-TACE	74	73.0	37.2	87.8	-	52.2	25.0
Uyama *et al*[49]	Japan	2008	CDDP80 mg[1] /Lip (40-100mg) + GS (CDDP/Lip: 20 mg/mL)	Lip-TACE	24	45.8	-	-	-	-	-
Yamashita *et al*[50]	Japan	2009	CDDP 35 mg/sq (CDDP/Lip: 10-20 mg/mL)	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: Trasctheter arterial infusion; TACE: Trasctheter arterial chemoembolization; RR: Response rate; MST: Median survival time; 1yrs: 1 year survival rate. [1]Mean.

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 Traitment du Carcinome Hepatocellulaire[51]	France	1995	CDDP/Lip (70 mg/10 mL) + GS	Lip-TACE	50	16.3	62.0	37.8	-
			Conservative management	-	46	5.0	43.5	26.0	-
Lo *et al*[39]	Hong Kong	2002	CDDP/saline + Lip (1:1), (median: 10 mg/20 mL/body max: 30 mg/60 mL/body) + GS	Lip-TACE	40	39.0	57.0	31.0	26.0
			conservative management	-	39	6.0	32.0	11.0	3.0

CDDP: Cisplatin; GS: Gelatin sponge; Lip: Lipiodol; TACE: Trasctheter arterial chemoembolization; RR: Response rate; MST: Median survival time; 1yrs: 1 year survival rate.

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, 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[57]. 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[58].

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.

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