Biochemical modulation of 5-fluorouracil (5-FU) has been verified the evidence of significant improvement of survival and quality of life in patients with advanced colorectal carcinoma. We investigated the therapeutic and adverse drug reaction of intensive chemotherapy using cisplatin (CDDP), 5-FU and dl-leucovorin (LV) (PFL-therapy), which may be producing dual biochemical modulation effect of 5-FU for advanced colorectal carcinoma.

Administration schedule was 13 mg/m$^2$ of CDDP, 300 mg/m$^2$ of 5-FU, and 30 mg/body of dl-LV for 5 consecutive days. This regimen was repeated at 3-week intervals in hospital.

Sixteen patients were enrolled in this study, most of whom had a history of previous chemotherapy as adjuvant treatment, and the response rate was 25%, with four patients having “partial response” and eight “no change”. In respect to performance status, 46% of patients who completed the protocol were markedly improved in spite of their poor performance status before treatment. Moreover, when patients were classified into two groups based on changes of the serum level of CEA, “responder in CEA level” showed better prognosis than “non-responder in CEA level”. Major toxicities were nausea, hyperglycemia and neutropenia. Three patients experienced Grade 4 hematological side effect, but these complications resolved quickly in all patients except for one patient.

PFL-therapy is effective for advanced colorectal cancer with large tumor burden and showed the same prognostic result as the American and European trials in spite of smaller number of treatment cycles and a history of previous chemotherapy. We will be able to demonstrate the usefulness of this regimen for Japanese patients with advanced colorectal cancers after adding new cases to the present report.

**Key words**: colorectal carcinoma, intensive chemotherapy, biochemical modulation, 5-FU, CDDP.

### Introduction

It is in agreement with most of oncologists that gastrointestinal cancer, especially colorectal carcinoma, is resistant to anticancer drugs. 5-fluorouracil (5-FU) has been the only effective drug for these malignancies in the past 40 years. Recently, combination chemotherapy against advanced colorectal carcinoma using 5-FU with other anticancer drugs has been in use worldwide. Moreover, modulating agents strengthening the anticancer effect and decreasing adverse drug
reaction of 5-FU have been used based on detailed pharmacodynamic studies.

In the United States, 5-FU/leucovorin (LV) therapy has been noted to have remarkable therapeutic effects on advanced colorectal carcinoma. The method of administration of 5-FU was mainly intravenous bolus, but the continuous infusion method has been recently adopted.

In 5-FU/LV therapy for advanced colorectal and gastric carcinoma in Japan, intravenous bolus administration of 5-FU was more effective than drip infusion over 30 minutes. It is thought that dysfunction of RNA as well as inhibition of synthesis of DNA would make 5-FU/LV therapy more effective for advanced colorectal carcinoma although serum concentration of 5-FU might decrease rapidly.

Currently, cisplatin (CDDP) is recognized as a powerful anticancer drug for gastrointestinal cancer. The use of CDDP alone was scarcely effective for colorectal carcinoma, but in combination with 5-FU a synergistic effect was shown by its role not only as an effector but also a biochemical modulator to 5-FU. Moreover, It was reported that low dose CDDP would potentially increase the cytotoxic activity of lymphocytes, and on the other hand, high dose administration would decrease antitumor activity of lymphocytes.

Considering these results, we designed our regimen of PFL-therapy to include administration of low doses of CDDP over a five-day period.

We have been performing intensive chemotherapy using CDDP, 5-FU, and dl-leucovorin (PFL-therapy) for unresectable or recurrent colorectal carcinoma for the past 7 years. In this article, we report results of our investigation of the clinical usefulness of this regimen with regard to adverse drug reaction and therapeutic effects.

**Patients and Methods**

Eligibility criteria were as follows. Patients were required to have histologically-confirmed inoperable locally advanced or metastatic colorectal cancer. Disease was defined as either bidimensionally measurable or non-measurable. Most of patients were ambulatory, but bedridden patients could be enrolled into the protocol if conscious level was normal. Previous chemotherapy was not allowed except for adjuvant chemotherapy which had been terminated over one year before study entry. Adequate organ function was required. Informed consent according to institutional regulations was obtained from all patients. The study protocol was approved by the local ethics committee of our university.

Chemotherapy consisted of low-dose LV, 5-FU and CDDP. 30 mg/body/day of LV and 300 mg/m²/day of 5-FU were injected by intravenous push at the start of infusion of 13 mg/m²/day of CDDP for 5 consecutive days in hospital. CDDP was diluted in 500 ml of normal saline and infused intravenously during a 2-hour period at the time of injection of 5-FU and LV. Standard antiemetic regimens, i.e., 30 mg of granisetron, 20 mg of metoclopramide plus 125 mg of methylprednisolone sodium succinate, were administered before and during infusion of CDDP. This protocol, PFL-therapy, was performed repeatedly every three weeks if the patient had recovered from adverse drug reaction of previous chemotherapy.

The therapeutic effects of chemotherapy were defined according to standards advocated by WHO. Therapeutic effects were defined as follows: complete response (CR), complete disappearance of tumor; partial response (PR), 50% reduction of tumor volume; no change (NC) in tumor size; and progressive disease (PD), increase in tumor size or appearance of a new lesion. Moreover, we grouped patients by the change of the serum level of carcinoembryonic antigen (CEA). If it decreased after treatment, classified into “responder in CEA level”, to the contrary, unchanged or slightly elevated after treatment, called it “non-responder in CEA level”.

If we could resect the cancer tissue after PFL-therapy, therapeutic effects were evaluated using the following histological criteria: Grade I, characteristic changes consistent with effects of chemotherapy were noted in tumor cells, but tumor structures had not been destroyed; Grade II, in addition to characteristic cellular changes, tumor structures were destroyed as a result of disappearance of tumor cells, however, a variable number of "viable cells" still remained; Grade III, markedly altered, presumably nonviable tumor cells were present singly or in small clusters and "viable cells" were barely seen; and Grade IV, no tumor cells remained in any of sections of the specimens.

Toxicity grades were evaluated according to WHO criteria, and patients were classified by the worst degree of treatment complication as follows: Grade 1, mild complication; Grade 2, moderate; Grade 3, severe; and Grade 4, worst. Moreover, performance status was defined into five grades, from “Grade 0” to “Grade 4”, according to the KARNOFSKY scale or ECOG scale.
Statistically, we analysed the intention-to-treat population and calculated response rates for the intention-to-treat and evaluable populations. $X^2$ tests were used to compare categorical variables between two groups, which were classified into "responder and non-responder in CEA level". For continuous variables, we determined below 5% as significantly different using the Student's t test. We estimated survival curves by the Kaplan-Meier method, and compared the two groups by the log-rank test.

Results

Patient characteristics and treatment

Our university hospital recruited 16 patients between 1992 and 1997. Median duration of follow-up was 16 months (range, 0-31 months). Three patients were not assessable for objective response. They did not complete their first and only full course of therapy because of intercurrent medical problems. All of these patients were classified as having treatment failures.

The demographic features of the patients entered in this study and completed the protocol are shown in Table 1. The mean age of eligible patients was 59 (45-70) years old. With regard to the primary site of colorectal carcinoma, nine were in the colon and four in the rectum. Concerning histological grade, four were well differentiated and nine were moderately differentiated adenocarcinoma. Ten patients had received adjuvant chemotherapy previously using mainly 5-FU. Regarding the site of distant metastasis or recurrence, six were in the lung, eight in the liver, two in the bone and three were peritoneal dissemination.

The average number of treatment courses was 1.5 (range, 1-3 course).

Response to treatment

The serum levels of carcinoembryonic antigen (CEA) of six patients (case1, 3, 6, 9, 11 and 13) were decreased, whereas those of the other patients were unchanged or slightly elevated after treatment. The former patients were classified into "responder in CEA level", the latter into "non-responder in CEA level". The distribution of patient and tumor characteristics was well balanced between two groups.

Performance status before treatment was Grade 1 in one, Grade 2 in nine, Grade 3 in two and Grade 4 in one patient. All were able to take a meal, and none had severe hepatorenal dysfunction. Performance status of 46% of patients were improved (Table 2).

Degree of response was PR in four patients, NC in...
Survival
Time to death was longer for responder (PR): the mean duration to death was 17.3 months in responder (95% confidence interval, 0.192–34.3 months), compared with that of 13.1 months in non-responder (NC plus PD) (95% confidence interval, 7.76–18.4 months) (P = 0.433). There was no relation between response to treatment and survival (log-rank test: P = 0.376 if PR compared with NC plus PD; 0.324 when PR by comparison with PD).

The mean overall survival was 18.8 months (95% confidence interval, 9.65–28 months) in “responder in CEA level” and 11.3 months (95% confidence interval, 5.59–17 months) in “non-responder in CEA level” (P = 0.099) and the one-year actuarial survival 83.3% and 40%, respectively. Survival distributions for the study patients according to “response in CEA level” are illustrated in Fig. 1 (log-rank test: P = 0.120).

Toxicity
Adverse drug reactions related to PFL-therapy were nausea/vomiting, diarrhea, stomatitis and skin rash and hematological complications were frequently observed (Table 3). Two patients had leukopenia and thrombocytopenia grouped into Grade 4, respectively. These complications treated successfully in all except for one patient (case 7), who received the treatment at the early period of palliative surgery.

Case presentation
We present two cases, to whom our treatment was useful for reducing large tumor burden.

Case 3: A 62-year-old male patient had sigmoid resection for intestinal obstruction by colon carcinoma, after which low anterior resection for local recurrence and extended left lobectomy of the liver for liver metastasis were performed.

Serum tumor marker values were elevated: 24 ng/ml of CEA, 452 U/ml of CA19-9 and 452 U/ml of TPA. After three cycles of PFL-therapy for the recurrent tumor around the pubis, the recurrent mass rapidly

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Serum CEA level</th>
<th>P.S.</th>
<th>Response</th>
<th>Indicator</th>
<th>Survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
<td>Post</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>334</td>
<td>30.9</td>
<td>4</td>
<td>2</td>
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</tr>
<tr>
<td>2</td>
<td>103</td>
<td>132</td>
<td>2</td>
<td>2</td>
<td>NC</td>
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<tr>
<td>3</td>
<td>23.8</td>
<td>2.4</td>
<td>2</td>
<td>1</td>
<td>PR</td>
</tr>
<tr>
<td>4</td>
<td>2.7</td>
<td>5.4</td>
<td>2</td>
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<td>NC</td>
</tr>
<tr>
<td>5</td>
<td>77</td>
<td></td>
<td>3</td>
<td>3</td>
<td>PD</td>
</tr>
<tr>
<td>6</td>
<td>61.7</td>
<td>26.7</td>
<td>2</td>
<td>1</td>
<td>NC</td>
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<tr>
<td>8</td>
<td>1.9</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>NC</td>
</tr>
<tr>
<td>9</td>
<td>84.5</td>
<td>46.5</td>
<td>1</td>
<td>0</td>
<td>NC</td>
</tr>
<tr>
<td>10</td>
<td>3.6</td>
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<td>2</td>
<td>2</td>
<td>NC</td>
</tr>
<tr>
<td>11</td>
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<td>16.7</td>
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</tr>
<tr>
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<td>14.9</td>
<td>19.2</td>
<td>2</td>
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<td>NC</td>
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<td>13</td>
<td>120.9</td>
<td>7.1</td>
<td>2</td>
<td>1</td>
<td>PR</td>
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</tbody>
</table>
began to decrease in size (Fig. 2).

We achieved en bloc resection of recurrent tumor with partial resection of urinary bladder and pelvic lymph node dissection. Histopathological examination of the resected specimen revealed coagulation necrosis of cancer tissue and formation of organized and ossificated tissue (Fig. 3). On the basis of histological criteria for evaluation of therapeutic effects, the lesion was evaluated as Grade II. All serum tumor marker values were within the normal range on the 13th postoperative day. The patient had only mild to moderate side

effects following chemotherapy.

**Case 11:** A 62-year-old male patient suffered from sigmoid colon cancer with multiple liver metastases, occupying the both lobes of the liver. He was performed one treatment course of PFL-therapy after sigmoid resection and metastatic lesions of the liver were reduced in size (Fig. 4).

**Discussion**

It is considered that systemic chemotherapy for unresectable or recurrent colorectal carcinomas should be started when patients are in stable condition and have a lesser tumor burden. If patients have a poor performance status, sufficiently intensive chemotherapy cannot be carried out and side effects are inclined to be severe.

In a clinical study, O'Connell\(^2\) reported that a regimen of injections of 20 mg/m\(^2\)/day of LV and 425 mg/m\(^2\)/day of 5-FU for 5 consecutive days was effective for 45% of advanced colorectal carcinomas. On the contrary, in the anterior period of a phase II study of 5-FU/LV therapy for advanced colorectal carcinomas in Japan, a protocol of weekly administration of l-leucovorin showed a higher effective rate than that of 5 consecutive days’ administration of low or high dose leucovorin\(^21\). In the posterior period of the phase II study, 30% of 70 patients who had completed the protocol showed a partial response to the treatment of advanced colorectal carcinoma, but only 17% exhibited

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**Table 3.** Toxicity (percent of patients)

<table>
<thead>
<tr>
<th>Grade</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea/vomiting</td>
<td>8(62)</td>
<td>2(15)</td>
<td>2(15)</td>
<td>0</td>
<td>1(8)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>12(92)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1(8)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>11(85)</td>
<td>1(8)</td>
<td>0</td>
<td>1(8)</td>
<td>0</td>
</tr>
<tr>
<td>Nephrotoxicity</td>
<td>10(77)</td>
<td>1(8)</td>
<td>1(8)</td>
<td>1(8)</td>
<td>0</td>
</tr>
<tr>
<td>Skin rash</td>
<td>11(85)</td>
<td>2(15)</td>
<td>0</td>
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<td>0</td>
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<tr>
<td>Neurotoxicity</td>
<td>13(100)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>4(31)</td>
<td>4(31)</td>
<td>2(15)</td>
<td>3(23)</td>
<td>0</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>2(15)</td>
<td>1(8)</td>
<td>4(31)</td>
<td>4(31)</td>
<td>2(15)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>5(36)</td>
<td>2(15)</td>
<td>3(23)</td>
<td>1(8)</td>
<td>2(15)</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>10(77)</td>
<td>0</td>
<td>1(8)</td>
<td>1(8)</td>
<td>1(8)</td>
</tr>
</tbody>
</table>
partial response at the time the first cycle of the regimen had been completed\textsuperscript{22}. Recently, focusing on the importance of 5-FU scheduling, Guglielmi\textsuperscript{23} have tested the hypothesis that pulse and continuous infusion of the fluoropyrimidine have different mechanisms of cytotoxicity.

We performed PFL-therapy in patients with recurrent colorectal carcinoma who had mostly received previous chemotherapy using 5-fluoropyrimidines and who showed performance status lower than Grade 2. We anticipated optimal effects on colorectal cancer using PFL-therapy because of dual biochemical modulation effect of 5-FU given by LV and CDDP. Moreover, CDDP would strengthen synergistic anticancer effect of 5-FU and LV by DNA damage through intrastrand bridge formation. Characteristic features of our combination chemotherapy were as follows: bolus intravenous injection of low dose LV and 5-FU and drip infusion of low dose CDDP over five days in hospital. We hoped that this protocol would lessen the side effects of such intensive chemotherapy, especially, renal tubular disturbance by CDDP.

Scheithauer studied the 5-FU/LV and the 5-FU/LV/CDDP treatment for unresectable colorectal carcinoma\textsuperscript{24}. The overall responses were 19\% and 28\% for the 5-FU/LV and the 5-FU/LV/CDDP treatment arms, respectively. Although the three-drug combination appeared superior to 5-FU/LV for time to progression or death (8.5 versus 5.2 months; \( P = 0.042 \)), there was no evidence that the adoption of CDDP will translate into a definite survival advantage\textsuperscript{25}. They implied that the addition of CDDP to 5-FU/LV therapy might decrease side effects, since severe stomatitis was obviously decreased in the protocol using three drugs. Our study showed the same prognostic result as his trial in spite of smaller number of treatment cycles and a history of previous chemotherapy.

Recently, some researchers\textsuperscript{26,27,28} have reported effectiveness of three-drug regimens using 5-FU, LV and CDDP for advanced colorectal carcinoma. In most of studies, more than two cycles of the regimen were needed to obtain good results. Moreover, in patients with poor performance status, many dropped out of the protocol. Most of our patients had a performance status worse than Grade 2 and we could complete two cycles of our regimen in six patients. Response rate of our regimen for unresectable or recurrent colorectal carcinoma was 25\%, which was satisfactory as combination intensive chemotherapy for advanced colorectal carcinoma.

Recently, irinotecan became to be used for second-line anticancer drug to advanced colorectal cancer. Irinotecan inactivates topoisomerase I and has no cross-resistance with 5-FU. Data suggest that the development of well-tolerated regimens that combine irinotecan with 5-FU and leucovorin may be beneficial in the first-line treatment of advanced colorectal cancer\textsuperscript{29,30}. However, one weekly regimen combining irinotecan with 5-FU and leucovorin was discontinued by high rate of treatment-related death in 2001.

With regard to side effects with our regimen, patients with severe hematological side effects recovered almost within one week, and the condition of none except for one patient, who received PFL-therapy.
within one month after palliative operation for recurrent rectal cancer and subsequent hepatic arterial infusion of 5-FU, deteriorated because of the chemotherapy. Most cisplatin-induced emesis was prevented by drip infusion of 30mg of granisetron HCl, and stomatitis worse than Grade 2 was relieved by gargling with Foipan gargle and cooling of the oral cavity during the administration of 5-FU. Moreover, no patient experienced severe diarrhea since we began to administer a chemical preparation using daily 750mg of metronidazole and 300mg of ofloxacin.

In respect to performance status, 46% of eligible patients were improved in spite of their poor performance status before treatment. Moreover, when patients were classified into two groups based on changes of the serum level of CEA, “responder in CEA level” showed better prognosis than “non-responder in CEA level”. One patient classified into “responder in CEA level” died of cecum cancer 6 months after treatment in spite of improvement of performance status. We speculated that CEA level might be affected by hematogenous metastases, but this patient deteriorated by peritoneal dissemination without relation to the change of CEA level.

We might be able to use our regimen more effectively for unresectable or recurrent colorectal carcinoma if we could select patients in “responder in CEA level” and administer anticancer drugs according to the chemosensitivity assay.

References


