Eur J Cancer Clin Oncol, Vol. 24, No. 7, pp. 1199–1203, 1988.
Printed in Great Britain

0277–5379/88$3.00+0.00

Intra-hepato-arterial Chemotherapy with CDDP and 5-FU for Metastases to the Liver from Colorectal and Gastric Cancers

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Abstract—*Thirty-five patients with metastases to the liver from colorectal* (26 *patients*) *and gastric* (*nine patients*) *cancers were treated with intra-hepato-arterial* (*IHA*) *injections of* cis-*diamminedichloroplatinum* (*II*) (*CDDP*) *plus* 5-*fluorouracil* (5-*FU*). *Therapeutic schedules consisted of manual bolus injections of CDDP* (25–35 mg/m^2/*week*) *and* 5-*FU* (150–180 mg/m^2/*day*) *Regimen I, and CDDP* (25–35 mg/m^2/10–14 *days*) *and* 5-*FU* (60–70 mg/m^2/*day Regimen II. In patients with colorectal cancer metastatic to the liver, partial response* (*PR*) *rates in Regimens I and II were* 38% *and* 62%, *respectively. By contrast, in patients with metastases to the liver from gastric cancer, a PR was obtained in only one of nine patients* (11%). *IHA chemotherapy with CDDP plus* 5-*FU, especially following Regimen II, appears to be a strongly recommendable strategy for treatment of metastatic liver tumors derived from colorectal cancer.*

INTRODUCTION

Cis-DIAMMINEDICHLOROPLATINUM (II) (CDDP) is one of group of platinum compounds which has demonstrated clinical activity in a broad spectrum of malignancies, which includes testicular, ovarian, bladder, and head and neck cancers [1, 2]. However, with the exception of esophageal cancer, the effectiveness of CDDP in cancers of the digestive organs has not been fully evaluated [3–7]. To evaluate the efficiency of CDDP in treatment of metastatic liver tumors, we initiated the intra-hepato-arterial (IHA) injection of CDDP plus 5-FU in January 1983. We now report the clinical effects of this combined IHA chemotherapy in patients with unresectable liver tumors which had metastasized from colorectal and gastric cancers.

PATIENTS AND METHODS

Patients

Since January 1983, we have treated 35 patients with metastatic liver tumors by IHA injections of CDDP and 5-FU. There were 26 and nine patients with metastases to the liver from colorectal cancer and from gastric cancer, respectively. Because of the widespread nature or multiplicity of the metastatic lesions in the liver, hepatectomy was indicated in none of the 35 patients. None had previously been treated with any drugs for any of their lesions.

Of patients with metastases to the liver from colorectal cancer, 23 of the 26 were males, and the 26 ranged in age from 39 to 74 years (mean: 58 years). In 18 of the patients, the liver tumors were detected synchronously with the diagnosis of their colon or rectal cancers. In the other eight patients, the liver tumors were found metachronously after the resection of the primary colon or rectal cancers.

Of patients with metastases to the liver from gastric cancer, seven of the nine were males, and the mean age of all patients was 67 years. All metastatic tumors in the liver were detected synchronously at the time of diagnosis of the gastric cancers.

Catheterization

Silicone catheters (Fr. 5.0, Dow Corning Co., Japan) were introduced into the gastroduodenal artery via an upper median laparotomy. After positioning the catheter tip in the hepatic artery, the catheter was fastened to the arterial wall of the arteriotomy and to the skin. In the 18 and nine patients with colorectal and gastric cancers, respectively, in whom the metastases to the liver were identified synchronously with diagnosis of the pri-

Accepted 25 February 1988.
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mary cancer, catheterization was performed immediately after palliative resection of the primary colorectal or gastric cancers.

Chemotherapy

Regimen I was applied from Jan. 1983 to Dec. 1984 (Table 1). However, because of severe bone marrow toxicity associated with Regimen I, as described later, Regimen I was changed to Regimen II from Jan. 1985. The agents were administered manually by bolus injection over 10-min (CDDP) and 1-min (5-FU) periods. After each injection of a drug, the catheter was filled with 4 ml of physiologic saline solution containing 500 units of heparin. When the levels of thrombocytes and/or leucocytes decreased to below $7 \times 10^4/mm^3$ or $3 \times 10^3/mm^3$, respectively, the drugs were withheld until the levels recovered. When the levels of thrombocytes and/or leucocytes decreased to below $3 \times 10^4/mm^3$ and $2 \times 10^3/mm^3$, respectively, administration of drugs was discontinued.

Definition of response

The anticancer effect was evaluated with the aid of computerized axial liver tomographs and ^{99m}TC liver scintigrams at 1 or 2 months postoperatively.

Responses were evaluated as follows: partial response (PR): 50–99% decrease in the sum of the products of the two longest dimensions of all liver lesions for at least 4 weeks; no change (NC): less than 50% decrease or less than 25% increase in these parameters; progressive disease (PD): greater than 25% increase in the parameters. In PR patients, duration of tumor reduction (weeks) were also evaluated.

Table 1. Schedule of treatment

Regimen I (Jan. 1983–Dec. 1984)
CDDP 25–35 mg/m²/week 5-FU 150–180 mg/m²/day
Regimen II (from Jan. 1985)
CDDP 25–35 mg/m²/10–14 days 5-FU 60–75 mg/m²/day
The scheduled total dose was CDDP was 130–150 mg/m². 5-FU was continued till discharge and 150–180 mg/m² every week after discharge.
The treatment was continued till severe side-effects appeared or CDDP doses reached 130–150 mg/m² as a rule.
In PR patients treatment was continued till the total doses of CDDP became 130–150 mg/m² and after discharge 150–180 mg/m² 5-FU were administered every day.
At the time of CDDP administration, an i.v. infusion, lasting for 2–3 h, of 1000 ml of physiologic saline containing 40 mg of furosemide, 200 mg of hydrocortisone and 20–40 mEq of potassium was given.

RESULTS

Table 2 shows the mean total doses and mean number of administration of each drug in Regimens I and II. In patients with colorectal cancer, CDDP would be administered high doses in Regimen II then in Regimen I. In patients with gastric cancer, the doses of each drug were almost same.

Antitumor effects

Table 3 shows the antitumor effect of IHA injections of CDDP plus 5-FU. Favorable results were obtained for patients with metastases to the liver from colorectal cancer. For patients with colorectal cancer, a PR was obtained in five of 13 patients for Regimen I and eight of 13 patients for Regimen II, respectively; overall a PR was observed in 13 of 26 evaluable patients (50%). For patients with gastric cancer, a PR was obtained in only one of nine patients (11%).

In PR patients with colorectal cancer, the mean duration of tumor reduction was 43.6+ weeks in Regimen I and 26.5+ weeks in Regimen II.

Serum levels of CEA

Serum levels of carcinoembryonic antigen (CEA) were measured by radioimmunoassay 6–7 days after each administration of CDDP. Figure 1 shows the changes of these levels in patients evaluable for the antitumor effects of the two regimens. There was a close correlation between the antitumor effects and the levels of serum CEA in patients with colorectal cancer.

Table 2. Mean total doses of each drug

Metastases to liver from	Regimen I					Regimen II				
	No. of patients	Mean total doses				No. of patients	Mean total doses			
		CDDP	(mg/m²)	5-FU	(g/m²)		CDDP	(mg/m²)	5-FU	(g/m²)
Colorectal cancer	13	107.5	(3.5)*	6.9	(41.5)	13	137.7	(4.1)	4.9	(74.0)
Gastric cancer	3	90.0	(2.7)	5.2	(31.1)	6	89.3	(2.8)	3.9	(59.0)

*Numbers in parentheses indicate the mean number of administrations of each drug.

Table 3. Antitumor effects of IHA injections of CDDP plus 5-FU

Metastases to liver from	Regimen I					Regimen II					Total No. of PR
	No. of patients	Antitumor effects*				No. of patients	Antitumor effects				
		PR	NC	PD	NE		PR	NC	PD	NE	
Colorectal cancer	13	5	1	3	4	13	8	4	1	0	13/26 (50%)
Gastric cancer	3	0	1	1	2	6	1	2	2	1	1/9 (11%)

*PR: partial response; NC: no change; PD: progressive diseases; NE: not evaluable.

Survivals

Survival curves (by Kaplan–Meier's method) for patients with metastases to the liver are shown in Fig. 2. Survivals for patients with colorectal cancer were far more favorable than those for patients with gastric cancer. Median survival months from the onset of IHA chemotherapy for patients with colorectal and gastric cancers were 8.5+ (eight patients are still alive at the time of writing) and 4.3+ (one alive), respectively. There were no differences in survivals between patients on Regimens I and II. In patients with colorectal cancer, median survival months for patients with PR, NC and PD were 16.0+ (five alive), 5.0+ (one alive) and 2.5+ (one alive), respectively.

Toxicity related to IHA chemotherapy

Renal function (a transient and slight increase in serum BUN and creatinine) was only slightly affected in this series (Table 4). Both returned to normal within several days. Mild nausea and vomiting occurred in 14 of 35 patients within 24 h of receiving CDDP; however, the course of treatment was not affected. There was no difference in frequency of these parameters between Regimens I and II.

Bone marrow suppression was the most frequently observed adverse side-effect in this series.

Severe leucocytopenia (1000/mm^3) and thrombocytopenia (30,000 mm^3) were more often found in Regimen I. Bone marrow suppression in Regimen I occurred most frequently at relative low total doses of CDDP (100 mg/m^2). Of these cases of progressive bone marrow toxicity, two patients died of sepsis (colorectal cancer and gastric cancer in one case each), one (colorectal cancer) died of massive tracheal bleeding and one (colorectal cancer) died of diffuse necrotizing enterocolitis.

Bone marrow toxicity was remarkably alleviated in Regimen II and progressive pancytopenia was not found and no patients died of bone marrow suppression.

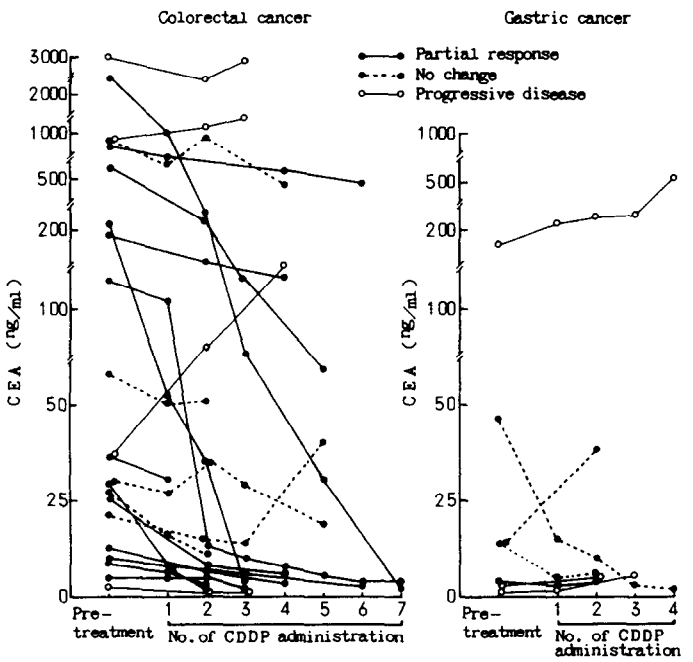

Fig. 1. Changes in serum levels of CEA in evaluable patients. Values were measured 6–7 days after each administration of CDDP.

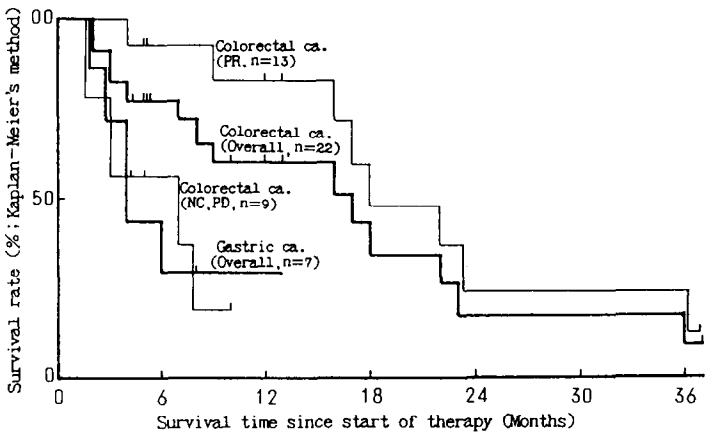

Fig. 2. Survival curves (Kaplan–Meier method) for patients with metastatic liver tumors from colorectal and gastric cancers.

Table 4. Toxicity related to IHA chemotherapy

Renal toxicity (increase of serum BUN and creatine)			6/19* (32%)	
Nausea and vomiting			14/35 (40%)	
Bone marrow suppression		Regimen I	Regimen II	Total
leucocytopenia	(under 3000/mm^3)	11 (69%)	7 (37%)	18/35 (51%)
	(under 1000/mm^3)	6 (32%)	0	6/35 (17%)
thrombocytopenia	(under 70,000/mm^3)	8 (50%)	6 (38%)	14/35 (40%)
	(under 30,000/mm^3)	7 (44%)	0	7/35 (20%)
Sudden death by cardiac attack		1 (6%)	1 (5%)	
Ototoxicity		0	0	
Hepatic toxicity		0	0	

*Patients who received total doses of CDDP greater than 100 mg/m^2.

One patient each on Regimens I and II had a sudden cardiac attack: on the 6th day after the second administration of CDDP (Regimen I, colorectal cancer); and on the 3rd day after the third administration of CDDP (Regimen II, gastric cancer). It is unclear whether these deaths are ascribable to CDDP; permission to perform an autopsy was refused in both cases.

There was no ototoxicity or severe hepatic toxicity in our series; two patients reported temporary numbness in the upper and lower extremities after administration of CDDP.

DISCUSSION

Prior to December 1982, we treated patients with unresectable metastatic tumors in the liver with IHA injections of mitomycin C (MMC) and 5-FU. However, the therapeutic results were far from satisfactory. To improve our results and to evaluate the efficiency of CDDP, in January 1983, we began substituting CDDP (25–35 mg/m^2/week) for MMC (4–6 mg/m^2/week): the accompanying administration of 5-FU (150–180 mg/m^2/day), in terms of doses and administration schedules, was retained (Regimen I). Although we were strongly encouraged by the high PR rate for Regimen I, we had to make modifications in the treatment schedule in Regimen I because of severe bone marrow toxicity.

In the revised schedule (Regimen II) (January 1985), the interval between administrations of CDDP was prolonged and the single daily dose of 5-FU-administration was reduced. In Regimen II, bone marrow toxicity was remarkably alleviated without any decrease in the antitumor effectiveness against liver tumors, as compared with Regimen I. Overall, a PR was obtained in 13 of 26 patients (50%) with metastases to the liver from colorectal cancer, with a marked decrease in serum levels of CEA, while in patients with metastases to the liver from gastric cancer only poor antitumor effects were observed. We were unable to elucidate the reason for these marked differences in the results of treatment of metastatic tumors in the liver between colorectal and gastric cancers. These results may depend on essential differences in oncobiologic features and drug sensitivities of gastric and colorectal cancers.

Regarding the therapeutic results in patients with liver tumors treated with IHA infusions of CDDP alone, Patt *et al.* [8], Kiba *et al.* [9] and Jacobs *et al.*

[10] reported objective tumor responses in three of 10, two of five and four of seven patients, respectively. Although these results were superior to those [4, 11] obtained with systemic chemotherapy with CDDP, our results with patients with colorectal cancer are still better.

We attribute the high efficiency of treatment in our series of patients with colorectal cancer metastatic to the liver to two factors. First, rapid bolus IHA injections of the agents were performed manually and, second, in the combination of CDDP plus 5-FU exerted a synergistic anticancer effect on the liver tumors. The rationale behind IHA chemotherapy is based on the desirability of exposing the tumor to very high concentrations of drugs, which usually cannot be achieved by i.v. administration of the same dose. Campbell *et al.* [12] reported the pharmacokinetics of IHA-administered CDDP. They concluded that the concentration of CDDP in the tumor blood flow during IHA administration is higher than during systemic administration. The data of Schabel [13] indicate that CDDP is strongly potentiated by combination with 5-FU in treatment of mouse L-1210 leukemia. Ellerby *et al.* [14], Kish *et al.* [15] and Carey [16] reported that systemic combination therapy of CDDP plus 5-FU resulted in favorable antitumor effects in patients with a variety of malignancies.

The dose-limiting factor for CDDP in our series was neither nephrotoxicity, nausea nor vomiting, but bone marrow suppression [17]. Marrow suppression occurred most frequently at a relatively early stage of treatment, after the administration of relatively small doses (<100 mg/m^2). CDDP-induced marrow toxicity, as well as high anticancer effectiveness, may be enhanced by the combined use of 5-FU [14] or by our manual bolus injection of CDDP itself. Although severe bone marrow toxicity which was observed in Regimen I was completely alleviated by the modifications in Regimen II, further studies are under way to determine the optimal doses of drugs and administration schedules to improve the therapeutic effectiveness of this treatment of metastatic tumors in the liver from not only colorectal cancer but also from gastric cancer.

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