*Eur J Cancer Clin Oncol*, Vol. 24, No. 10, pp. 1671–1674, 1988.
Printed in Great Britain

0277-5379/88$3.00 + 0.00


# 'Two-route Chemotherapy' Using Intra-arterial Cisplatin and Intravenous Sodium Thiosulfate, Its Neutralizing Agent, for Hepatic Malignancies

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**Abstract**—*Seventeen patients with primary or metastatic malignancy in the liver were treated with 'two-route chemotherapy' (TRC). One course of this TRC consisted of hepatic artery infusion of cisplatin, 120 mg/m², in combination with concurrent intravenous administration of sodium thiosulfate, its neutralizing agent, at a dose of 9.0 g/m² by a rapid push, followed by 1.2 g/m²/h by continuous infusion for 6 h. Five of 11 (45%) hepatocellular carcinoma and two of six (33%) metastatic tumors achieved partial response. Although almost all patients experienced nausea or vomiting, severe side-effects, including nephrotoxicity, peripheral neuropathy or ototoxicity, were not encountered. Myelosuppression was observed in one patient after seven courses of this TRC. The results indicate that TRC may be relatively effective against hepatic malignancies in patients without severe toxicity.*

## INTRODUCTION

ATTEMPTS to increase the therapeutic effectiveness of anti-cancer agents have included the use of regional arterial administration of chemotherapeutic drugs directly into the organ containing malignant disease. Theoretically, intra-arterial infusion would have the pharmacological advantage of achieving a higher drug concentration delivered to the tumor than would be possible with conventional intravenous administration. However, the dose is still limited because of the unavoidable side-effects due to drugs which have entered the systemic circulation after passing through the tumor.

It has been suggested that regional intra-arterial infusion of anticancer agents in combination with the inactivation of the agents that reach the systemic circulation by their neutralizing agent may enhance the therapeutic effectiveness. Recently, Baba and colleagues [1–3] have reported that an improvement in the therapeutic efficacy of intra-arterial chemotherapy against bladder tumors and liver and lung metastases in experimental animals has been achieved by means of a combination of an anticancer agent, cisplatin (DDP), and its neutralizing agent, sodium thiosulfate (STS). They called it 'two-route chemotherapy' (TRC).

Accepted 13 June 1988.
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Clinically, hepatic arterial infusion chemotherapy has been reported to be effective in the control of primary and metastatic malignancies in the liver [4–6]. In the present study, we explored the applicability and the effectiveness of intrahepatic DDP in combination with systemic STS (TRC) in patients with a variety of regionally confined malignancies of the liver.

## MATERIALS AND METHODS

Seventeen patients with hepatic tumors of various types were included in this clinical trial of TRC. Eleven had unresectable primary hepatocellular carcinoma. Five patients were treated for metastatic carcinoma, including one from gastric carcinoma, one from gall bladder carcinoma and three from colon carcinoma. One was proved to have a metastatic leiomyosarcoma of the intestine. There were 14 men and three women with a mean age of 61.6 years. None of the patients had evidence of extrahepatic metastasis. The characteristics of these patients are shown in Tables 1 and 2.

Clinical evaluation before treatment included blood cell count, serum creatinine, blood urea nitrogen, and a radiograph of the chest, liver function tests and serum alphafetoprotein determination. A computerized tomogram (CT), an ultrasonogram and/or celiac angiogram was also performed. The anatomical extent of carcinoma was classified according to the staging of liver cancer described by Ariel and Pack [7] (stage 1, <10%; stage 2,

*Table 1. Two-route chemotherapy for treatment of hepatocellular carcinoma*

| Patient No. | Age/sex | Staging of carcinoma | No. of courses | AFP (ng/ml) Before therapy | AFP (ng/ml) After therapy | Response/duration (months) | Survival from treatment initiation (months) |
|---|---|---|---|---|---|---|---|
| 1 | 48/M | 4 | 16 | 32,000 | 32,000 | PR/9 | 11 |
| 2 | 54/M | 2 | 8 | 4700 | 192 | NC | 7 |
| 3 | 57/M | 4 | 2 | 108,700 | 103,100 | <PR/1.5 | 2 |
| 4 | 58/M | 4 | 3 | 9700 | 6860 | PR/1.5 | 2 |
| 5 | 60/M | 4 | 7 | 20> | 20> | PR/25 | 27 |
| 6 | 60/M | 2 | 7 | 100 | 20> | NC | 35+ |
| 7 | 71/M | 2 | 1 | 380 | 390 | PR/5 | 7 |
| 8 | 71/M | 3 | 3 | 10,000 | 170 | PR/3.5 | 6 |
| 9 | 53/M | 1 | 2 | 500 | 120 | NC | 13 |
| 10 | 67/F | 4 | 2 | 576 | 589 | NC | 8+ |
| 11 | 63/F | 3 | 3 | 20> | 20> | NC | 5+ |

*Table 2. Two-route chemotherapy for treatment of hepatic metastasis*

| Patient No. | Age/sex | Staging of carcinoma | No. of courses | Primary tumor | Response/duration (months) | Survival from treatment initiation (months) |
|---|---|---|---|---|---|---|
| 1 | 68/M | 4 | 3 | Leiomyosarcoma of intestine | PR/7 | 9 |
| 2 | 66/M | 4 | 7 | Gastric carcinoma | <PR/3 | 4 |
| 3 | 48/F | 4 | 2 | Gallbladder carcinoma | <PR/3 | 4 |
| 4 | 59/M | 4 | 1 | Colon carcinoma | PR/1 | 2 |
| 5 | 83/M | 4 | 3 | Colon carcinoma | NC | 5+ |
| 6 | 51/M | 3 | 3 | Colon carcinoma | NC | 3+ |

20–30%; stage 3, 30–50%; stage 4; >50% involvement).

In 13 patients, the catheter was inserted operatively into the right distal gastroepiploic artery and advanced into the proximal hepatic artery proper. In the remaining four patients, the catheter was introduced percutaneously into the hepatic artery by the Seldinger technique before each course of therapy. Angiography through the catheter was performed to verify that the catheter was positioned so as to infuse the tumor-bearing portions of the liver.

One course of TRC consisted of the following: DDP, 120 mg/m$^2$ body surface area (400 ml), was administered through the catheter into the hepatic artery within 3 min. Concurrent with the infusion of DDP, STS at a dose of 9.0 g/m$^2$ was given by a rapid intravenous push at the start of the DDP injection and followed by 1.2 g/m$^2$/h, dissolved in 2 l of physiologic saline, given by continuous infusion for 6 h. All patients were hydrated prior to treatment with 500 ml of intravenous fluid but did not receive mannitol or diuretics. The courses were repeated at 1 or 2 week intervals a total of 1–16 courses, mean of 4.3, were given.

Tumor response was evaluated by CT, ultrasonogram and/or celiac angiogram. Partial response (PR) was defined as greater than 50% reduction in the tumor size as a product of the two largest perpendicular diameters of each tumor mass. Shrinkage of less than 50% in tumor size was also called a <PR. In patients with hepatocellular carcinoma, the evaluation of response was also supported by serial measurement of serum alphafetoprotein.

## RESULTS

The 17 patients were divided into stage 1 ($n$ = 1), stage 2 ($n$ = 3), stage 3 ($n$ = 3) and stage 4 ($n$ = 10), according to the extent of the tumor [7]. Before treatment, hyperbilirubinemia (>3 mg/dl) was present in four (24%) patients. Seven of 11 patients with hepatocellular carcinoma had ascites and four of them had low serum albumin (<30 g/l).

All of these patients had an adequate number of sequential CTs, ultrasonograms and/or celiac angiograms to determine changes in the extent of hepatic neoplasic disease. Seven of 17 (41%) patients, including five of 11 hepatocellular carcinomas and two of six metastatic malignant tumors, achieved

PR with a mean duration of 7.4 months. Three additional patients also had a <PR, but lasting only from 1.5 to 4 months (mean 2.5 months). Seven patients showed no measurable change in the size of tumor (NC) and failed to respond to this therapy. These patients were followed by treatment with tegafur 600 mg by mouth every day. Nine of 11 patients with hepatocellular carcinoma had elevated levels of alphafetoprotein (≥20 ng/ml) before treatment ranging from 100 to 108,700 ng/ml. After this treatment, a reduction of greater than 50% of the levels before therapy was observed in four of these patients.

Twelve of these patients died 2–27 months (mean 7.8 months) after starting this therapy. Five patients were alive 3–35 months (mean 11.2 months) after the treatment.

Fifteen of 17 (88%) patients in our study reported nausea within 24 h of receiving this therapy and 14 (82%) of them also experienced vomiting. Clinically demonstrable nephrotoxicity, with elevation of blood urea nitrogen and serum creatinine above normal limits following DDP administration, was not observed in any patient. There was no severe hematotoxicity, except one patient (Table 1, patient No. 6) who developed myelosuppression, lasting for 2 months, with a drop in the white cell count 1600/cu mm and the platelet count to 25,000/cu mm, after seven courses of this TRC (Fig. 1). There was

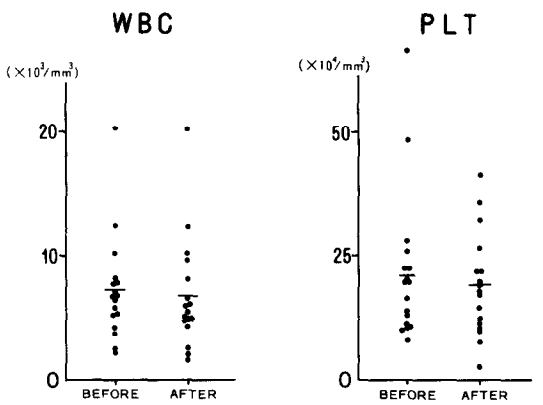


*Fig. 1. Maximum changes in the white blood cell count (WBC) and platelet count (PLT) during the 3-week period after intrahepatic DDP and systemic STS. Horizontal bars indicate arithmetic means.*

no case of chemical hepatitis requiring the treatment to be withdrawn.

## DISCUSSION

The results of this small study demonstrated that this form of TRC could be used clinically without any severe toxicity. Seven of 17 patients with various malignant tumors in the liver exhibited partial response when treated with this therapy.

The toxicity of DDP has been shown to be reduced by STS [8–11], which produces little toxicity and is readily available for use in man. Regional perfusion of DDP chemotherapy with concurrent protection of the systemic circulation by STS has been demonstrated to improve the therapeutic efficacy in peritoneally disseminated tumors, bladder tumors and lung metastasis in animals [1, 2, 12]. The antitumor effect of DDP on metastatic liver tumors in rats could also be remarkably enhanced by the combination of intrahepatic DDP and systemic STS [3]. Furthermore, a clinical trial of this procedure in patients with intraperitoneal tumors was reported [13]. The present study was undertaken to investigate the clinical applicability and effectiveness of two-route chemotherapy against malignant tumors of the liver.

Iwamoto *et al.* [10], using a microbiological assay system, demonstrated that the biologically active DDP in the plasma in rabbits was inactivated completely by coadministration of STS in a molar ratio of 400-fold excess. The rabbits were almost completely protected against both blood urea nitrogen increase and body weight loss normally caused by DDP. We have investigated the protective effect of STS on antiproliferative action of DDP against human cells by using the phytohemagglutinin stimulation assay of human peripheral blood mononuclear cells [11]. In this system, effective protection against DDP cytotoxicity could be achieved by concurrent presence of STS at molar STS/DDP ratios greater than 500. In the present study, STS could be administered intravenously to achieve a concentration almost 500-fold that of DDP in the patient's plasma [14].

Intra-arterial infusion of DDP has been tried in patients with a variety of regionally confined malignancies [15, 16]. Pharmacokinetic studies showed that hepatic artery infusion of DDP was associated with significantly lower peak plasma concentration and concentration × time, despite the general similarities in pharmacokinetics after intravenous and intra-arterial DDP administration [17]. However, Calvo *et al.* [16] reported that the incidence of side-effects from intra-arterial DDP, including intrahepatic infusion, was not different from that observed after intravenous administration. When a DDP dose of 120 mg/m$^2$ alone, which was the same dose used in our study, was given intra-arterially, nephrotoxicity was detected in sporadic cases. The incidence of hematological toxicity was relatively low, whereas peripheral neuropathy or ototoxicity was noted in 6% of the treatment courses. In our study, there was no renal toxicity, even after 16 courses of this therapy. There were no severe side-effects, except for one case of myelosuppression. These results indicated that intravenous administration of STS in combination with intra-arterial DDP might protect against systemic DDP toxicity without interfering with the regional anticancer effect of the drug, since the

response rate in our study was rather higher than that reported by Calvo *et al.* [16], in which three of 20 patients with various malignancies of the liver achieved partial response after intrahepatic infusion of DDP alone.

The response rates reported for anticancer agents given by hepatic artery infusions have often been superior to those for the same agents given intravenously. In a review of the therapeutic opinions currently available for hepatic metastasis, the incidence of tumor response to hepatic artery infusion chemotherapy was found to range from 15% to 76% in patients treated with a variety of agents [4, 5]. Intrahepatic infusion in hepatocellular carcinoma produced tumor regression in 0–75% [6]. Although based on smaller numbers, our results demonstrated that 45% patients of hepatocellular carcinoma and 33% patients of metastatic tumors in the liver exhibited a partial response.

Ten (56%) of our patients had stage 4 liver cancer. When our patients with hepatocellular carcinoma were divided into the stages according to the clinical classification of Okuda *et al.* [18], eight of 11 (73%) patients belonged to stage II or III. Therefore, the relatively short survival after therapy in our study appeared to be related to the advanced stage of cancer in these patients.

These results showed that this TRC might be relatively effective against malignant tumors of the liver in patients without any severe side-effects. A technique to achieve much higher DDP concentration in the infused area as compared to systemic drug levels or to isolate the regional area from the systemic circulation containing STS may provide further improvement of the therapeutic efficacy of two-route chemotherapy. Such procedures are under investigation.

## REFERENCES


1. Sagiyama K, Uozumi J, Aoki K, Baba T. Efficacy of 'two-route chemotherapy' using intra-arterial cisplatin and i.v. sodium thiosulfate, its antidote, in rat bladder tumor. *Cancer Treat Rep* 1983, **67**, 567–572.
2. Iwamoto Y, Aoki K, Kawano T, Baba T. Upper hemibody infusion of *cis*-diamminedichloroplatinum (II) followed by systemic antidote, sodium thiosulfate, for lung metastasis in rats. *Clin Exp Metast* 1984, **2**, 261–266.
3. Uozumi J, Sagiyama K, Aoki K, Iwamoto Y, Baba T. Effectiveness of 'two-route chemotherapy' using cisplatin and its antidote, sodium thiosulfate, on life span of rats bearing metastatic liver tumors. *Cancer Treat Rep* 1983, **67**, 1067–1074.
4. Lightdale CJ, Sherlock P. Management of metastatic liver disease. *Prog Liver Dis* 1982, **7**, 649–662.
5. Schwartz SI, Jones LS, McCune CS. Assessment of treatment of intrahepatic malignancies using chemotherapy via an implantable pump. *Ann Surg* 1985, **201**, 560–567.
6. Ramming KP. The effectiveness of hepatic artery infusion in treatment of primary hepatobiliary tumors. *Semin Oncol* 1983, **10**, 199–205.
7. Ariel IM, Pack GT. Treatment of inoperable cancer of the liver by intra-arterial radioactive isotopes and chemotherapy. *Cancer* 1967, **20**, 793–804.
8. Howell SB, Taetle R. Effect of sodium thiosulfate on *cis*-dichlorodiammineplatinum (II) toxicity and antitumor activity in L1210 leukemia. *Cancer Treat Rep* 1980, **64**, 611–616.
9. Ishizawa M, Taniguchi S, Baba T. Protection by sodium thiosulfate and thiourea against lethal toxicity of *cis*-diamminedichloroplatinum (II) in bacteria and mice. *Jpn J Pharmacol* 1981, **31**, 883–889.
10. Iwamoto Y, Kawano T, Ishizawa M, Aoki K, Kuroiwa T, Baba T. Inactivation of *cis*-diamminedichloroplatinum (II) in blood and protection of its toxicity by sodium thiosulfate in rabbits. *Cancer Chemother Pharmacol* 1985, **14**, 228–232.
11. Abe R, Akiyoshi T, Tsuji H, Baba T. Protection of antiproliferative effect of *cis*-diamminedichloroplatinum (II) by sodium thiosulfate. *Cancer Chemother Pharmacol* 1986, **18**, 98–100.
12. Iwamoto Y, Kawano T, Uozumi J, Aoki K, Baba T. 'Two-route chemotherapy' using high-dose i.p. cisplatin and i.v. sodium thiosulfate, its antidote, for peritoneally disseminated cancer in mice. *Cancer Treat Rep* 1984, **68**, 1367–1373.
13. Howell SB, Pfeifle CE, Wung WE, Olshen RA. Intraperitoneal *cis*-diamminedichloroplatinum with systemic thiosulfate protection. *Cancer Res* 1983, **43**, 1426–1431.
14. Abe R, Akiyoshi T, Wada T, Arinaga S, Tsuji H. Inhibitory effect of thiosulfate on cisplatin cytotoxicity: measurement with PHA blastogenic response of human lymphocytes. *Proc Jpn Cancer Assoc*, 44th Ann Meet 1985, 264.
15. Pitchard J, Mavligit G, Benjamin R *et al.* Regression of regionally confined melanoma after intra-arterial *cis*-dichlorodiammineplatinum (II). *Cancer Treat Rep* 1979, **63**, 555–558.
16. Calvo DB, Patt YZ, Wallace S *et al.* Phase I–II trial of percutaneous intra-arterial *cis*-diamminedichloroplatinum (II) for regionally confined malignancy. *Cancer* 1980, **45**, 1278–1283.
17. Stewart DJ, Benjamin RS, Zimmerman S *et al.* Clinical pharmacology of intra-arterial *cis*-diamminedichloroplatinum (II). *Cancer Res* 1983, **43**, 917–920.
18. Okuda K, Ohtsuki T, Obata H *et al.* Natural history of hepatocellular carcinoma and prognosis in relation to treatment. Study of 850 patients. *Cancer* 1985, **56**, 918–928.