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Treatment of hepatocellular carcinoma with a CDDP-epirubicin-lipiodol suspension: a pilot clinico-pharmacological study

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Summary. Lipiodol injection is a useful method for detecting liver tumors, especially hepatocellular carcinoma (HCC). We therefore prepared and tested a new emulsion of lipiodol containing epirubicin and *cis*-diammine-dichloroplatinum (CDDP), drugs that are very effective against HCC. This CDDP-epirubicin-lipiodol suspension (CELS) was injected into 18 HCC patients via a celiac angiographic catheter. In 11 of these patients, CELS was followed by transcatheter arterial embolization (TAE) therapy. Clinical and pharmacological investigations were performed in all 18 patients, and the following results were obtained. CELS is pharmacologically and chemically stable, and both the results of the dissolution test and the serum levels of these two drugs indicate that slow release can be obtained. After the injection of CELS, serum levels of AFP and PIVKA-II decreased immediately, and no fatal clinical side effects were encountered. Although no statistically significant difference was observed, the survival (Kaplan-Meier method) of patients injected with CELS in the presence or absence of TAE therapy can be estimated to be much longer than that of patients receiving CDDP-lipiodol suspension injection in the presence (16 patients) or absence (6 patients) of TAE therapy. A combination of CELS injection and TAE therapy might be effective and useful for the treatment of HCC.

Introduction

Lipiodol is an oily contrast medium that is characterized by being selectively accumulated in liver vascular tumors, especially hepatocellular carcinoma (HCC) [1, 3]. As a practical clinical application of this specific behavior, lipiodol injection via a celiac angiographic catheter has been performed for the detection and treatment of HCC [4]. Several kinds of anticancer agents were used to make a suspension or emulsion with lipiodol-containing phosphatidyl choline. Theoretically, this suspension/emulsion should show slow release of the anticancer agent into the tumor tissues. In this study, we employed the most effective drugs for the treatment of HCC, i.e., *cis*-diamminedichloroplatinum (CDDP) [5] and epirubicin, a derivative of doxorubicin [2]. We performed a pharmacological and clinical pilot study of a CDDP-epirubicin-lipiodol suspension (CELS) in the treatment of unresectable HCC.

Patients and methods

Preparation of CELS. The preparation of CELS was carried out as follows. In all, 240 mg phosphatidyl choline (Asahi Kasei Co., Tokyo) was mixed with 6 ml lipiodol (Kodama Co., Tokyo) in an agate mortar. The mixture was collected in a vial and heated to obtain a transparent liquid. The transparent liquid was again mixed with 80 mg CDDP in an agate mortar (CDDP-lipiodol emulsion, CLS). In parallel, 60 mg epirubicin hydrochloride (Kyowa Hakko Kogyo Co., Ltd., Tokyo) was dissolved in 1.8 ml distilled water, after which 4.2 ml Urografin 76 was added (Nihon Schering Co., Ltd., Osaka). Immediately, the two mixtures were combined and emulsified in a cylinder, resulting in well-dispersed CELS. CELS was employed in the experiments immediately after its preparation.

Sustained-release study in vitro. A dissolution test was performed in accordance with the Japanese Pharmacopeia. That is, 1 ml CELS was placed in a saline solution (1000 ml) and stirred at 25 rpm at 37° C. The sample solution was then analyzed for CDDP and epirubicin using a high-performance liquid chromatography (HPLC) system equipped with an ultraviolet detector.

Serum levels of CDDP and epirubicin. The serum concentrations of both CDDP and epirubicin were analyzed in five patients until 24 h postinjection.

Patients. In all, 18 patients with unresectable HCC received CELS via a celiac angiographic catheter, and 11 of them subsequently underwent

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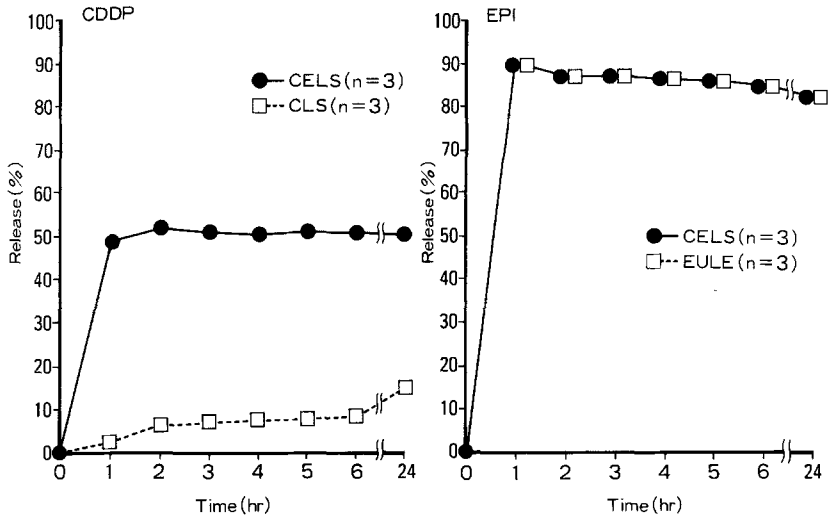

Fig. 1. Dissolution test on CDDP and epirubicin (*EPI*) in CELS. *CELS*, CDDP-epirubicin-lipiodol suspension; *CLS*, CDDP-lipiodol emulsion; *EULE*, epirubicin-Urografin-lipiodol emulsion

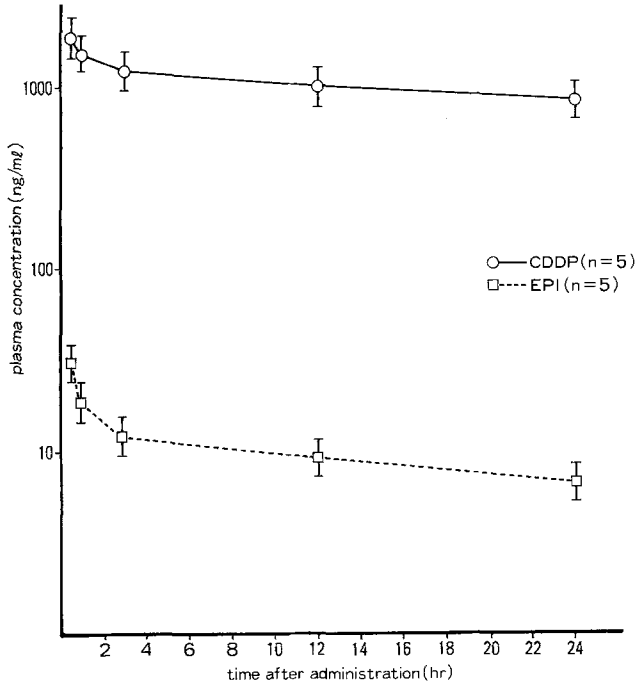

Fig. 2. Serum concentrations of CDDP and EPI after one-shot injection of CELS

transcatheter arterial embolization (TAE) therapy with Gelfoam particles. In a comparative clinicopharmacology study, we also injected CLS via a celiac angiographic catheter into 22 HCC patients, 16 of whom subsequently underwent TAE therapy. None of these patients satisfied the indications for either surgical resection or percutaneous ethanol injection therapy. The decision of whether to perform TAE therapy depended on the liver function, the tumor growth anatomy, and the grade of portal vein invasion in each case.

Survival and clinical effect. Survival was estimated by Kaplan-Meier's method. The serum level of AFP and the plasma level of PIVKA-II were measured immediately and at 2–8 weeks after injection. Computed tomography (CT) was performed prior to and at 2 weeks after administration, and celiac angiography was carried out prior to and at 1 month after administration.

Results

Dissolution test on anticancer agents

The results of dissolution of CDDP indicated that the percentage of CDDP release from CLS was less than 20% over a 24-h observation period (Fig. 1). In contrast, the percentage of CDDP release from CELS was approximately 50% over the same period. Marked differences were observed between these two suspensions. However, the result of dissolution of epirubicin showed that the percentage of epirubicin release from both CELS and EULE (epirubicin-Urografin-lipiodol emulsion) was similar, i.e., approximately 90%.

Serum levels of anticancer agent

The serum levels of CDDP and epirubicin are shown in Fig. 2. The moment calculation estimating the area under the curve (AUC) showed that approximately 54% of the CDDP and 34% of the epirubicin was retained in the organs.

Light microscopy of CELS

A histogram of CELS revealed that the mean diameter of the droplets on the glass slide was 13.697 ± 15.539 μm.

Survival

Following the administration of CELS and CLS as one-shot therapy, the 200-day survival values were 85% in the CELS group and 50% in the CLS group. Moreover, the 350-day survival values were 64% in the CELS group and 25% in the CLS group. In patients who received CELS or CLS and subsequently underwent TAE therapy, the 300-day survival was 100% for the CELS group and 75% for the CLS group, and the 600-day survival value calculated for the CLS group was 32%. However, no statistically

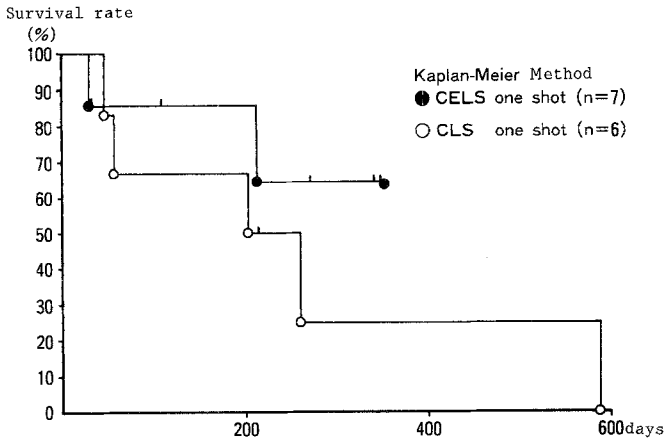

Fig. 3. Survival curves generated for patients who received a one-shot injection of CELS or CLS (Kaplan-Meier method)

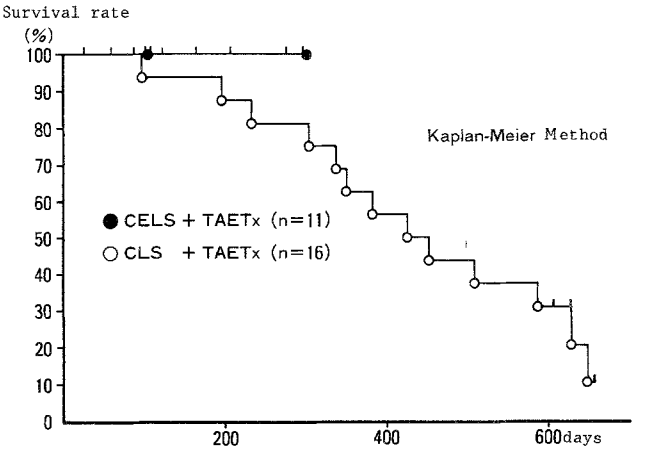

Fig. 4. Survival curves constructed for patients who received either CELS or CLS and underwent subsequent TAE therapy with Gelfoam particles (Kaplan-Meier method)

significant difference was found between the CELS group and the CLS group (Figs. 3, 4).

Change in tumor markers

The serum level of AFP and the plasma level of PIVKA-II decreased immediately after CELS or CLS injection followed by TAE therapy in five of the six patients possessing positive AFP and in all eight patients possessing positive PIVKA-II. The responses of both AFP and PIVKA-II were mild in two of the five patients with positive AFP and in two of the six patients with positive PIVKA-II in the one-shot therapy groups as compared with the combination therapy groups that also received TAE therapy.

Change in CT scans and angiograms

After CELS one-shot injection followed by TAE therapy, a marked accumulation of lipiodol in the tumor was seen. Follow-up CT scan studies revealed that in seven of 11 HCC cases, the reduction in the size of the tumor and the accumulation of lipiodol corresponded well with the decreases in tumor markers. Follow-up angiographic investigations also revealed decreased vascularity and the disappearance of tumor vessels in 8 of 11 HCC patients (Figs. 5, 6).

Side effects

Low-grade fever was observed in 6 of the 18 patients. These patients recovered immediately after they had received antiinflammatory medicine. A mild decrease in urinary volume and a slight elevation of creatinine and BUN levels were recognized in 3 of the 18 patients. No renal insufficiency and no abnormal ECG finding could be observed.

Discussion

The present study demonstrates that CELS, which was produced as a new suspension, achieved slow release of both CDDP and epirubicin and accumulated well in HCC tissues. Furthermore, the injection of CELS in the presence

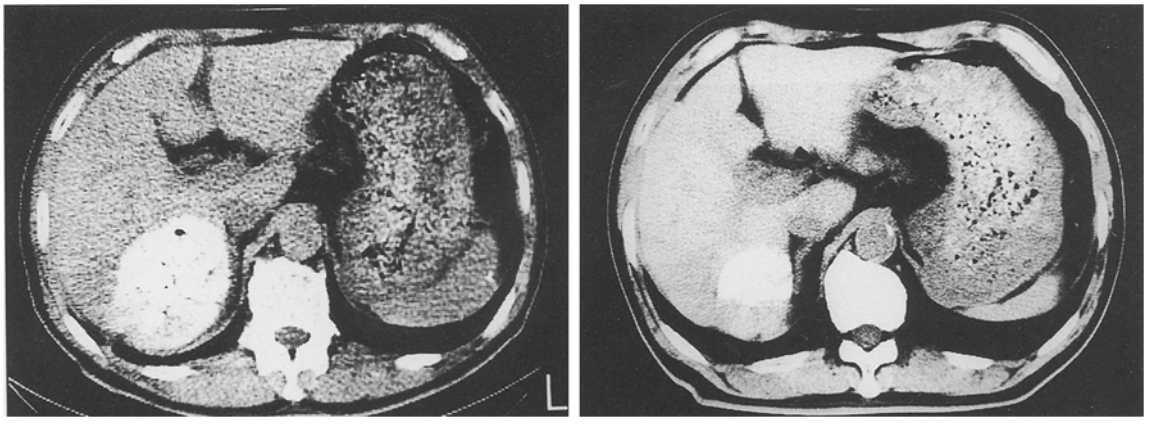

Fig. 5. *Left:* A 75-year-old man received CELS followed by TAE therapy. The CT scan shows a large tumor in the right lobe of the liver at 2 weeks after the therapy (May 22, 1988). *Right:* A subsequent CT scan shows a marked reduction in the tumor size after long-term therapy (November 8, 1990)

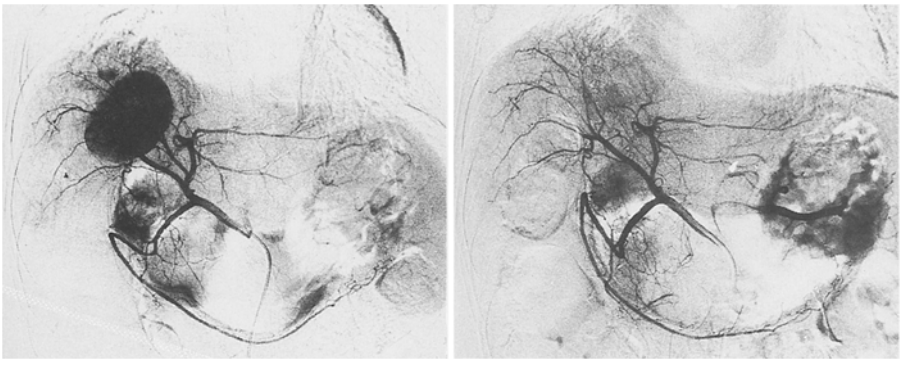

Fig. 6. *Left:* A 56-year-old man received CELS followed by TAE therapy. The angiogram shows marked tumor staining in segment 4 along with micro-intrahepatic metastasis. *Right:* A subsequent angiogram shows no tumor staining at 6 months after therapy

or absence of subsequent TAE therapy resulted in a clear increase in survival as compared with CLS injection [6].

Pharmacologically, the use of phosphatidyl choline might be a key for the preparation of a fine suspension or emulsion. Limited water content and the addition of a membrane stabilizer such as albumin should next be considered for the preparation of even finer and more stable suspensions. The putative mechanism of CELS containing fine oily droplets involves its ability to penetrate deeply into tumor capillaries and sinusoids, where it causes microembolization and slowly releases CDDP and epirubicin into the tumor tissues. As a result of the dissolution test and the drug concentrations obtained in the serum, we surmise that epirubicin release occurs first and is followed by the gradual release of CDDP into HCC tissues. In addition, the subsequent TAE therapy using Gelfoam particles introduces embolic particles that are relatively larger than lipiodol oily droplets and are capable of obstructing the relatively large blood vessels that serve as the major blood supply to the tumor.

A comparison of the CELS and CLS treatment groups revealed that the survival of patients was enhanced following therapy with CELS, which differs from CLS merely by the addition of epirubicin. For the estimation of the clinical effects of these therapies, follow-up studies using CT scans and celiac angiograms, which were opacified by subtraction angiograms, were useful. Imaging evaluation of the therapeutic effect on the bases of both CT scans and angiography revealed that the majority of patients in the CELS plus TAE group showed a reduction in the size of the tumor as judged from CT scans and a decrease in the number of tumor vessels as determined from subtracted angiograms. In addition, no fatal side effect was encountered during this pilot study.

In spite of the short period of clinical observation, our results provide evidence of the clinical usefulness of this new suspension containing two anticancer agents. Further clinical observation of the treatment of HCC with this new suspension should be performed.

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