of this regimen (10 mg/m^2, twice-a-week) was identical to that identified by the previous JFMC27-9902 study. (4 mg/m^2, five times per week) (5). In the JFMC27-9902 trial, three and five patients were treated with 4 mg/m^2 CDDP, five times-a-week (the dosage is identical to Level 2 in the current study) or 6 mg/m^2 CDDP, five times-a-week (corresponding to Level 3 in the current study), respectively. Although none of the three patients treated with 4 mg/m^2 CDDP experienced a DLT, two of the five treated with 6 mg/m^2 CDDP suffered Grade 3 anorexia. Thus, the JFMC27-9902 research team selected a dose of 4 mg/m^2 CDDP for future research. Additionally, Grade 1 anorexia was observed in two out of the three patients treated with 4 mg/m^2 CDDP, but no Grade 2/3/4 anorexia occurred in JFMC27-9902 at this treatment level. In the current JFMC27-9902 Step2 study, Grade 1 anorexia was observed in two out of the eight patients on Level 2 treatment, but Grade 2/3/4 anorexia was not observed in the first cycle. During the twice-a-week administration of 10 mg/m^2 CDDP, two patients (25%) experienced Grade 2 gastrointestinal toxicities during the two cycles. An additional study reported that with the weekly administration of 20 mg/m^2 CDDP, 54% patients suffered Grade 2 gastrointestinal toxicity during the two cycles (4). These results suggest that the mild gastrointestinal adverse events caused by twice-a-week CDDP administration with S-1 may provide adequate safety. Additionally, no other Grade 3/4 non-hematological toxicities were observed at the RD level in the current study.

The present study showed three (37.5%) of the eight patients were assessed at the RD acquired PR. The overall RR in the 13 patients was 23.1%. Therefore, twice-a-week CDDP administration with S-1 may seem to provide lower efficacy, compared with the weekly CDDP administration with S-1 proposed by Hyodo et al. (RR: 61%) (4), the high-dose CDDP administration with S-1 (RR: 74%) (7), and the S-1 mono-therapy (RR: 44–54%) (1–3). However, because the present study was a Phase I trial examining the efficacy of the regimen in such a small number of patients, the estimation of RR was not necessarily reliable. The examination of the RR at the RD is underway in a larger population of patients in the subsequent Phase II trial. With respect to the CDDP concentrations achieved, one report showed that twice-a-week administration of 7 mg/m^2 CDDP maintained a serum CDDP concentration comparable to that attained by 5 weekly doses of 3.5 mg/m^2 CDDP. Additionally, the CDDP concentration attained by the administration of 10 mg/m^2 twice-a-week might be equal to that attained by 4 mg/m^2 five times per week (17). In the ongoing JFMC27-9902 Step2 Phase II study, the pharmacokinetics of CDDP at the RD level determined here (10 mg/m^2, twice-a-week) will be compared with those determined with the 4 mg/m^2, five times per week regimen used in JFMC27-9902.

We applied the CRM to determine a final recommended treatment dose for future Phase II trial(s). In the present study, it took 28 months to enroll all the 13 patients. Although CRM designs have not been used so often because of their longer study duration compared with conventional study designs (18), the long time period for patient enrollment of this study was also due to low patient enrollment rate. The assessment of DLT was carried out during the first treatment course consisting of 6 weeks. Thus, if patients had been treated in cohorts of one and all patients had been consecutively enrolled with no gap, it would have taken at most 20 months to complete a study. In addition, Goodman et al. (18) reported that if one assigns more than one subject at a time to each dose level, the study duration can be reduced by >50% compared with the one-patient/cohort CRM design. Due to the relatively small number of patients enrolled in this study, the confidence intervals for the probability of DLT events at the three treatment levels are not clearly separable. Such uncertainty, however, is typical for Phase I dose-finding trials (19). However, we further performed a sensitivity analysis to estimate the DLT occurrence probabilities under a variety of assumptions to more clearly define the dose-toxicity relationship, and this analysis suggested that treatment Level 2 most closely approximated the study treatment goals. The robust results obtained through the sensitivity analysis supports the validity of the dose recommendation we reached. However, we must continue monitoring both the toxicity and efficacy of the combination regimen in the Phase II trial. A study design simultaneously monitoring both efficacy and toxicity, as proposed by Thall and Cook (20,21), may be useful in this context. Given the small number of patients we studied, despite the CRM algorithm, it is essential that the safety of the combination therapy be evaluated further with a larger patient population. As described in the study protocol, the RR of the RD will be further examined during the subsequent Phase II trial, and we will also monitor toxicity using CRM to reconfirm the safety of the RD (13). The sample size for the Phase II was set at 42.

In conclusion, we demonstrated that the combination regimen consisting of S-1 40 mg/m^2 twice daily for days 1–28 and CDDP 10 mg/m^2 on days 1 and 4 per week for 4 weeks followed by a 2-week washout period should be evaluated further in a Phase II trial in patients with unresectable or recurrent gastric cancer.

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Conflict of interest statement
None declared.

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Continuous Infusion of 5-fluorouracil with Versus without Low-dose, Consecutive Administration of Cisplatin in Advanced Colorectal Cancer. A Prospective Randomized Phase II Study

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Recently, the treatment of advanced gastric cancer by continuous infusion of 5-fluorouracil (5-FU) with low-dose cisplatin (CDDP) has improved efficacy without severe toxicities. The possible effectiveness of 5-FU+low-dose CDDP for colorectal cancer (CRC) is intriguing. One hundred fifty-five patients with far-advanced CRC including at least one measurable lesion were enrolled in a prospective randomized clinical trial funded by the Japanese Foundation for Multidisciplinary Treatment of Cancer. These patients were assigned to the two arms to assess the value of low-dose CDDP when added to a continuous intravenous infusion of 5-FU at a dose of 300 mg/m^2/24 hrs in a one-week cycle consisting of 5 days of treatment and 2 days of rest for at least 12 weeks. CDDP was given intravenously at a dose of 3 mg/m^2 on days 1-5 and days 8-12, and then at a dose of 7 mg/m^2 twice a week. Three patients were excluded from the trial. The response rate in the 5-FU+low-dose CDDP arm (n=75) was significantly higher than that in the 5-FU arm (n=77) (25.3% vs. 11.7%; P = 0.037). There was no significant difference in the median overall survival time between the 5-FU+low-dose CDDP arm and the 5-FU arm (479 and 491 days, respectively). Grades 3/4 toxicities occurred infrequently in both arms. The quality of life was almost the same between the arms. Low-dose CDDP improved the response rate while keeping toxicities within clinically acceptable limits. However, this combined treatment did not confer a survival advantage over treatment with continuous infusion of 5-FU alone for patients with far-advanced CRC; that might be attributable to the short CDDP administration setting of 12 weeks.

Key Words: 5-fluorouracil, Low-dose cisplatin, Colorectal cancer

Phase III trials in patients with colorectal cancer (CRC) demonstrated that continuous infusion of 5-fluorouracil (5-FU) resulted in a significantly higher response rate and reduced myelosuppression compared to bolus 5-FU (1-3). However, there were no statistically significant differences in overall survival between the two treatments. Recently, continuous infusion of 5-FU combined with low-dose and consecutive administration of cisplatin (CDDP) for gastric cancer has been widely used in Japan, and its high efficacy and low toxicity have been recognized (4-6). CDDP enhances the anticancer effect of 5-FU by the following mechanism: CDDP inhibits methionine uptake into tumor cells and decreases the volume of methionine pools in the cells. In response to the lack of methionine pools, the cells may increase methionine biosynthesis and the pools of folate cofactors. The increased 5,10-methylenetetrahydrofolate enhances 5-FU's cytotoxicity by increasing the reduction of thymidylate synthase (TS) to form a ternary complex, in which a 5-FU

metabolite fluorodeoxyuridylate, TS, and CH_2-H_4 folate are tightly bound together (7-9). The Japanese Foundation for Multidisciplinary Treatment of Cancer (JFMC) planned to investigate whether or not the low-dose, consecutive administration of CDDP in association with continuous infusion of 5-FU could confer tumor-suppression and survival advantages on patients with CRC.

Patients and Methods

Patient Selection

Patients between 20 and 80 years of age with a histologic diagnosis of unresectable, noncuratively operated, or recurrent CRC were eligible. Enrollment in the study envisaged an Eastern Cooperative Oncology Group performance status (PS) of 2 or less, a life expectancy of 12 weeks or more, and a measurable disease. Subjects who had received prior adjuvant treatment for CRC were allowed to participate provided they completed the treatment at least 28 days before enrolling in the study. Other eligibility requirements included adequate bone marrow function (Hb 9.0 g/dl or more, white blood cells between 4,000 and 12,000 /μl, neutrophils 2,000/μl or more, platelets 100,000/μl or more), total bilirubin 2.0 mg/dl or less, AST (GOT) and ALT (GPT) 100 IU/l or less, BUN 25 mg/dl or less, serum creatinine 1.5 mg/dl or less, and creatinine clearance 50 ml/min or more. Patients with psychiatric or medical problems rendering them unable to give informed consent were ineligible, as were patients with a serious concurrent, uncontrolled medical condition. The study was approved by the ethics and scientific committees of each participating institution. Each patient provided written informed consent before being randomly assigned to a treatment arm.

Treatment Regimens

Patients were randomized to receive either continuous infusion of 5-FU with low-dose, consecutive administration of CDDP or continuous infusion of 5-FU alone. The latter was considered a control arm against the combination chemotherapy arm in this study to allow us to observe the effect of adding CDDP. In the 5-FU+low-dose CDDP arm, 5-FU was given at a dose of 300 mg/m²/24 hrs as a continuous intravenous infusion by a balloon pump (Baxter Infuser Multiday Type 2C1080KJ, Baxter International Inc., Deerfield, IL, USA) via a subcutaneous reservoir connected to a central venous infusion catheter for 5 consecutive days followed by 2 days of rest. The cycle was repeated every 7 days. CDDP was given at a dose of 3 mg/m² as a 1 hr IV infusion on days 1-5 and 8-12, and then CDDP was given at a dose of 7 mg/m² as a 1 hr IV infusion twice a week at 2- or 3-day intervals. In the 5-FU arm, the 5-FU regimen was the same as that in the combination therapy. Both regimens were continued for at least 12 weeks. Hydration to protect against nephrotoxicity was not given to any patient. No prophylactic administration of anti-emetic agents or granulocyte colony-stimulating factor (G-CSF) was allowed. The patients in both arms were admitted to the hospital for at least two weeks to implant the subcutaneous reservoir, to get practize in the management of the infusional balloon pump, and to observe the adverse effects of the regimens. The rest regimens were carried out on an outpatient basis.

Assessment of Toxicity

Blood counts and biochemical profiles were performed at least once a week. We monitored patients for the occurrence of nonhematologic toxicities such as appetite loss, nausea/vomiting, stomatitis, diarrhea, skin pigmentation, eczema, hand-foot syndrome, and general fatigue. Toxicity during each course was evaluated according to the National Cancer Institute - Common Toxicity Criteria version 2.0.

Dose Modification and Regimen Interruption, Resumption, and Cessation

Doses of 5-FU and CDDP were modified in accordance with the following guidelines. When white blood cells decreased to less than 3000/μl or platelets decreased to less than 75,000/μl, when nonhematologic toxicities reached Grade 2 or higher, or when PS 3/4 occurred, the dose of 5-FU was reduced from 300 mg/m² to 200 mg/m² per day, the dose of CDDP during the first 2 weeks was reduced from 3 mg/m² to 2 mg/m² per day, and the dose of CDDP at 3 weeks or later was reduced from 7 mg/m² to 3 mg/m². Should these dose modifications not reduce the toxicities to their previous levels, the regimen was then interrupted to be resumed as soon as the patient recovered from the adverse effects of the previous doses. The regimen was stopped if the treatment interruption lasted more than 2 weeks, if the disease progressed, if unacceptable levels of toxicity occurred, or if the patient declined further participation.

Evaluation of Response Rate and Survival Data

Lesions noted at baseline and every 4 weeks during treatment were measured by computed tomography, ultrasonography, magnetic resonance imaging,

colonoscopy, and/or barium enema radiography. Objective responses were classified according to the World Health Organization criteria for primary and metastatic lesions as follows. Complete response (CR) was defined as the disappearance of all cancerous lesions for at least 4 weeks. Partial response (PR) required a reduction of 50% or greater in the sum of the cross-product of the maximum perpendicular diameters of all measurable lesions lasting for at least 4 weeks. Progression of disease (PD) was determined if there was a 25% or more increase in the sum of the cross-product of the maximum perpendicular diameters of all measurable lesions, or if a new lesion appeared. Legions not meeting the criteria for response or progression were considered to have stable disease (SD). Patient eligibility and response to treatment were reviewed extramurally. The extramural review was conducted by three clinical oncologists and one radiologist from institutions not participating in the study. Progression-free survival (PFS) meant survival from the date of registration until progression. Overall survival (OS) was measured from the date of registration to the date of death. The follow-up time was measured from the date of registration to the last contact or death. The Response Evaluation Criteria in Solid Tumors (RECIST) was not employed here, because the evaluation method in this protocol had been established before the RECIST criteria were opened to the public in 2000.

Evaluation of Quality of Life (QOL)

The Japanese Quality of Life Research Group has developed a QOL questionnaire suitable for patients who receive chemotherapy (10) the so-called QOL Questionnaire for Cancer Patients Treated with Anticancer Drugs (QOL-ACD). The JFMC has modified the QOL-ACD. This modified version is a 26-item questionnaire covering four categories: daily activity (Question numbers (Q#) 1-6), physical condition (Q# 7-13), mental and psychological status (Q# 14-18), and social activities (Q# 19-23). Q# 24 is a global QOL, which asks about overall QOL. Q# 25 is a face scale. The last item, Q# 26, asks whether or not the patient intends to continue the present treatment. All questionnaires answers,except Q# 24, range from 1 to 5, with higher scores indicating better status. For Q# 24, the patients marked their overall sense of well-being using a linear analog scale, which was transformed to a scale of 0 to 100, with higher scores indicating better status. Patients' QOL was assessed at the base line and 2, 4, 8, and 12 weeks after the day the first treatment was given. In this study, the total score of Q#1 to 23 (with a range of 23 to 115), the linear analog scale of overall QOL (0 to 100), the face scale (1 to 5), and the intention to continue the present treatment (1 to 5) were compared between the 5-FU+low-dose CDDP arm and the 5-FU arm at each assessment time.

Statistical Considerations

The primary endpoint in this trial was response rate. Secondary endpoints were duration of response (DR), PFS, OS, toxic effect, and QOL.

Statistical analyses were carried out at the JFMC data center using Statistical Analysis System software (version 8.2., SAS Institute, Cary, NC, USA). An intent-to-treat analysis was applied. Background factors were compared using the Fisher's exact method and the Mann-Whitney U-test. Objective response was examined using Fisher's exact method. The cut-off dates were August 31, 2004, for overall survival, with a 31-month median potential follow-up time for the entire cohort. DR, PFS, and OS curves were generated by the Kaplan-Meier method, and the log-rank test was used to compare the curves. The Cochran-Mantel-Haenszel test was used to compare proportions of toxicities. QOL scores were analyzed using a repeated measures, mixed effects model (SAS Mixed procedure). All P-values reported were two-tailed. Statistical significance was set at a level of 0.05 except for background or QOL assessments. For background assessment, $P < 0.15$ was considered statistically significant. For QOL assessment of each point, $P < 0.0125$ (Bonferroni correction) was considered significant. The statistical analyses and their interpretations were approved by the JFMC clinical trial committee.

Results

Patient Characteristics

A total of 155 patients from 27 institutions were enrolled in this study between May 2000 and April 2003. Three patients judged ineligible by extramural reviewers were excluded from the analysis. Therefore, 152 patients were analyzed in this study. Two patients, one in each arm, did not receive any protocol treatment after moving to a nonparticipating study site in one case and after a rapid worsening of general status in the other. They were kept in the statistical analyses of antitumor effect and survival data because the results were obtained on an intent-to treatment basis. However, data regarding both these patients were excluded from adverse-effect analysis. The demographic characteristics of the patients are listed in Table I. There were no

Table I - Comparison of clinical characteristics at baseline between 5-FU+low-dose CDDP arm and 5-FU arm

Characteristics	Treatment arm		*P*-value
	5-FU+low-dose CDDP	5-FU	
No. of patients	75	77	
Age median (range)	64 (41-79)	63 (39-79)	0.245
Sex (Male : Female)	49:26	51:26	1.00
Performance status			0.859
0	57	58	
1	16	15	
2	2	4	
Primary tumour location			0.697
Colon	45	41	
Rectum	29	35	
Colon+Rectum	1	1	
Tumour status			0.751
Residual tumour after noncurative operation	40	38	
Recurrent tumour after potentially curative operation	32	35	
Unresectable tumour	3	4	
Site of disease			0.750
local abdominal mass	18	19	
local recurrent mass	9	9	
liver	46	45	
lung	23	26	
brain	2	3	
lymph node	26	22	
peritoneal dissemination	9	12	
skin	0	1	
bone	4	7	
other	5	5	
ascites	5	1	
pleural effusion	0	2	
Number of organs involved			0.309
1	32	38	
2	26	18	
3 or more	17	21	
Differentiation			0.174
Well differentiated	36	23	
Moderately differentiated	32	46	
Poorly differentiated	5	5	
Mucinous carcinoma	2	2	
Adenocarcinoma (cytology)	0	1	
Previous chemotherapy			0.857
Yes	20	22	
No	55	55	

5-FU, 5-fluorouracil. CDDP, cisplatin.

statistical differences in background between the arms, such as age, sex, PS, primary tumor location, tumor status, site of disease, number of organs involved, histological differentiation, or previous chemotherapy. The treatments results after the 12-week regimen are shown in Table II. Although there was no statistical significance between the post-regimen treatments in the two arms, somewhat more patients in the 5-FU arm were treated with 5-FU+low-dose CDDP than in the 5-FU+low-dose CDDP arm.

Table II - Comparison of treatments after protocol regimen between 5-FU+low-dose CDDP arm and 5-FU arm

Characteristics	Treatment arm		*P*-value
	5-FU+low-dose CDDP	5-FU	
Chemotherapy			0.370
oral fluoropyrimidine	13	11	
S-1 (oral DIF)	3	0	
S-1+CDDP(+irinotecan)	1	1	
infusional 5-FU	2	0	
5-FU+low-dose CDDP	7	17	
5-FU+leucovorin	5	4	
5-FU+irinotecan	5	6	
irinotecan	7	5	
irinotecan+CDDP	3	5	
hepatic arterial infusion (5-FU or 5-FU+CDDP)	6	8	
Radiotherapy	4	5	1.000
Immunotherapy	5	3	0.492
Surgery			0.354
Hepatectomy	2	1	
Pneumonectomy	1	3	
Local mass resection	0	1	
Gastrointestinal Bypass	0	2	

5-FU, 5-fluorouracil. CDDP, cisplatin.
DIF, dihydropyrimidine dehydrogenase inhibitory fluoropyrimidine

Compliance

The completion rates of the defined 12-week treatment were 78.7% (59/75) in the 5-FU+low-dose CDDP arm and 71.4% (55/77) in the 5-FU arm (P = 0.351). The major reasons for stopping the regimen were worsening of general status (43.8%; 7/16) and PD (18.8%; 3/16) in the 5-FU+low-dose CDDP arm; in the 5-FU arm, the reasons were PD (54.6%; 12/22), worsening of general status (18.2%; 4/22), and patients' and their families' intents not to continue the regimen (18.2%; 4/22). Catheter troubles, such as occlusion, occurred only in two patients (1.3%).

The median total administration of CDDP in the 5-FU+low-dose CDDP arm was 250 mg/body (maximum; 1330 mg/body). The median total 5-FU administration in the 5-FU+low-dose CDDP arm was 29.3 g/body (maximum 148.5 g/body), and that in the 5-FU arm was 30.0 g/body (maximum, 191.3 g/body); there was no statistical difference in total 5-FU administration between the arms (P = 0.802). Doses were modified for 14 patients (18.7%) in the 5-FU+low-dose CDDP arm and for 3 patients (3.9%) in the 5-FU arm; there was a statistical difference in the dose modification rate between the two arms (P = 0.004).

Efficacy

A statistical difference was observed between the response rate of the 5-FU+low-dose CDDP arm and that of the 5-FU arm (25.3% vs 11.7%; P = 0.037)(Tab. III). No statistical differences between the arms were seen in DR or PFS (Tab. III). The median survival time (MST) of the 5-FU+low-dose CDDP arm was 15.7 months (479 days: 95% confidence interval (CI), 363-593 days) and that of the 5-FU arm was 16.1 months (491 days: 95% CI, 330-596 days); there was no statistical difference between the two arms (Fig. 1, Table III)(P = 0.582).

Toxicity

In the 5-FU+low-dose CDDP arm, neutropenia, anemia, and nausea were the most common effects of toxicity. However, grade 3/4 toxicities were infrequent. The rates of grade 3 neutropenia, anemia, and nausea were 8.1%, 6.8% and 4.1%, and grade 4 toxicity was observed only in thrombocytopenia (1.4%). In the 5-FU arm, grade 3/4 toxicities occurred at very low rates (0 to 3.9%). Statistical differences between the toxicity profiles of the arms were observed in neutropenia, anemia, and nausea (Tab. IV). Anti-emetic agents were

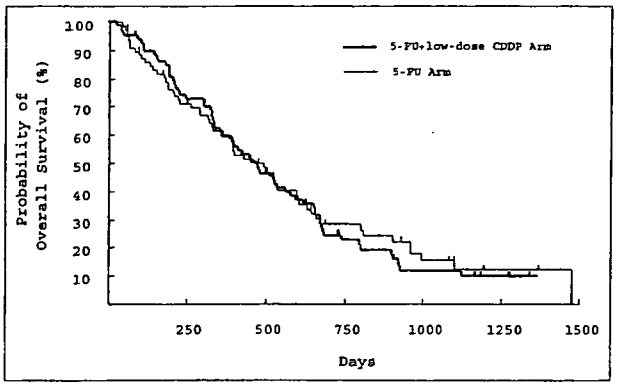

Fig. 1 - Kaplan-Meier curve of overall survival.

given to 31 (41.3%) patients in the 5-FU+low-dose CDDP arm and to 14 (18.2%) patients in the 5-FU arm; this difference was statistically significant (P = 0.002). G-CSF was given to 2 (2.7%) patients in the 5-FU+low-dose CDDP arm, whereas no patients in the 5-FU arm needed to use the agent.

QOL

The rates at which the questionnaire was answered completely and correctly were 78.5% in the 5-FU+low-dose CDDP arm and 86.4% in the 5-FU arm. The total scores in the 5-FU+low-dose CDDP arm tended to be lower than those in the 5-FU arm prior to and during the 12-week regimen, but the difference was not statistically significant. There were no statistically significant differences between the arms in the linear analog scale or the face scale during the 12-week regimen. The intention to continue treatment in the 5-FU+low-dose CDDP arm gradually decreased, whereas that of the 5-FU group was maintained. However, no statistically significant differences were observed except at 4 weeks from randomization (Fig. 2).

Discussion

The effectiveness of chemotherapeutic treatment for CRC has improved substantially in the past decade. In advanced CRC patients with unresectable metastatic lesions treated with 5-FU/leucovorin with oxaliplatin regimen (FOLFOX) or by 5-FU/leucovorin with irinotecan regimen (FOLFILI), response rates and MST of 39-56% and 14.8-21.5 months, respectively, have been reported (11-13). However, high rates of the grade 3/4 toxicities (53-74%) and some therapy-related deaths by these regimens have also been reported (11-

Table III - Comparison of chemotherapeutic effects between 5-FU+low-dose CDDP arm and 5-FU arm

Characteristics	Treatment arm		*P*-value
	5-FU+low-dose CDDP	5-FU	
Total No. of patients	75	77	
Efficacy			0.037
CR	0	0	
PR	19 (25.3%)	9 (11.7%)	
SD	36 (48.0%)	35 (45.5%)	
PD	15 (20.0%)	25 (32.5%)	
NE	5 (6.7%)	8 (10.4%)	
Median duration of response (95% CI)	226 days (185-232)	148 days (91-336)	0.494
Median progression-free survival (95% CI)	178 days (141-256)	131 days (92-197)	0.282
Median overall survival (95% CI)	479 days (363-593)	491 days (330-596)	0.582

5-FU, 5-fluorouracil. CDDP, cisplatin. CR, complete response. PR, partial response. SD, stable disease. PD, progressive disease. NE, not evaluable. CI, confidence interval.

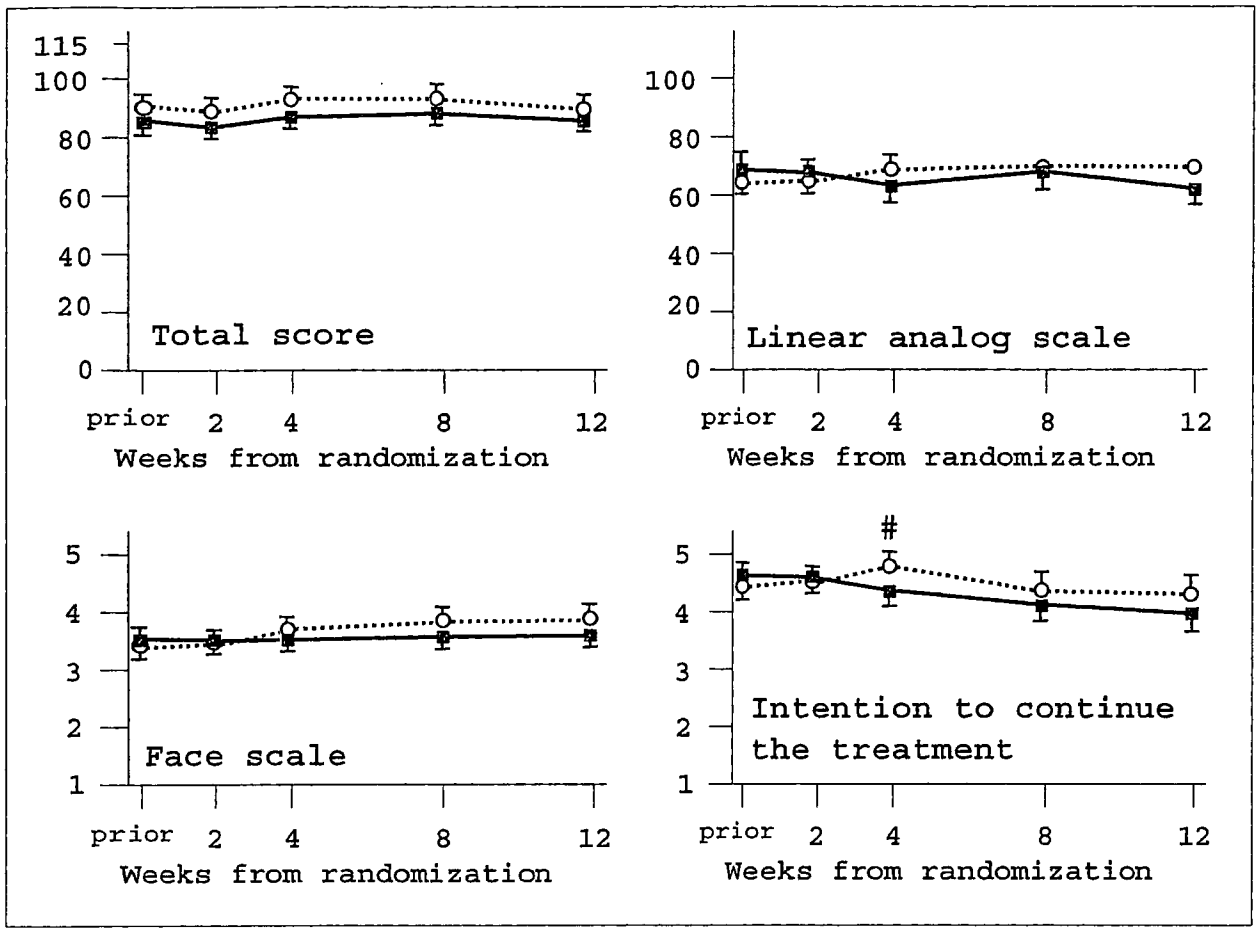

Fig. 2 - Changes in quality-of-life scores. #, P<0.125. ●, 5-FU+low-dose CDDP arm. ○, 5-FU arm.

14). An ideal chemotherapy would provide long survival without severe toxicities or deterioration of QOL.

Three phase III clinical trials comparing continuous infusion of 5-FU versus continuous infusion of 5-FU+low-dose CDDP for CRC are reported in literature (2, 15, 16). In these previous studies, all conducted in the United States, response rates were similar or significantly higher in the 5-FU+CDDP treatment groups than in the 5-FU treatment groups. However, increased toxicity and no improvement in OS were observed in the 5-FU+CDDP treatment group (Tab. V). The dose of CDDP was 20 mg/m^2/day one to five times a week in the previous US trials for CRC, while substantially lower doses (3.5-7.5 mg/m^2/day for five consecutive days per week) were given in the treatment of gastric cancer in Japan (4-6). The JFMC performed the low-dose (1-6 mg/m^2/day) and consecutive administration (five times a week) of CDDP with novel oral fluoropyrimidine S-1 for gastric cancer as a phase I trial, and observed an acceptable level of toxicity as well as a promising degree of efficacy (17). It is interesting that patients with CRC may receive a survival benefit and strong efficacy from a similar very low-dose and frequent administration of CDDP with continuous infusion of 5-FU. In this study, CDDP was given at a dose of 3 mg/m^2 on days 1-5 and 8-12. Five weekly administrations of CDDP are difficult to manage on an outpatient basis. To shorten hospitalization, CDDP was given at a dose of 7 mg/m^2 twice a week at 2- or 3-day intervals in the third week and later. The CDDP dosages in this study were determined on the basis of a previous report; it was demonstrated that the CDDP administration of 7 mg/m^2 twice a week maintained the serum CDDP concentration which was attained by the 5 time administrations of 3.5 mg/m^2 CDDP per week (18).

The backgrounds of the two arms were well bal-

anced in this study (Tab. I). The response rate was significantly higher in the 5-FU+low-dose CDDP arm than in the 5-FU arm. However, contrary to our expectation, survival was not prolonged in the 5-FU+low-dose CDDP arm compared to the 5-FU arm (Tab. III, Fig. 1). These results are consistent with those of the previous phase III studies carried out in the United States; those studies used higher doses of CDDP compared to our regimen (Tab. V). However, MSTs in our series were longer than in the previous trials (Tab. V). Improved survival may be attained by a multidisciplinary therapy including the effective second-line chemotherapies after the 12-week regimen in both arms (Tab. II). Although the addition of CDDP to 5-FU enhanced the adverse effects of neutropenia, anemia, and nausea, it should be noted that grade 3/4 toxicities were rare in both arms (Tab. VI). Therefore, it may be feasible to continue the 5-FU+low-dose CDDP regimen for more than 12 weeks without severe adverse effects. The low toxicities of the continuous infusion of 5-FU with or without CDDP described above were an advantage with respect to the recent standard regimens such as FOLFOX or FOLFILI with or without bevacizumab, a molecular targeting agent. However, the necessity for the patient to carry a balloon pump for most of the treatment period of twelve weeks and to come to hospital for CDDP infusion twice a week may be a disadvantage.For example, in the "FOLFOX6" regimen, the patient is restrained only for 46 hrs with balloon pump infusion of 5-FU and visits hospital at day 1 for infusion of 5-FU/LV and oxaliplatin every course of two weeks.

It was also noteworthy that the response rates of the 5-FU arm in the US studies were higher than that in our study (Tab. V). This difference may be attributable to the evaluation method, particularly with regard to the observation period; in the US studies, the response rates were evaluated every 8-12 weeks until the tumor showed PD or the patient died, whereas in the 12-week regimen of our study the response rate was evaluated every 4 weeks. In other words, if we had continued the regimen for more than 12 weeks in the 5-FU arm, the response rate might have been higher. Further prolongation of survival by more than 12 weeks in 5-FU+low-dose CDDP might also be expected when considering the survival achieved by the 12-week regimen. However, it is also possible that the difference of response rates between the 5-FU arm and the 5-

Table IV - Comparison of chemotherapeutic adverse effects between 5-FU+low-dose CDDP arm and 5-FU arm

Features	% of Patients (5-FU+CDDP vs 5-FU)				*P* value
	Grade 1	Grade 2	Grade 3	Grade 4	
Hematologic					
Neutropenia	16.2 vs 11.8	18.9 vs 3.9	8.1 vs 0	0 vs 0	<.001
Thrombocytopenia	2.7 vs 1.3	2.7 vs 1.3	0 vs 1.3	1.4 vs 0	0.497
Anemia	12.2 vs 13.2	16.2 vs 9.2	6.8 vs 0	0 vs 0	0.015
Nonhematologic					
Nausea	28.4 vs 7.9	6.8 vs 3.9	4.1 vs 2.6	NA	0.012
Vomiting	6.8 vs 6.6	5.4 vs 1.3	0 vs 1.3	0 vs 1.3	0.928
Diarrhea	2.7 vs 3.9	1.4 vs 2.6	1.4 vs 2.6	0 vs 0	0.374
Stomatitis	10.8 vs 11.8	1.4 vs 1.3	0 vs 0	0 vs 0	0.879
Hand-foot syndrome	13.5 vs 7.9	1.4 vs 3.9	0 vs 0	NA	0.952
Eruption/Exfoliation	2.7 vs 1.3	4.1 vs 1.3	0 vs 0	0 vs 0	0.229
Alopecia	2.7 vs 1.3	0 vs 0	NA	NA	0.556
Fatigue	10.8 vs 6.6	8.1 vs 2.6	2.7 vs 2.6	0 vs 1.3	0.407
Arrhythmia	1.4 vs 1.3	0 vs 0	0 vs 0	0 vs 0	0.985
Albumin	16.2 vs 10.5	5.4 vs 2.6	1.4 vs 1.3	0 vs 0	0.241
Total bilirubin	10.8 vs 9.2	4.1 vs 2.6	4.1 vs 0	0 vs 1.3	0.305
AST	16.2 vs 23.7	5.4 vs 2.6	1.4 vs 0	0 vs 1.3	0.768
ALT	6.8 vs 14.5	1.4 vs 1.3	1.4 vs 2.6	0 vs 0	0.203
Creatinine	14.9 vs 5.3	0 vs 3.9	0 vs 0	0 vs 0	0.795

5-FU, 5-fluorouracil. CDDP, cisplatin. NA, not applicable.
Numbers of patients in 5-FU+low-dose CDDP group and 5-FU group were 74 and 76, respectively.

Table V - Randomized trials comparing continuous infusional 5-fluorouracil with or without cisplatin

References	Dose	Response rate			MST (Months)		
		5-FU+CDDP	5-FU	*P*-value	5-FU+CDDP	5-FU	*P*-value
Kemeny (1990)	5-FU 1000 mg/m² days 1 to 5	25% (15/61)	3% (2/59)	0.001	10	12	NS
	CDDP 20 mg/m² days 1 to 5 repeat every 4 weeks						
Lokich (1991)	5-FU 300 mg/m² every day	33% (25/85)	35% (29/83)	NS	11.2	11.8	NS
	CDDP 20 mg/m²	weekly					
Hansen (1996)	5-FU 300 mg/m² every day	31% (47/153)	28% (45/159)	NS	13	13	NS
	CDDP 20 mg/m² weekly						
Present study	5-FU 300 mg/m² days 1 to 5 repeat every week	25.3% (20/75)	11.7% (9/77)	0.037	15.7	16.1	NS
	CDDP 3 mg/m² days 1 to 5, 8 to 12 followed by 7 mg/m² twice a week for 10 weeks						

5-FU, 5-fluorouracil. CDDP, cisplatin. MST, median survival time; NS, not significant.

FU+low-dose CDDP arm in this 12-week regimen might be lost during the longer treatment period than 12 weeks. These speculations should be tested by a further clinical trial.

Recently, the QOL in patients following a chemotherapy regimen has attracted much attention and has been evaluated in clinical trials (11, 12). In the present study, QOL questionnaires answered by the patients themselves were analyzed, whereas the three previous phase III trials of 5-FU+low-dose CDDP for CRC did not use self-reporting questionnaires (2, 15, 16). No statistically significant differences between the arms were found, except for the intention to continue treatment at 4 weeks from randomization. This may mean that the addition of CDDP to 5-FU administration scarcely deteriorated the QOL during the 12-week regimen (Fig. 2).

Taken together, the results indicate that 5-FU+low-dose CDDP for CRC may be given safely and attain moderate tumor reduction. However, this combination chemotherapy did not improve survival and induced slightly higher adverse events, compared to continuous infusion of 5-FU. Taking into account the additional cost of CDDP infusion twice a week, the 5-FU+low-dose CDDP in the short regimen setting of 12 weeks rendered no clinical benefit.

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外来がん化学療法と地域連携

近年，対象患者数の増加や diagnosis procedure combination（DPC）をはじめとする医療状況の変化により，がん化学療法は入院から外来への移行が進んでいる。また一方でがん連携拠点病院の指定などにより，がん化学療法患者の拠点病院への一極集中が強まりつつある。このため，都市圏では増加の一途をたどる患者数に対応するため，また地域では医療資源の不足に対応するために，地域連携は，がん化学療法における重要事項となり，地域医療機関も積極的に受け入れの準備を進めるようになった。

ところが実際の地域連携は思いのほか進んでおらず，このことは多くの拠点病院共通の問題点ともなっている。なぜこういったことが起こっているのだろうか。実際には，地域の病院は，可能な患者は受け入れたいと考えている。それなのになぜ受け入れがうまくいっていないのだろうか。この問題に関しては化学療法のハードルが高いからなどといった声もよく聞かれる。ではハードルが高くなっている原因はなんであろうか。“担当医の個人的関係での連携”の限界や“地域連携室相互のコミュニケーション経験不足”などが理由にあげられているが，実際にはさらに基本的なところに問題点があるように感じられる。

現在の地域連携では，いわゆる“手間のかかる患者さん”の層が多くを占めている一方で，good risk で収益が上がり，“手間のかからない患者さん”は地域連携の対象患者となることは少なく，主治医はそういった患者は連携を行わず手元に置きがちであった。つまり“ハードルが高い患者さん”を連携の主な対象としていたために，連携が進んでこなかったのではないだろうか。

実際，高知医療センターにおける初期の連携時には，種々の理由により連携先に根付かない患者もみられた。しかし連携対象患者のセレクションを行い，“手のかかる患者さんは紹介を延期し，副作用の十分なマネージメントを行ったのち，状況が良くなった患者さんから紹介する”を基本方針として以降は，連携先とのこういった問題点は解消した。「自分がやって楽勝」と思うようでないとなかなか他所ではやってもらえないし，さらには「こんなに楽でいいのかな」と簡単に実績が上げられることを連携先に知ってもらうことで，従来障害となっていたハードルを取り去ることが可能ではないかと思われる。こういったことは従来，拠点病院の担当医が紹介先である連携病院の担当医に「もう少し状況の良い人を紹介してほしい」「もう少し早くに紹介してほしい」と感じていたことと，表裏をなしているのではないだろうか。

地域連携は患者のためのものであり，患者主体の地域連携のために，成熟した連携システムの構築が必須である。連携の担当者はこれらのことを十分に理解したうえで地域連携を開始することが重要である。野球のキャッチボールも，上手な人が教えるときには，取りやすくやさしい球から始め，しだいに速い球を投げるように，地域連携も連携しやすい患者から始め，経験を積み重ねれば，しだいにリスクの高い患者の連携も可能となってくるのではないかと思われる。化学療法に習熟した担当医が連携を指導すれば，早く上手になり，レベルの高い地域連携ができるのは自明の理である。そして“手間のかからない患者さん”でも数多く連携を行うことで，拠点病院の診療は実際楽

になっていくし，連携先は収益も向上し，さらなる受け入れを行ってくれるだけでなく，長期的には紹介患者の増加にもつながるなど，メリットも多いと思われる（図1）。

また一方で，十分な患者教育を行い患者のレベルアップ向上を行うことや，化学療法のマニュアル化などによる拠点病院連携先医療機関のレベルアップや医療情報，ノウハウの共有など必須である（当院では『がん化学療法施行時の検査，有害事象対策の手引き』を作成し，地域へも配布している）。こういったことにより“手間のかからない患者さん”を増加させ，さらに連携が広がっていくことが期待される。

また，連携先医療機関のレベルアップに努め，地域での標準治療の確実な施行を可能とするがん治療の均てん化を推進することで，患者のがん化学療法に対する意識も変わり，「近くにコンビニがあるのにわざわざ遠くのコンビニまで買い物に行くことはない」のと同じように，「標準的化学療法を行うのに，わざわざ遠方のがん拠点病院に毎回受診する必要はない」となってくることが期待される。

いずれにせよ，今後は拠点病院ばかりでなく，地域の医療機関にとってもがん化学療法の地域連携は最重要事項のひとつとなってくると思われる。地域連携室などの整備も進みつつあるが，まずは確実に連携できそうな患者を担当医と連携担当者で選定し，経験を深め，地域連携の基盤構築を進めるべきではないかと感じている。さらには患者，地域および拠点病院の三位一体のレベルアップを行っていくことにより，がん化学療法の地域連携は成熟していくのではないだろうか。

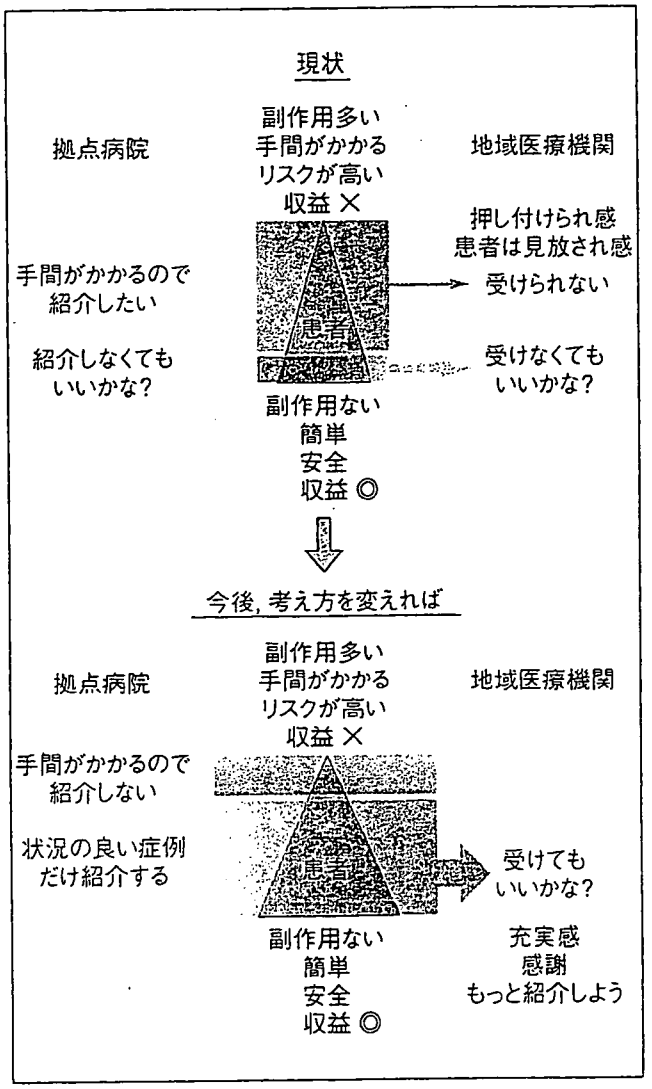

図 1　がん化学療法における地域連携

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