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CLINICAL TRIAL REPORT

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Feasibility study of ambulatory continuous infusion of 5-fluorouracil followed by cisplatin through hepatic artery for metastatic colorectal cancer

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Abstract *Purpose*: A great synergy has been reported in a number of preclinical studies when 5-fluorouracil (5-FU) precedes cisplatin (CDDP). The objective of this study was to determine the feasibility of ambulatory continuous infusion of 5-FU followed by CDDP through hepatic artery for metastatic colorectal cancer. *Patients and methods*: Seventeen patients with unresectable liver metastases, who underwent primary tumor resection, were treated with 5-FU (450 mg/m^2/day) for seven consecutive days followed by CDDP (100 mg/body/week) for seven consecutive days, each administered continuously by using a balloon pump via Infuse-A-Port catheter inserted into common hepatic artery. The doses of drugs were reduced 20% in patients older than 70 years. The treatment was repeated every 4–6 weeks until disease progression. *Results*: Of 17 assessable patients, nine patients showed PR (53%; 95% CI, 29.3–76.7%) and eight patients had SD (47%; 95% CI, 23.3–70.7%), with disease control rate of 100%. The median overall survival was 26 months (95% CI: 17.5–41 months) and TTP 14 months (95% CI: 11–20.3 months). Two patients (11.8%), who showed progression due to collateral feeding arteries, responded to HAI again after occlusion. Grade 3 toxicity included leukopenia (12%) and anemia (24%). Grade 4 toxicity was absent. Four patients (23.5%) progressed at extrahepatic sites. *Conclusions*: This sequential combination of 5-FU followed by CDDP through hepatic artery is active and safe in an outpatient setting, and warrants further multi-institutional study, although prevention of micrometastasis would be mandatory to further prolong overall survival.

Keywords 5-Fluorouracil · Cisplatin · Hepatic arterial infusion · Colorectal cancer · Liver metastasis

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Introduction

The incidence of colorectal cancer (CRC) is increasing worldwide. Approximately 20% of patients have metastatic liver disease when the primary tumor is diagnosed [10]. Furthermore, an additional 35–45% of patients will develop hepatic metastases during the course of their disease [1]. Complete resection of hepatic metastases yields 3- and 5-year average survival rates of 23–65% and 25–45%, respectively [13]. Approximately, 75% of the patients who undergo resection of liver metastases will have a recurrence, 50% in the liver [11]. Therapeutic options are limited for patients who are not resectable, and such patients with liver metastases have an median survival of approximately 9 months, with three year survival less than 3% [3, 17, 28]. Conventional systemic chemotherapy is associated with low response rate and overall survival remains poor. Therefore it is of extreme importance to define ideal regional remedies for maximizing benefits but minimizing mortality and adverse effects for those patients.

Metastatic liver cancers derive approximately 80% of their blood supply from the hepatic artery [4]. This unique blood supply of the liver allows hepatic arterial infusion active and feasible for patients with liver metastasis, not only because when injected into the hepatic artery, the regional drug concentration is

significantly higher than systemic concentration, but also because the drugs are largely extracted by the liver during the first pass, resulting in minimal systemic toxicity [18]. In a number of randomized studies using fluoropyrimidine derivatives, response rates were significantly higher for hepatic arterial infusion (HAI), as compared with intravenous administration. However, the prolongation of survival in patients treated with HAI still remains controversial in the United States and Europe where floxuridine (FUDR) alone has been used for hepatic arterial infusion [2, 5, 16, 19, 20, 22, 26]. FUDR is almost exclusively extracted by the liver, therefore it seems to be difficult to control the micrometastases in the extrahepatic region. Unlike FUDR, a certain level of 5-fluorouracil (5-FU) remains in the systemic when injected into the hepatic artery [6, 23].

The combination of 5-FU and cisplatin (CDDP) exhibits sequence-dependent synergy both in vitro and in tumor-bearing animals [25, 29, 30]. Several in vivo studies including the investigations of human tumor xenografts in nude mice demonstrated that the sequence of 5-FU followed by CDDP was more active than the reverse sequence or either drug alone [21, 25, 32, 33]. The clinical efficacy of 5-FU and CDDP combination has been confirmed. However, such a sequence-dependent antitumor activity has yet to be clinically determined in the treatment of metastatic colorectal cancer confined to the liver. Therefore, the current study was designed to assess the efficacy and tolerability of ambulatory continuous HAI of 5-FU followed by CDDP for such patients who underwent complete resection of primary tumor. The primary objectives of the research were to observe objective response rate, survival, time to progression (TTP) and toxicities in outpatient setting.

Patients and methods

Eligibility criteria

We included patients with histologically confirmed colorectal cancer, who had multiple and/or massive metastases confined to the liver that were not amenable to surgery replacement (the presence of more than 60% liver by unresectable metastasis) after complete resection of primary tumor. Inclusion criteria were as follows: a history of primary colorectal cancer excision; no evidence of extrahepatic metastasis on computed tomography, bone scintigraphy, and magnetic resonance imaging (MRI) if needed; age 20–80 years; Eastern Cooperative Oncology Group performance status ≤ 2; measurable liver lesions; leukocyte count $\geq 3{,}500/mm^3$; neutrophil count $\geq 1{,}500/mm^3$; platelet count $\geq 100{,}000/mm^3$; serum creatinine ≤ 1.5 mg/dl; serum bilirubin ≤ 2.0 mg/dl; AST ≤ 100 IU/l, ALT ≤ 100 IU/l; a life expectancy ≥ 3 months; and adequate cardiac function. Previous fluorouracil-based treatments were eligible if treatment had been completed more than 4 weeks before study entry. Exclusion criteria were: extrahepatic metastases; active uncontrolled infection; unresolved bowel obstruction; known contraindications to fluorouracil (angina pectoris, myocardial infarction in the past 6 months); and portal vein occlusion. This study was approved by the local ethics committee, and patients were informed of the investigational nature of the study and provided their written informed consent before registration in the study.

Treatment plan

Hepatic arterial infusion was given by percutaneous catheterization of the femoral artery. Procedures for pump placement are as follows. A catheter was inserted into common hepatic artery from right femoral artery. Under celiac angiography, the right gastric artery, and gastroduodenal artery were occluded by a steel coil, to avoid inflow of anticancer drugs to other organs. The collateral arteries which feed the liver, if any, were also occluded. After confirming the presence of the tip of a heparin-coated catheter in the common hepatic artery, a reservoir connected to the catheter was implanted in a subcutaneous pocket in the right subinguinal portion and the catheter was secured in the artery. An intraoperative injection of contrast material was used to check the flow immediately after placement.

Patients were treated with 5-FU (450 mg/m^2/day) on days 1–7, which was followed by CDDP (100 mg/body/week) on days 8–14. Each of them was administered continuously using a LV 1.5 Baxter balloon pump (275 ml) at a flow rate of 1.5 ml/h via Infuse-A-Port catheter inserted into common hepatic artery. Dexamethasone 8 mg and heparin 35,000 unit were mixed in balloon pump and concurrently infused. The doses of 5-FU and CDDP were reduced 20% in patients above 70 years. To prevent nausea and vomiting, 5-hydroxytryptamine-3 antagonists were intravenously administered before chemotherapy. G-CSF was used when neutropenia less than $500/mm^2$ or febrile neutropenia less than $1{,}000/mm^3$ were present. Treatment was continued until evidence of progression, unacceptable toxicity, or patient refusal. Treatment was delayed if, on the planned day of treatment, there was leucopenia less than $3{,}000/mm^3$, thrombocytopenia less than $100{,}000/mm^3$, infectious fever, persistent diarrhea, or non-hematological toxicities greater than grade 3, except for nausea and vomiting. If toxicities greater than grade 3 were observed, the doses of both 5-FU and cisplatin were reduced by 20% on the next cycle. This treatment was repeated every 4–6 weeks.

Assessment of treatment and response

Pretreatment evaluation included a complete history, physical examination, performance status assessment and laboratory examinations including hepatic and renal

functions, urinalysis, complete blood count with differential leukocyte profile, serum alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA) and CA19-9. Computed tomography (CT) scans of the chest, abdomen and pelvis were performed before commencement of chemotherapy. During treatment, a physical examination, a complete blood count and urinalysis were performed once a week. Hepatic and renal functions were examined once a month. CEA and CA19-9 were checked every 2 months. Liver metastatic lesions were reevaluated every 8 weeks. A chest radiograph and abdominal ultrasonography or CT scan were repeated at least every 2 month to exclude lung or other abdominal metastases. For evaluating the response to the treatment, the tumors were measured bidimensionally by computed tomography (CT) both before and after chemotherapy. Responses were evaluated every 8 weeks according to World Health Organization Criteria. Toxicities were monitored weekly and scored according to standard NCI-CTC.

Statistical analysis

The data were statistically analyzed using JMP software (SAS Institute Inc, Cary, NC, USA). Survival estimates were calculated using Kaplan-Meier curves and confidence intervals were calculated using Greenwood variance formula. Survival was calculated until death as a result of any cause, and progression-free survival was calculated from start of chemotherapy until progression of disease or death as a result of any cause.

Results

From May 1997 to September 2003, we randomly enrolled 17 patients with extensive and/or massive metastases confined to the liver from colorectal cancer. Patient characteristics were listed in Table 1. There were 4 women and 13 men. The median age was 68 years, with a range from 45-year-old to 80-year-old. Among 17 patients recruited in the group, 15 were in ECOG performance status 0 and the other two in performance status 1 and 2, respectively. Of the five patients who received prior chemotherapy, three were administered CPT-11-based systemic regimen, one 5-FU-based systemic treatment, and one HAI treatment. Patients were given the HAI treatment after we confirmed that they had normal vasculature and could have a catheter inserted to perfuse the liver completely. Infusion via collateral arteries was done in two patients. Total 176 cycles (median 10, range 3–20 per patient) were done so far.

All patients enrolled were assessable for responses. Nine out of 17 patients (53%) showed PR (95% CI, 29.3–76.7%), one of them received a resection of liver metastases after the treatment. Eight patients (47%; 95% CI, 23.3–70.7%) experienced NC. Therefore, disease control rate was 100%. Two patients (11.8%), who showed progression due to collateral feeding arteries, responded to HAI again after occlusion of these vasculature. As shown in Fig. 1, the median overall survival was 26 months (95% CI, 17.5–41 months). The

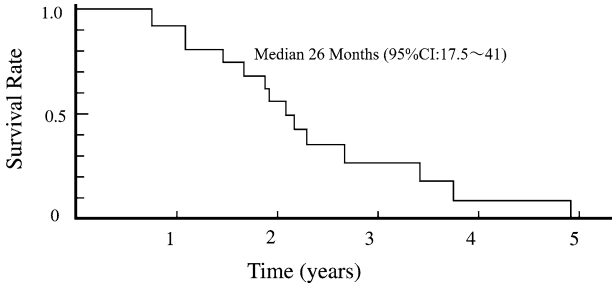

Fig. 1 Kaplan-Meier survival curve of overall survival

Table 1 Patient characteristics and treatment results (As of October 30th, 2004)

Pts	Age/Sex	ECOG PS	Primary site	Histology	Liver metastases	No. of cycles	Response	Survival (Months)
1	56/M	0	Rectum	Well-mod	Multiple	17	PR	27.5
2	70/F	0	Sigmoid	Well-mod	Multiple	18	PR	32
3	77/M	1	Rectum	Well-mod	Multiple	11	NC	13
4	73/M	0	Rectum	Mod	Multiple	9	PR	23
5	73/M	0	Descending	Well	Multiple	10	PR	59
6	80/F	0	Rectum	Well	Multiple	19	PR	45
7	55/M	0	Sigmoid	Mod	Multiple	20	PR	41
8	72/M	0	Sigmoid	Well	Multiple	11	NC	20
9	76/M	2	Sigmoid	Well-mod	Multiple	7	NC	13
10	59/M	0	Rectum	Well-mod	Multiple	6	PR	17.5
11	63/F	0	Ascending	Well-mod	Multiple	6	NC	9
12	70/M	0	Rectum	Mod	Multiple	3	NC	22.5
13	56/F	0	Rectum	Well-mod	Multiple	14	NC	29+
14	67/M	0	Descending	Well-mod	Multiple	3	PR	26
15	45/M	0	Rectum	Well	Massive	12	PR	25+
16	59/M	0	Sigmoid	Mod	Multiple	7	NC	13+
17	68/M	0	Sigmoid	Well	Multiple	10	NC	25

ECOG Eastern Cooperative Oncology Group, *PS* performance status, *Well* well-differentiated adenocarcinoma, *Mod* moderately-differentiated adenocarcinoma, *Well-mod* well to moderately differentiated adenocarcinoma. + alive, *Pts* patients

1-, 2-, and 3-year overall survival rates were 94.1, 57, and 27.1%, respectively. Three patients (17.6%) are alive at present. Median time to progression (TTP) was 14 months (95% CI, 11–20.3 months) (Fig. 2). Four patients (23.5%) progressed at extrahepatic sites, mostly lung (three patients), bone (one patient), brain (one patient).

All the patients were assessable for toxicities and catheter-related complications. There were no treatment-related deaths during the entire courses of study. Five patients experienced the replacement of catheter due to the obstruction. There was no evidence of chemical hepatitis, biliary sclerosis, catheter-induced thrombosis, and duodenal ulceration and hemorrhage that have been associated with HAI administration of chemotherapy. No patient developed severe abdominal pain suggestive of gastroduodenal ulcer or gastroduodenitis. Elevated liver enzymes in documented disease progression were not considered treatment-related toxicities. Non-hematological toxicity was rare with one patient (6%) showing grade 1 vomiting. Hematological and renal toxicities were summarized in Table 2. Grade 3 toxic effects were leukocytopenia (12%) and anemia (24%). No grade 4 toxicities were observed. Cardiac and neurological adverse effects were not encountered in any of the patients. As a result, all the patients received the doses as scheduled.

Discussion

The unique blood supply of the liver allows hepatic arterial infusion active and feasible for patients with liver metastasis [18]. In a number of randomized studies using fluoropyrimidine derivatives, response rates were significantly higher for hepatic arterial infusion (22–62%), as compared with intravenous administration (9–19.6%). However median survivals for HAI treatment groups (12.6–17 month) were not always significantly longer than those for systemic treatment groups, which ranged from 7.5 months to 16 months, indicating that the prolongation of survival remains controversial [2, 5, 16, 19, 20, 22, 26]. Moreover in a randomized study to compare an intrahepatic arterial 5-FU plus leucovorin regimen with the standard intravenous de Gramont fluorouracil plus leucovorin regimen for patients with metastatic colorectal cancer confined to the liver, the objective response rate was 22% and the stable disease rate 32%, median overall survival and TTP were 14.7 and 7.7 months, respectively, 57% of patients were alive at 1 year, and 22% at 2 years in the HAI treatment group. Moreover, there was no evidence of advantage in TTP and overall survival in HAI treatment group, as compared to systemic treatment group [20]. In the present study, sequential hepatic arterial infusion of 5-FU followed by CDDP demonstrated PR and SD in 53 and 47% of treated patients respectively, with disease control rate (PR + SD) of 100%. The median overall survival was 26 months (95% CI: 17.5–41 months) and median TTP 14 months (95% CI: 11–20.3 months). Therefore, sequential hepatic arterial infusion of 5-FU followed by CDDP appears superior to previous HAI treatment employing fluoropyrimidine derivatives. In addition, 3-year overall survival rate was 27.1%, being significantly higher than patients with unresectable liver metastases, who showed a median survival of approximately 9 months and 3 year survival of less than 3% [3, 17, 28].

Recent progresses have been achieved in the treatment of colorectal cancer by introducing CPT-11 or oxaliplatin. Several phase III trials investigating combination regimens with FU/LV plus CPT-11 or FU/LV plus oxaliplatin as a first-line therapy have achieved overall survival of 14.8–21.5 months [14]. The use of all three active drugs in advanced colorectal cancer produced the longest overall survival [15]. Indeed, triple-combination protocols using FU-LV plus irinotecan plus oxaliplatin have consistently resulted in high response rates of 57–78% in patients with previously untreated advanced CRC and have produced the longest overall survival of 22.5 months in one trial [12, 24, 27, 31]. In comparison with these systemic treatments, we obtained a survival benefit of at least 3.5 months with sequential HAI treatment despite patients having liver metastasis, an extremely poor prognostic factor.

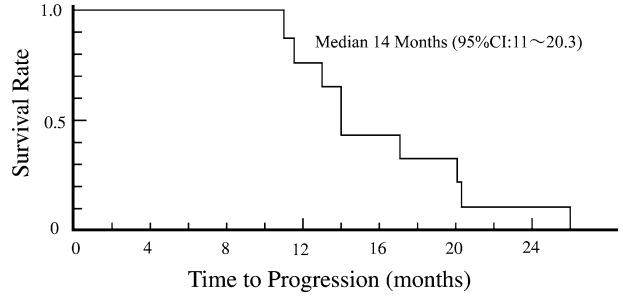

Fig. 2 Kaplan-Meier survival curve of time to progression

Table 2 Hematological and renal toxicities

NCI-CTC Grade	Number of patients (%)			
	Leucocytopenia	Thrombocytopenia	Anemia	Renal dysfunction
1	1 (6%)	7 (41%)	2 (12%)	1 (6%)
2	1 (6%)	–	4 (24%)	2 (12%)
3	2 (12%)	–	4 (24%)	–
4	–	–	–	–

Data are indicated as the maximum number of patients with the most severe grade of toxicity

Therefore, it seems likely that this sequential treatment would be a much better option for patients with metastatic CRC confined to the liver.

The rationale of HAI is based on increased local drug concentrations and hepatic clearance of the drug before entering systemic flow. Continuous hepatic infusion of 5-FU and CDDP has been shown to yield fivefold to tenfold and fourfold to sevenfold higher local concentration than systemic administration, respectively [7]. In addition, protracted infusion may expose a relatively larger proportion of cycling tumor cells to 5-FU, thereby increasing the efficacy of 5-FU. Moreover, the combination of 5-FU and CDDP has been shown to exhibit a sequence-dependent synergy in vitro and in vivo, with sequence of 5-FU followed by CDDP being the most active schedule. This sequence-dependent synergy can be explained by the mechanism of DNA damage repair and detoxification processes; i.e., pretreatment of 5-FU increased CDDP cytotoxicity and even circumvents CDDP resistance by inhibiting repair of platinum-DNA interstrand cross-links as well as by reducing the cellular GSH levels [8, 9].

Although our treatment improved response rate and prolonged the survival of the CRC patients with liver metastases, further follow-up of these patients and accrual of more numbers of patients are needed. Moreover, four patients (23.5%) experienced extrahepatic metastases which led to the patients' death. Therefore, prevention of extrahepatic micrometastases with systemic chemotherapy appears to be mandatory to further improve overall survival. In conclusion, this sequential combination of 5-FU followed by CDDP through hepatic artery is active and safe in an outpatient setting for patients with colorectal cancer metastasized only to the liver, and warrants further multi-institutional studies.

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