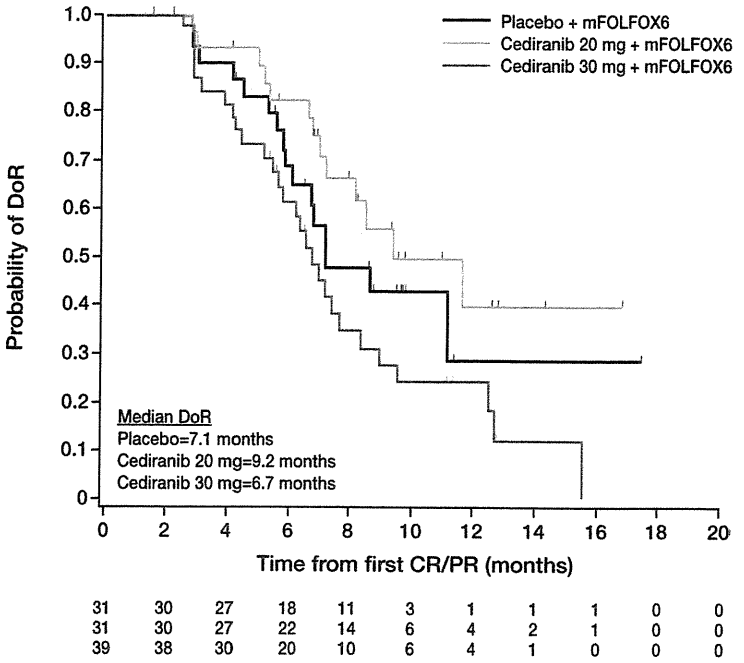

Figure 3. Duration of response for patients who received cediranib 20 mg, cediranib 30 mg or placebo, each in combination with modified FOLFOX6.

Table 3. AEs (frequency ≥30% in any group)

AE, *n* (%)	Cediranib 20 mg + mFOLFOX6 (*n* = 58)	Cediranib 30 mg + mFOLFOX6 (*n* = 56)	Placebo + mFOLFOX6 (*n* = 58)
Diarrhoea	53 (91.4)	49 (87.5)	22 (37.9)
Hypertension	47 (81.0)	48 (85.7)	18 (31.0)
Decreased appetite	43 (74.1)	43 (76.8)	39 (67.2)
Fatigue	39 (67.2)	40 (71.4)	36 (62.1)
Peripheral neuropathy	42 (72.4)	35 (62.5)	38 (65.5)
Nausea	39 (67.2)	37 (66.1)	37 (63.8)
PPES	31 (53.4)	34 (60.7)	8 (13.8)
Stomatitis	33 (56.9)	30 (53.6)	25 (43.1)
Vomiting	24 (41.4)	27 (48.2)	14 (24.1)
Dysphonia	24 (41.4)	16 (28.6)	2 (3.4)
Dysgeusia	18 (31.0)	17 (30.4)	18 (31.0)
Constipation	21 (36.2)	14 (25.0)	16 (27.6)
Alopecia	12 (20.7)	17 (30.4)	15 (25.9)
Epistaxis	15 (25.9)	19 (33.9)	9 (15.5)
Dysphonia	24 (41.4)	16 (28.6)	2 (3.4)

AE, adverse event; mFOLFOX6, modified FOLFOX6; PPES, palmar–plantar erythrodysaesthesia syndrome (hand–foot syndrome).

and to ~130 pg/ml thereafter. In the cediranib 30 mg group, levels increased to 160–170 pg/ml from days 28 to 84 before decreasing to 151 pg/ml by day 112.

Median sVEGFR-2 levels ranged from 9095 to 10 126 pg/ml at baseline. In the placebo group, median levels decreased to 7204 pg/ml on day 112. In the cediranib 20 mg group, median levels decreased to 7091 pg/ml on day 28 and 6403 pg/ml on day 112. The corresponding median levels in the cediranib 30 mg group were 5836 and 5789 pg/ml.

extended follow-up

At second data cut-off, PFS events had been observed in 47 (81%), 46 (82%) and 46 (79%) patients in the cediranib 20 mg, cediranib 30 mg and placebo groups, respectively. The PFS HR for the cediranib 20 mg group versus placebo was 0.76 (95% CI 0.51–1.15), two-sided $P = 0.0879$. Median PFS was 10.9 and 8.3 months, respectively. In the cediranib 20 mg group, 40.5% of patients were event free at 12 months compared with 28.9% in the placebo group. The PFS comparison for cediranib 30 mg versus placebo was 0.96 (95% CI 0.64–1.46), two-sided $P = 0.429$. Median PFS was 9.8 and 8.3 months, respectively, and 36.1% of patients were event free at 12 months in the cediranib 30 mg group versus 28.9% in the placebo group.

At final data cut-off, 24 (41.4%), 27 (48.2%) and 23 (39.7%) patients had died in the cediranib 20 mg, cediranib 30 mg and placebo groups, respectively. For the comparison of cediranib

Table 4. CTC grade 3/4 AEs (>5% frequency in any arm)

AE, *n* (%)	Cediranib 20 mg + mFOLFOX6 (*n* = 58)	Cediranib 30 mg + mFOLFOX6 (*n* = 56)	Placebo + mFOLFOX6 (*n* = 58)
Decreased appetite	11 (19.0)	10 (17.9)	1 (1.7)
PPES	8 (13.8)	12 (21.4)	0
Diarrhoea	6 (10.3)	12 (21.4)	1 (1.7)
Hypertension	4 (6.9)	6 (10.7)	1 (1.7)
Peripheral neuropathy	5 (8.6)	3 (5.4)	2 (3.4)
Peripheral sensory neuropathy	2 (3.4)	5 (8.9)	2 (3.4)
Neutropenia	3 (5.2)	0	0
Ileus	0	0	3 (5.2)

AE, adverse event; CTC, Common Terminology Criteria; mFOLFOX6, modified FOLFOX6; PPES, palmar–plantar erythrodysaesthesia syndrome (hand–foot syndrome).

20 mg versus placebo, the HR was 1.09 (95% CI 0.61–1.95), two-sided $P = 0.543$; median OS was not reached in the cediranib 20 mg group. For the comparison of cediranib 30 mg versus placebo, the HR was 1.28 (95% CI 0.73–2.24), two-sided $P = 0.706$. Median OS was 22.4 and 23.3 months in the cediranib 30 mg and placebo groups, respectively.

discussion

Patients enrolled in this study were representative of the target population of Japanese patients with previously untreated mCRC and consistent with previous studies [26, 27]. Although baseline characteristics were generally well balanced across the three groups, imbalances were noted. The imbalances in ALP and albumin levels probably occurred because the data were analysed at a central laboratory, whereas stratification according to baseline liver function was carried out in individual centres.

The median PFS of patients who received mFOLFOX6 alone in this study (8.3 months) was consistent with the SWIFT-2 (8.2 months) [27] and TREE-1 (8.7 months) [28] studies, in which patients received mFOLFOX6 as first-line treatment of mCRC. Furthermore, the median PFS of patients in this study who received cediranib 20 mg plus mFOLFOX6 (10.2 months) compares well with the time to progression (9.9 months) for patients who received bevacizumab plus mFOLFOX6 in the TREE-2 study [28]. It is worth noting that TREE-2 was conducted in non-Japanese patients and there is a lack of phase III data for bevacizumab plus FOLFOX in the first-line setting in Japanese mCRC patients. A recent phase I/II study of first-line therapy comprising capecitabine plus oxaliplatin (XELOX) and bevacizumab in 64 Japanese patients with mCRC revealed a median PFS of 11 months, although the primary end points of this study were safety and ORR [29].

Here, the higher response rate observed in patients treated with cediranib 30 mg compared with the other arms did not translate into prolonged PFS, possibly due to differences in tolerability profiles of the cediranib arms. More patients in the cediranib 30 mg group experienced AEs (in particular, grade 3/4 diarrhoea) that led to discontinuation, dose reduction or dose interruption, than in the cediranib 20 mg or placebo groups. This appeared to impact on chemotherapy delivery—patients in the 30 mg arm received a lower dose intensity of oxaliplatin, which may reflect the differences in PFS outcomes. Due to these differences in tolerability, results from this study suggest that cediranib 20 mg is more suitable than 30 mg for long-term dosing in combination with mFOLFOX6 in Japanese patients with previously untreated mCRC. Cediranib 20 mg plus mFOLFOX6 was generally well tolerated, although the incidence of SAEs was higher compared with the placebo group. The most frequently reported AEs for the combination of cediranib 20 mg and mFOLFOX6 were diarrhoea and hypertension. The >50% incidence of palmar–plantar erythrodysaesthesia syndrome (hand–foot syndrome) in patients who received cediranib is consistent with a previous phase I study of cediranib monotherapy in Japanese patients and with studies of other targeted agents in Japanese patients with advanced cancer [30, 31]. Overall, no new safety issues were identified; no fatal AEs occurred and the AE profile was consistent with previous cediranib studies [10, 15]. With the exception of hypertension, diarrhoea, proteinuria, hypothyroidism, reversible posterior leukoencephalopathy syndrome, fatigue, hepatotoxicity, haematological toxicity and thrombocytopenia (for which specific management protocols were employed), cediranib-associated AEs were managed by dose interruption of up to 14 days or, if longer, treatment discontinuation. The incidences of grade ≥3 AEs and SAEs observed in this trial following addition of a TKI to FOLFOX therapy are consistent with those reported in trials involving vatalanib and bevacizumab in combination with a FOLFOX regimen [23, 32]. Cediranib treatment has shown a less favourable AE profile compared with bevacizumab in Western patients in the HORIZON III study [23]. In a phase I/II study in Japanese mCRC patients treated with XELOX plus bevacizumab, the most common grade 3/4 AEs were neurosensory toxicity (17%) and neutropenia (16%), both of which were managed by dose reduction of XELOX components; the incidence of grade 3/4 diarrhoea was only 3% [29]. It is not clear why the toxicity profiles of cediranib and bevacizumab differ, but it is probably related to differences in mechanism of action; cediranib is a potent inhibitor of the three VEGF receptor tyrosine kinases, whereas the activity of bevacizumab is dependent on preventing VEGF from binding to VEGF receptors, rather than blocking the receptors directly. In addition, the potential contribution of cediranib activity

versus non-VEGFR kinases, e.g. c-Kit inhibition [33], cannot be excluded. Furthermore, cediranib undergoes extensive metabolism, so it is possible that one or more metabolites may add to the toxicity profile.

An assessment of the levels of the soluble biomarkers VEGF and sVEGFR-2 was conducted as an exploratory objective. Owing to the limited data, caution should be taken when drawing conclusions from these findings; however, the observed increase in VEGF levels and decrease in sVEGFR-2 levels in cediranib-treated patients are consistent with previous cediranib trials [10, 21]. The increased VEGF levels may represent an acute stress response to inhibition of VEGF signalling by cediranib, whereas changes in sVEGFR-2 levels could be a surrogate marker for biological activity.

Analysis with an additional 8 months of follow-up data revealed similar findings to the pre-specified protocol analysis in both efficacy and safety outcomes. This additional analysis confirmed that PFS in this study (HR = 0.76) is consistent with the HORIZON II study (HR = 0.84), in which significantly improved PFS was observed with the addition of cediranib 20 mg to standard chemotherapy (FOLFOX/XELOX) [22].

This study met its primary end point for improved PFS with cediranib 20 mg plus mFOLFOX6 compared with placebo plus mFOLFOX6. The outcomes from this study, and from HORIZON II [22] and HORIZON III [23], provide some understanding of the potential role of VEGFR TKIs in the management of previously untreated mCRC. In unselected patient populations, cediranib provided marginal clinical benefit when added to standard oxaliplatin-based chemotherapy. These data did not support further development of cediranib in CRC; however, further investigation may reveal a particular benefit in a more selective patient population.

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disclosure

KY has received speaker fees (Merk Serono and Chugai Pharmaceutical). XS and KF are employees of AstraZeneca and own stock. All other authors have no conflicts of interest to declare.

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Multi-center Phase II Study of FLOX for Advanced Colorectal Cancer Patients in Japan: SWIFT 3 Study

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Abstract. *Aim: This is a multicenter phase II study to assess the efficacy and toxicity of the 5-FU, leucovorin, and oxaliplatin (FLOX) (SWIFT 3) regimen in Japanese patients with advanced colorectal cancer (CRC). Patients and Methods: Fifty-two patients were enrolled and evaluated from 12 institutions. The median age was 66 years, with 40.4% of patients with colon cancer and 59.6% with rectal cancer. Results: Forty-one patients underwent chemotherapy for first-line therapy and 11 patients for second-line. The response rate for first-line was 46.3% and that for second-line was 9.1%. The response rates categorized by metastatic sites were 59.4% for liver, 33.3% for lung, and 22.2% for lymph nodes. Grade 3/4 neutropenia occurred in 21.2% and Grade 3/4 non-hematologic toxicity in 46.1%. There were no deaths within 60 days following the administration. Conclusion: Standard FLOX regimen can be administered for Japanese patients. It is suggested that FLOX is an appropriate option for adjuvant therapy in CRC.*

In the past decade, significant progress has been made in the treatment of colorectal cancer (CRC), and it is one of the few malignant cancer types in which the 5-year survival rate for patients has improved. For many years, the treatment of metastatic CRC was restricted to 5-fluorouracil (5-FU) and the biomodulation of this agent (1, 2).

Oxaliplatin and irinotecan combined with continuous infusion of 5-FU significantly improved response rates, progression-free survival (PFS), and overall survival for CRC treatment (3, 4).

Oxaliplatin and irinotecan given with 5-FU and leucovorin (LV) are now standard chemotherapeutic agents for the treatment of advanced CRC (4-6). The National Surgical Adjuvant Breast and Bowel Project (NSABP) launched Protocol C-07 in 2000. This trial was designed to compare oxaliplatin and bolus 5-FU/LV to bolus 5-FU/LV alone (FLOX versus FULV, Roswell Park regimen (7) for resected stage II and III CRC). The results from this study confirmed the superiority of an oxaliplatin-based regimen in the adjuvant treatment of CRC. However, little is known about the feasibility of FLOX (SWIFT 3) regimens for advanced CRC in the Japanese population. Phase II studies of FOLFOX4 (SWIFT 1) and studies with modified FOLFOX6 regimens (SWIFT 2) for advanced CRC were conducted. The overall response rate was 50.9% (55.6% in SWIFT 1 and 46.6% in SWIFT 2) and toxicity was tolerable (8). To evaluate the value of FLOX (SWIFT 3) regimens in the treatment of advanced CRC, a retrospective analysis study was designed to assess the feasibility and efficacy of combining oxaliplatin with the LV5FU2 schedule (3) in a Japanese population. We therefore conducted a feasibility study of FLOX (SWIFT 3) in Japan.

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Key Words: Chemotherapy, FLOX regimen, metastatic colorectal cancer, phase II study, 5-FU, leucovorin, oxaliplatin.

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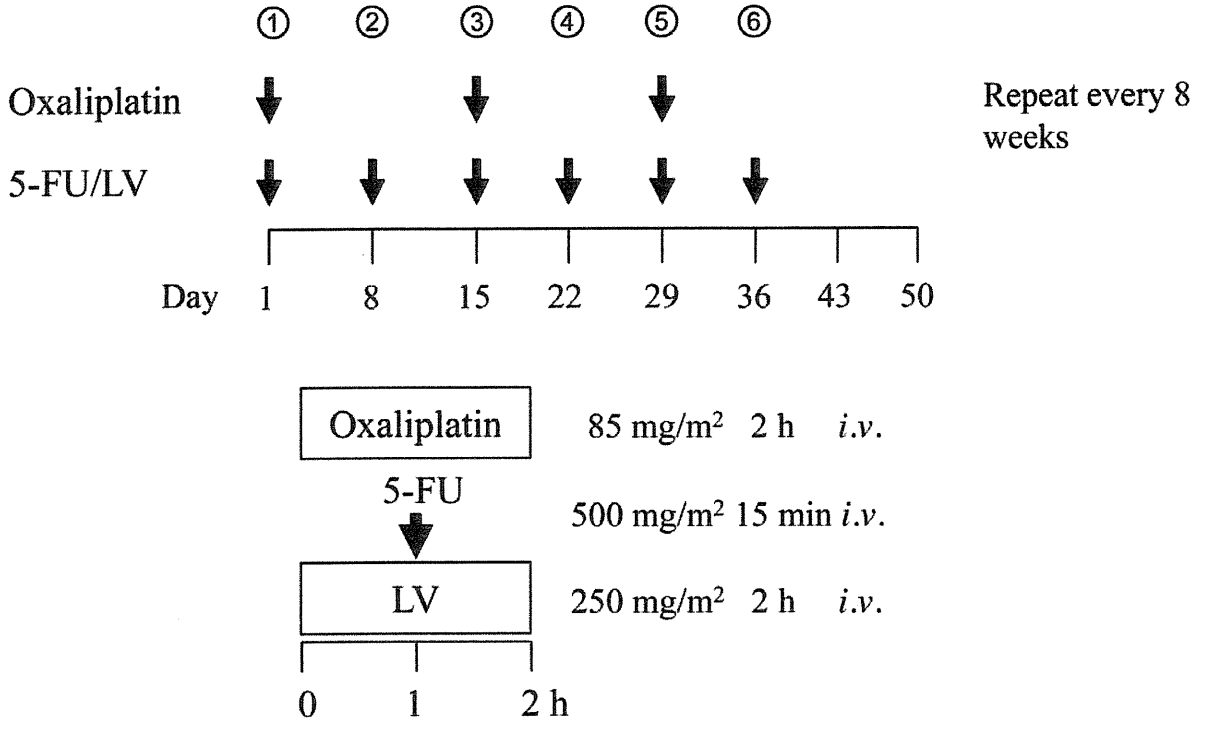

Figure 1. *Chemotherapy regimen of FLOX (SWIFT 3).*

Patients and Methods

Eligibility. Patients in this study had histologically proven metastatic CRC with measurable lesions; additionally, patient inclusion criteria were as follows: i) age of 20 to 80 years; ii) maximum of one prior chemotherapy regimen for metastatic disease and/or one adjuvant chemotherapy regimen completed 4 weeks before the current study; iii) Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 1; iv) life expectancy of more than 2 months; v) adequate bone marrow function (leukocyte count >3,000/mm^3, platelet count >100,000/mm^3, and hemoglobin >8.0 g/dl); adequate renal function (creatinine clearance >50 ml/min), adequate hepatic function (total bilirubin <1.5 mg/dl and Aspartate aminotransferase (AST), Alanine aminotransferase (ALT) < triple the normal upper limit); vi) no other severe medical condition; vii) no active cancer in other organs. All patients gave written informed consent, conforming to institutional guidelines, indicating that they were aware of the investigational nature of the study. This study was approved by the Ethics Committees of the participating institutions.

Treatment. To prevent adverse effects of the chemotherapy, pre-medication was administered, consisting of dexamethasone (16 mg, *i.v.*) for hypersensitivity and cimetidine (50 mg, *i.v.*) for peptic ulcer given 30 min before each administration. One shot of LV was given as a 2-hour drip infusion with a dose of 250 mg/m^2 weekly, with 5-FU administered as an *i.v.* bolus 1-hour after the LV infusion was begun at a dose of 500 mg/m^2 on days 1, 8, 15, 22, 29 and 36 of the treatment cycle, followed by a 2-week rest period. Oxaliplatin

Table I. *Patient characteristics.*

Parameter	No. of patients	%
	52	
Gender		
Male	28	53.8
Female	24	46.2
Age, years		
Median	66	
Range	47-78	
Performance status (ECOG)		
0	42	80.8
1	10	19.2
Primary cancer site		
Colon	21	40.4
Rectum	31	59.6
Site of metastases		
Liver	32	61.5
Lung	15	28.8
Lymph node	9	17.3
Prior treatment (colorectomy)		
Yes	41	78.8
Previous adjuvant chemotherapy		
Yes	11	21.2
Median number of courses		
Range	1-8	
Average	2.64	

Table II. *Toxicity due to FLOX therapy.*

Toxicity*	No. of patients (n=52) (%)					
	G0	G1	G2	G3	G4	G3 and 4
Leucocytopenia	21	12	17 (32.7%)	2 (3.8%)	0	2 (3.8%)
Neutropenia	29	2	10 (19.2%)	9 (17.3%)	2 (3.8%)	11 (21.2%)
Anemia	7	31	14 (26.9%)	0	0	0
Thrombocytopenia	18	21	10 (19.2%)	3 (5.8%)	0	3 (5.8%)
AST elevation	22	25	2 (3.8%)	3 (5.8%)	0	3 (5.8%)
ALT elevation	28	21	3 (5.8%)	0	0	0
Anorexia	18	22	6 (11.5%)	6 (11.5%)	0	6 (11.5%)
Nausea	25	18	7 (13.5%)	2 (3.8%)	0	2 (3.8%)
Vomiting	41	7	2 (3.8%)	2 (3.8%)	0	2 (3.8%)
Diarrhea	29	7	5 (9.6%)	11(21.2%)	0	11(21.2%)
Stomatitis	44	8	0	0	0	0
Hand-foot syndrome	41	11	0	0	0	0

AST: Aspartate aminotransferase; ALT: alanine aminotransferase; *according to NCI-CTCAE v3.0.

was administered in the experimental regimen as a 2-hour infusion with a dose of 85 mg/m^2 prior to LV and 5-FU on days 1, 15, and 29 of the treatment cycle (Figure 1). Administration of granulocyte-colony stimulating factor (G-CSF) was permitted when leukopenia or neutropenia of grade 4 occurred. This administration was continued until the leukocyte or neutrophil counts recovered to 10,000/μl or more or 5,000/μl or more, respectively.

Patient evaluation and follow-up. Pretreatment evaluation included a baseline medical history and physical examination, in addition to laboratory studies, chest X-ray, and electrocardiogram. Computed tomography (CT) and magnetic resonance imaging were performed to clarify and document the location, size, and extent of disease, when measurable. A complete blood cell count, urinalysis, electrolytes, and renal and liver function tests were evaluated at least once weekly and before subsequent cycles, and at the end of patient participation in the study.

Response to treatment and adverse events. Treatment response was assessed using Response Evaluation Criteria in Solid Tumors (RECIST) (9). A complete response (CR) was defined as the disappearance of all clinical evidence of tumor for a period of at least 4 weeks. A partial response (PR) was defined as a 30% decrease in bi-dimensional tumor measurements for at least 4 weeks, without the appearance of any new lesions or progression of any existing lesions. Progressive disease (PD) was defined as the development of any lesion or a 20% increase in the sum of the products of all measurable lesions. Stable disease (SD) was defined as a tumor response that did not meet the criteria for CR, PR or PD. Toxicities were evaluated based on the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 3, and peripheral sensory neuropathy was graded by following the Neurotoxicity Criteria of Debiopharm (DEB-NTC). During treatment, patients had weekly hematological blood cell counts, evaluation of hepatic and renal function, and assessment of non-hematological toxicities. Dose modification and treatment delay were performed as necessary according to the degree of hematological and organ toxicity.

Table III. *Neurologic toxicity due to FLOX therapy.*

Neurologic toxicity	No. of patients (n=52) (%)				
	G0	G1	G2	G3	≥G3
NCI-CTCAE	17 (32.7)	26 (50.0)	9 (17.3)	0 (0)	0 (0)
DEB-NTC	18 (34.6)	20 (38.5)	13 (25.0)	1 (1.9)	1 (1.9)

NCI-CTCAE: v3.0; DEB-NTC: oxaliplatin-specific scale. There were no G4 neurologic toxicities.

Statistical analysis. The primary endpoint of this study was the response rate to the FLOX regimen for advanced or metastatic CRC. Overall survival (OS) and progression-free survival (PFS) were secondary endpoints. OS was calculated from the start of the study registration until death. PFS was calculated from the start of registration until the date of progression. OS and PFS curves were obtained using the Kaplan-Meier method.

Results

Patient characteristics. A phase II study on FLOX (SWIFT 3) was initiated in patients with unresectable, advanced, and recurrent colorectal cancer in October 2006 as a multicenter cooperative clinical trial (by the SWIFT study group). Enrollment was completed in April 2008 with 52 patients with evaluable lesions from 12 medical institutions. The characteristics of all 52 patients are summarized in Table I. Twenty-eight patients were males and 24 females. The median age was 66 (range 47-78) years. Forty-two patients had ECOG PS 0, and 10 patients had PS 1. Eleven patients (21.2%) had received adjuvant chemotherapy. Major metastatic sites were liver (32 patients), lung (15 patients) and lymph nodes (9 patients).

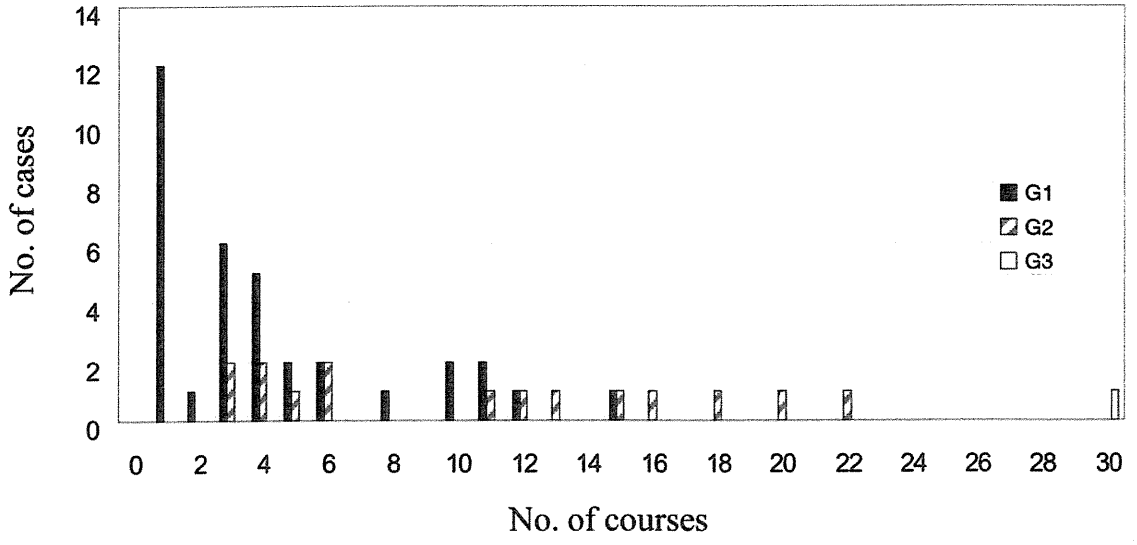

Figure 2. *Incidence of neuropathy during FLOX therapy.*

Toxicity. All 52 patients were fully evaluated for adverse reactions. Toxicities associated with treatment are listed in Table II and the incidence of neurotoxicity is listed in Table III. In this regimen, Grade 3 or more severe hematological toxicity included leukopenia, neutropenia and thrombocytopenia in 3.8%, 21.2% and 5.8% of patients, respectively. Grade 3 or greater non-hematologic toxicity included diarrhea and appetite loss in 21.2% and 11.5% of patients, respectively. Grade 2 or greater neurotoxicity, a characteristic adverse reaction of oxaliplatin, was 17.3% (9/52) by NCI-CTCAE and 26.9% (14/52) by DEB-NTC. Both hematological and non-hematological toxicities were tolerated. The incidence of neurotoxicity along with the number of treatment cycles is listed in Figure 2. Grade 1 neurotoxicity developed from the first treatment cycle. Grade 1 neurotoxicity was observed in 12 patients (23.1%) from the first cycle in SWIFT 3. In the third or later cycles, grade 2 neurotoxicity was frequently observed. The median relative dose intensities (RDI) in this trial were 91% for oxaliplatin, 87% for LV, and 86% for bolus 5-FU in SWIFT 3 (Table IV). Six patients (11.5%) were withdrawn from the study because of adverse events in SWIFT 3.

Efficacy. Overall, of 52 evaluable patients, the median number of treatment cycles was 2.64 (range 1-8 cycles). Objective responses are listed in Table V. Twenty patients had PR (38.5%) and 18 patients had SD (36.5%); 10 patients had PD (19.2%) as the best response and 4 patients could not be evaluated (7.7%). The objective response rate was 38.5% (95% confidence interval, CI=19.9% to 45.4%) to FLOX (SWIFT 3). The response by metastatic sites with a response rate (CR+PR) were 59.4% (19/32) in liver, 33.3% (5/15) in lung and 22.2% (2/9) in lymph nodes. The median PFS was 6.8 months (Figure 3) and the median OS was 25.5 months (Figure 4).

Table IV. *Relative dose intensity (RDI) (SWIFT 3).*

RDI (%)	Oxaliplatin	Leucovorin	5-Fluorouracil
Median	91	87	86
Min	53	47	43
Max	133	114	114

Discussion

The base of standard therapies to treat advanced CRC is oxaliplatin plus 5-FU/LV therapy (FOLFOX regimen) or irinotecan plus 5-FU/LV therapy (FOLFIRI regimen) (3, 5, 10). Phase III randomized controlled clinical trials have shown that combination therapies including irinotecan or oxaliplatin had a much better response rate and PFS period than 5-FU/LV (5, 11-13). Thus, these combinations replaced 5-FU/LV as the standard systemic treatments for metastatic advanced CRC. Additional molecular-targeting therapies and mean survival time (MST) after these therapies currently exceeds 20 months (14, 15). Additionally in Japan, infusion 5-FU/LV therapy was approved in February 2005, and the FOLFOX therapy became available. Phase II trials had been conducted in Japanese patients with advanced CRC to examine the combination therapies using FOLFOX4 or

Table V. *Response.*

	No. of patients (%)					
	CR	PR	SD	PD	NE	Response rate
All	0 (0)	20 (38.5)	18 (36.5)	10 (19.2)	4 (7.7)	20/52 (38.5)
First-line	0 (0)	19 (46.3)	13 (31.7)	7 (17.1)	2 (4.9)	19/41 (46.3)
Second-line	0 (0)	1 (9.1)	5 (45.5)	3 (27.3)	2 (18.2)	1/11 (9.1)

Table VI. *Comparison with other studies.*

	FLOX in first-line	FOLFOX4 in first-line				mFOLFOX6 in first-line		
	SWIFT3 Present study	SWIFT1 Nagata (8)	C95-1 de Gramont (3)	N9741 Goldberg (5)	OPTIMOX1 Tournigand (19)	SWIFT2 Nagata (8)	OxMdG Cheeseman (20)	FOCUS Seymour (21)
No. of patients	52	54	210	267	311	58	25	299
Age, years								
Median	65.87	62	63	61	65	63	62	64
Range	47-78	25-74	20-76	27-88	29-80	25-75	14-77	56-69
PS, %								
0	42	77.8	43.3	93	52	77.6	40	41
1	10	20.4	46.2	93	48	22.4	44	50
2	0			5	48		16	8
Metastatic site, %								
Liver	32	81.5	86.7	Unknown	71	70.7	Unknown	Unknown
Lung	15	22.2	23.4	Unknown	26	19.0	Unknown	Unknown
Others	15	27.8	12.4	Unknown	10	29.3	Unknown	Unknown
Adjuvant chemotherapy, %		24.1	20	16	22	20.7	24	Unknown
RR, %	38.5	55.6	50.7	45	58.5	46.6	72	56.2
PFS, months	6.8	9.4	9	8.7	9	8.5	10.6	9.1
OS, months	25.5	20.2	16.2	19.5	19.3	21.6	16.7	15.2

mFOLFOX6 (SWIFT 1&2) (8, 16). Adjuvant chemotherapy of oxaliplatin and bolus 5-FU/LV therapy (FLOX) has been performed. This regimen poses few difficulties when compared with continuous infusion chemotherapy (17). FLOX therapy does not require a central venous catheter and can be administered through a peripheral vein. It can be concluded that FLOX is an appropriate adjuvant therapy regimen for colon cancer (18). However, little is known about the feasibility of oxaliplatin and bolus 5-FU/LV regimen (FLOX) with advanced CRC in Japanese patients. Thus, this multicenter phase II clinical trial of FLOX was conducted to examine the feasibility in actual clinical practice.

This trial enrolled a total of 52 patients with evaluable lesions who were treated with FLOX (SWIFT 3). The overall response rate was 38.5% and the overall MST was 25.5 months, and the overall PFS was 6.8 months in SWIFT 3. These results are comparable to those reported in other regimens (3, 5, 19-21) and the study by Shimizu *et al.* (18). There was no significant difference in SWIFT 1 and 2 (8) (Table VI). It appears that FOLFOX and FLOX are similar in terms of efficacy. In this trial, many patients had liver metastases, and the response rate in the patients with liver metastasis was 59.4%, which was the highest value among patient groups by site of metastasis. This strongly suggests that FLOX therapy is effective and useful as an initial therapy in patients with liver metastases.

As for adverse reactions, the incidence of grade 3 or greater adverse events were 3.8% for leukopenia, 21.2% for neutropenia, and 0% for anemia. In this study, the FLOX regimen appeared to have reduced toxicity compared with previous reports of other regimens (3, 5, 19-21). The mean number of cycles administered to the patients was 2.6 (range 1-8) in the FLOX regimen. The incidence of grade 2

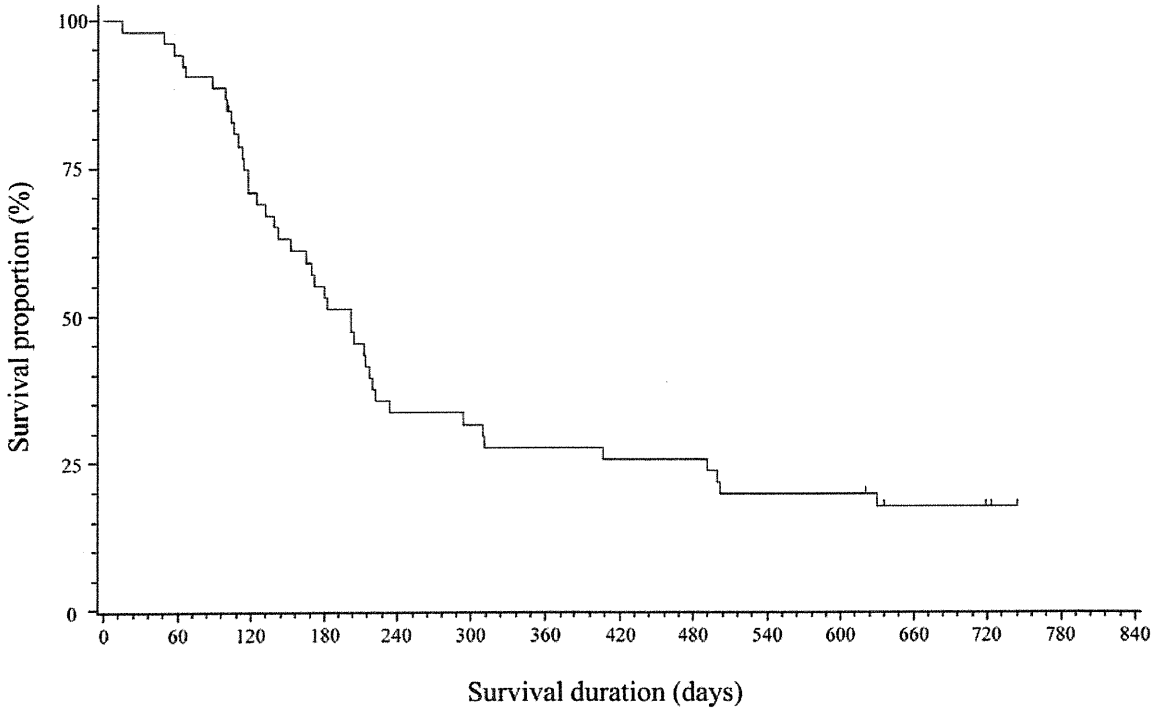

Figure 3. *Progression-free survival rate of all enrolled patients. The median progression-free survival time was 6.8 months in SWIFT 3.*

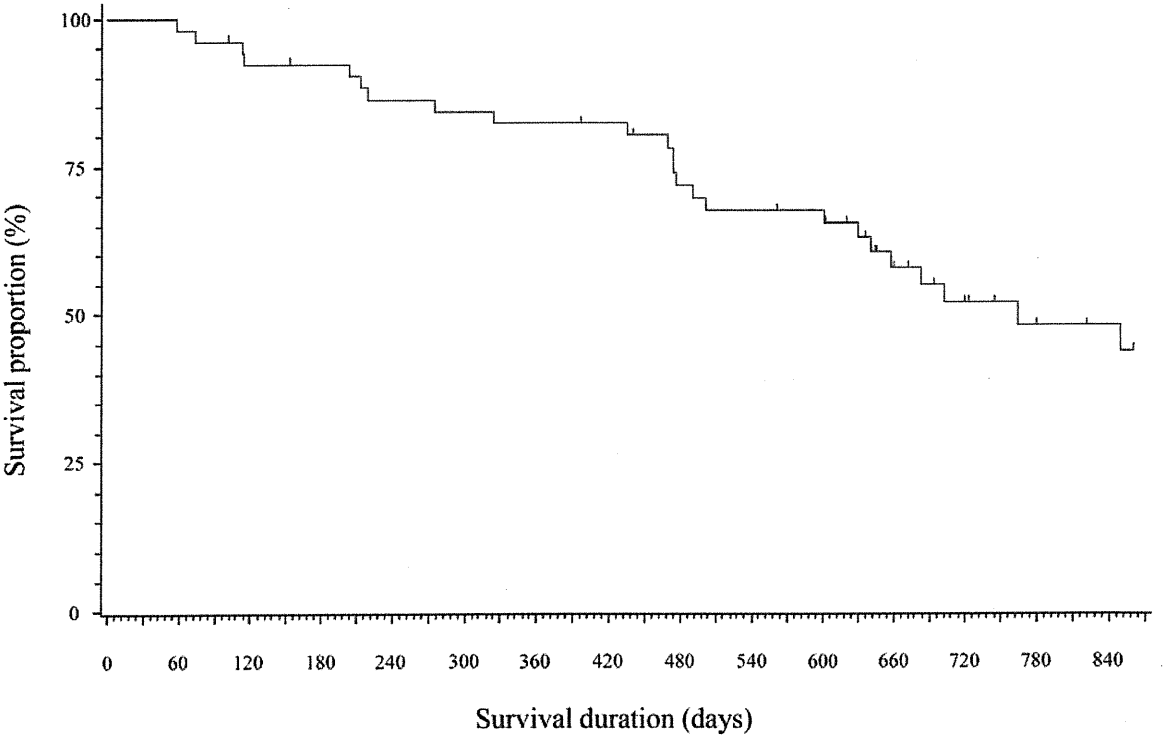

Figure 4. *Overall survival rate of all enrolled patients. The median survival time was 25.5 months in SWIFT 3.*

and grade 3 peripheral neuropathy, a characteristic adverse reaction to oxaliplatin, was 17.3%/0% by NCI-CTCAE and 25%/1.9% by DEB-NTC. In Western countries, the incidence of grade 2 and 3 peripheral neuropathy was reported as 29.2%/18.2% after the FOLFOX 4 therapy as the initial therapy (10, 19-21). Although a direct comparison is not appropriate, a higher incidence of grade 3/4 peripheral neuropathy occurred in FOLFOX-treated patients (18.2%) than FLOX-treated patients (1.9%). The significantly lower incidence of peripheral neuropathy seen in SWIFT 3 was likely a result of the lower cumulative dose of oxaliplatin given. Grade 1 peripheral neuropathy developed from the first cycle, and there was no difference in its frequency between FLOX and FOLFOX. In the third or later cycles, however, grade 2 and 3 peripheral neuropathy frequently developed. The grade of the disorder was higher in later courses as reported by de Gramont *et al.* (3). However, the toxicity profiles are different. These differences reflect both the different methods of administration of 5-FU and LV, as well as the addition of oxaliplatin. The rate of grade 3 or 4 diarrhea was 1.7% with SWIFT 1 and 2 versus 22.1% with SWIFT 3. Even though treatment-related mortality was not increased, clinicians using the FLOX regimen should be aware of the potential for severe diarrhea, select patients accordingly, carefully monitor patients (particularly during the first cycle of therapy), and provide vigorous supportive therapy if diarrhea occurs.

The relative dose intensities (RDI) in this trial were 91% for oxaliplatin, 86% for bolus 5-FU, and 87% for LV in FLOX. Factors for RDI decrease included hematotoxicity (leukopenia, neutropenia, and thrombocytopenia) and peripheral nerve disorder in this study. Response rates, PFS, MST and safety of FLOX combination therapies were equivalent in our multicenter phase II clinical trial, and were rather better than those reported from foreign trials and the SWIFT 1 and 2 studies. Although a direct comparison is not appropriate, these results are considered as almost comparable to those from FOLFOX (SWIFT 1 and 2).

The clinical trial demonstrated that FLOX therapy is as effective and safe in Japanese patients with unresectable advanced CRC as those in SWIFT 1 and 2 studies, and may provide significant clinical benefit when used in Japanese practice. However, since peripheral neuropathy increases with an increased number of doses, future treatment strategies need preventive measures in order to maintain the quality of life of patients.

Acknowledgements

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Circulating endothelial progenitor cells in metronomic chemotherapy using irinotecan and/or bevacizumab for colon carcinoma: Study of their clinical significance

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Abstract. The aim of the present study was to clarify the anti-tumor efficacy of metronomic chemotherapy using irinotecan (CPT-11) combined with or without bevacizumab against colon cancer, and the significance of circulating endothelial cell (CECs) and endothelial progenitor cells (CEPs) as a surrogate marker for metronomic chemotherapy. KM12SM cells were implanted into the subcutis of nude mouse. After confirming that the implanted tumors had grown 5 mm in size, group A received an intraperitoneal injection of 40 mg/kg CPT-11 every two weeks for 4 weeks [conventional maximum-tolerated dose (MTD)], group B received 10 mg/kg twice weekly (metronomic), group C received 10 mg/kg twice weekly combined with 5 mg/kg bevacizumab twice weekly (metronomic + anti-angiogenic), and the control group received 0.2 ml of PBS every week. Serial changes of CECs and CEPs in peripheral blood and microvessel density (MVD) in the tumor tissues were evaluated. The results showed that the antitumor activity in group B and in group C was significantly higher than that in group A. A significant inhibition in CEPs on day 15 in the metronomic therapy groups B and C was noted when compared to that in the control group, while there was no significant difference in CECs and CEPs between the groups on days 4 and 8. The MVD on day 15 in metronomic groups was significantly lower than that in group A. In conclusion, metronomic chemotherapy of CPT-11 with or without bevacizumab for colon cancer was more effective than the MTD therapy via anti-angiogenic effects. Sequential measurement of CEPs may be a predictive factor for the efficacy and a decisive factor for the optimal dose of metronomic therapy in colon cancer.

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Key words: circulating endothelial cell, irinotecan, anti-angiogenesis, maximum-tolerated dose, surrogate marker for angiogenesis

Introduction

Angiogenesis plays a pivotal role in tumorigenesis and metastasis (1). Tumor angiogenesis is a complex process and is based on the concept that a tumor requires a vascular blood supply to grow beyond 1 or 2 mm (2,3). Tumors that do not establish a neovascular supply may remain dormant for a long time (4). Neovascularization has been thought to result exclusively through proliferation, migration and remodeling of fully differentiated endothelial cells derived from pre-existing blood vessels. In addition, vascular endothelial growth factor (VEGF) has been found to induce mobilization of bone marrow-derived endothelial progenitor cells resulting in increased numbers of differentiated endothelial progenitor cells and augmented neovascularization (5,6).

Conventional cytotoxic chemotherapeutic drugs are sensitive to endothelial cells in addition to directly sacrificing or inhibiting the proliferation of rapidly dividing tumor cells (7). However, conventional chemotherapy, which is administered at the more toxic maximum-tolerated dosage (MTD), requires 2- to 3-week rest periods between successive cycles of therapy. The anti-angiogenic efficacy of chemotherapy appears to be optimized by administering comparatively low dosages of the drug on a frequent (daily, several times a week or weekly) or continuous schedule, with no extended interruptions. This concept is sometimes referred to as 'metronomic' chemotherapy (8). In such a situation, mature circulating endothelial cells (CECs) and endothelial progenitor cells (CEPs) have been used as a potentially useful surrogate marker for anti-angiogenic activity (9).

Recently, various drugs have been shown to have significant anti-angiogenic activity when administered at a low dosage using a metronomic schedule (10,11). Irinotecan (CPT-11), which has resulted in improved prognosis of patients with metastatic colorectal cancer (12,13), is always administered using a therapeutic MTD approach; thus, the antitumor and anti-angiogenic efficacy of metronomic CPT-11 administration is unknown.

Humanized monoclonal antibody bevacizumab against VEGF demonstrated an antitumor effect through its administration combined with chemotherapy using CPT-11 and

Table I. Administration schedules of CPT-11 and bevacizumab.

Treatment groups	Dose of CPT-11 (mg/kg)	Dose of bevacizumab (mg/kg)	Application	Total dose of CPT-11 over 4 weeks (mg/kg)
Group A (Conv-40)	40		Day 1, 15 i.p.	80
Group B (Metro-10)	10		Twice weekly i.p.	80
Group C (Metro-10 + Beva)	10	5	Twice weekly i.p.	80

Conv, conventional; Metro, metronomic; Beva, bevacizumab; i.p., intraperitoneal.

5-FU/LV in a phase III trial for advanced colorectal cancer (14,15). Angiogenesis inhibitors also have effects on CECs and CEPs, and these changes have emerged as a potentially useful surrogate marker (16). However, the serial change in the number of CECs/CEPs in chemotherapy, in particular in metronomic chemotherapy is still unknown. In the present study, we investigated the serial change of CECs/CEPs, and the relationship between antitumor efficacy and CECs/CEPs, in metronomic chemotherapy using CPT-11 combined with or without bevacizumab for colon cancer.

Materials and methods

Drugs. Bevacizumab was a kind gift from Genentech (South San Francisco, CA). CPT-11 was a gift from Yakult Honsha (Tokyo, Japan). CPT-11 solution was freshly prepared in 0.9% saline at a concentration of 1 mg/ml.

Cell culture. The human colon carcinoma cell line KM12SM, which produces a high level of VEGF in monolayer culture (supernatant: 2822 pg/ml/10^6/48 h, unpublished data), was kindly provided by Dr M. Nakajima (Johnson & Johnson KK, Tokyo, Japan). The tumor cells were harvested from subconfluent cultures by a 5-min treatment with trypsin-EDTA (Invitrogen, Tokyo, Japan). The dislodged cells were first washed in RPMI-1640 (Invitrogen) supplemented with 10% fetal bovine serum and re-suspended in phosphate-buffered saline (PBS) for injection. Only single cells in suspension with >90% viability were used for the injections.

Animals. Male BALB/c/nu/nu mice, aged 4 weeks, were purchased from Clea Japan, Inc. (Tokyo, Japan). The mice were maintained in a laminar-flow cabinet under specific pathogen-free conditions and were used for experiments at the age of 5 weeks. The mice were maintained in facilities according to the regulations and standards of the Kurume University School of Medicine.

Tumor xenografts and assessment of antitumor effects. A total of 1x10^6 KM12SM cells/PBS was transplanted into the subcutis of the dorsal skin in each nude mouse. The maximum tumor diameter was set at 5 mm and then CPT-11 combined with or without bevacizumab was administered intraperitoneally at a dosage of 10-40 mg/kg of CPT-11 [up to one-fourth and one-sixteenth the dosage of the LD_{50} of 177.5 mg/kg (17)] and 5 mg/kg of bevacizumab for 28 days. After confirming that the implanted tumor had grown 5 mm in size, mice were divided into 4 groups. Group A received 40 mg/kg of CPT-11 every two weeks (Conv-40), and group B received 10 mg/kg of CPT-11 twice weekly (Metro-10). Group C received 10 mg/kg of CPT-11 twice weekly combined with 5 mg/kg of bevacizumab twice weekly (Metro-10 + Beva). The control group received 0.2 ml of PBS every week (Table I). We calculated the body weight of each mouse from day 0 to 29, and these data were used as an indicator of side effects. The tumor size was measured twice weekly using calipers, and the tumor volume was calculated by the formula: [(Maximum tumor diameter)^2 x Minimum tumor diameter/2]. We then resected the tumors 29 days after the start of the drug administration, and the tumors were fixed with 10% formalin for histological examination.

Measurement of CECs and CEPs by flow cytometry. Mice were euthanized with diethyl ether on days 0, 4, 8 and 15, in each group, and heparinized blood was obtained from the heart for CEC and CEP evaluation. CECs and CEPs were counted using a FACSVantage SE flow cytometer (BD Biosciences, San Jose, CA), and the acquired data were analyzed with FlowJo version 6.3.2 flow cytometry analysis software (Tree Star, Inc., Ashland, OR). Heparinized whole blood was hemolyzed and stained with anti-mouse CD45 monoclonal antibody, anti-mouse Flk-1 antibody, anti-mouse CD31 monoclonal antibody and anti-mouse CD117 monoclonal antibody (all from BD Bioscience, San Diego, CA). After red cell lysis, cell suspensions were evaluated by a FACSVantage SE using analysis gates designed to exclude dead cells, platelets and debris. $CD45^+$ cells were excluded by gating, and then $CD31^+$ and $Flk\text{-}1^+$ cells were separated from the $CD45^-$ cells. Among these cells, $CD117^-$ cells were regarded as CECs, and $CD117^+$ cells were regarded as CEPs (Fig. 1). After acquisition of at least 100,000 cells/sample, analyses were considered as informative when adequate numbers of events (i.e., >50, typically 100-200) were collected in the CEC and CEP enumeration gates (18,19).

Immunohistochemistry for microvessels and assessment of microvessel density. The dorsal subcutaneous tumor was fixed by formalin and embedded into paraffin. Serial sections 3 μm were cut from each block. One section was stained using hematoxylin and eosin (H&E), and a second was immunostained for CD31. Immunoreactivities were determined using the avidin-biotin peroxidase complex method (Vector Laboratories, Burlingame, CA) using anti-mouse CD31 (Abcam, Cambridge, MA) at no dilution as the primary anti-

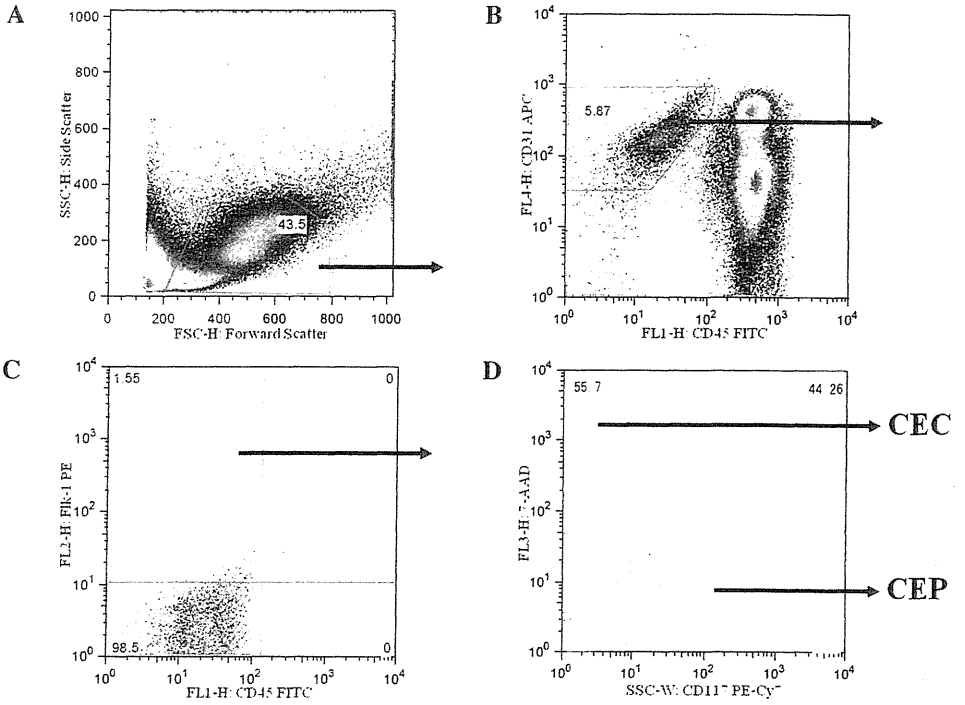

Figure 1. Representative flow cytometric evaluation of CEC and CEP enumeration. (A) Initial gate used to exclude red cells, platelets and debris. (B) Selection of $CD45^-$ and $CD31^+$ cells. (C) Gate for the enumeration of $CD45^-$, $CD31^+$ and $Flk\text{-}1^+$ cells. (D) Gate for enumeration of the $CD45^-$, $CD31^+$, $Flk\text{-}1^+$ and $CD117^-$ cells (CECs) and $CD45^-$, $CD31^+$, $Flk\text{-}1^+$ and $CD117^+$ cells (CEPs).

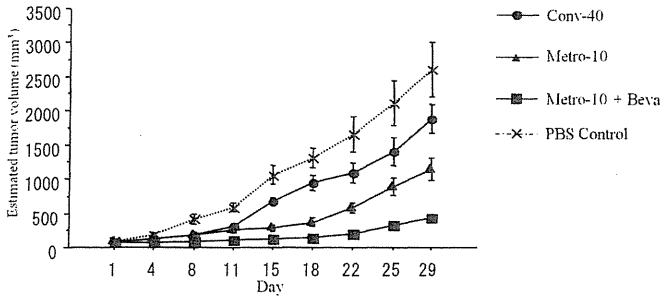

Figure 2. Growth curves of the subcutaneous (KM12SM cell) tumors implanted in nude mouse. The maximum tumor diameter was set at 5 mm, and CPT-11 combined with or without bevacizumab was administered intraperitoneally.

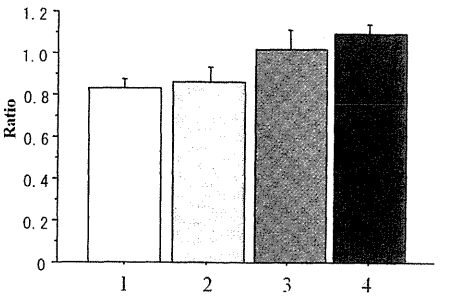

Figure 3. The weight-loss ratio (day 29/day 0): 1, PBS control; 2, Conv-40 group; 3, Metro-10 group; 4, Metro-10 + Beva group.

body. Hematoxylin was used as the counterstain. The negative controls used reagents except for the primary antibody. Positive staining of a small tubular formation for CD31 was defined as a macrovessel, and the microvessel density (MVD) was assessed as the average number of vessels/mm^2, over three areas, at x200 magnifi-cation (20).

Statistical analysis. The deta were analyzed using the Student's t-test. The tumor volume was analyzed using two-way repeated ANOVA. A P-value <0.05 was considered statistically significant. Analyses were computed using the StatView v.5.0 software (SAS Institute Inc., Cary, NC).

Results

Growth inhibition of the tumors implanted into the mouse subcutis. Conventional treatment of CPT-11 (Conv-40) showed significantly higher antitumor activity compared with the PBS control group (P=0.019). In addition, metronomic treatment using CPT-11 (Metro-10) showed more effective antitumor activity compared to the conventional (Conv-40) group (P<0.01). An additive antitumor effect was found when bevacizumab was combined with metronomic chemotherapy using CPT-11 (Metro-10 + Beva) (n=10 in each group) (P<0.01) (Fig. 2).

The weight-loss ratio (day 29/day 0) was statistically lower in the conventional group (Conv-40) than that in the metronomic-treated (Metro-10 ± Beva) groups (P=0.004), although there was no significant difference in the weight loss ratio between the conventional (Conv-40) group and that in the PBS control group (n=7 in each group) (P=0.909) (Fig. 3).

Serial changes of CECs and CEPs. CEC and CEP enumeration by flow cytometry is depicted in Fig. 1. The numbers of CECs in the control group and the conventional (Conv-40) group on day 4 and 8 showed no difference compared to the numbers on day 0, while the numbers of CECs on day 4 and 8 tended to

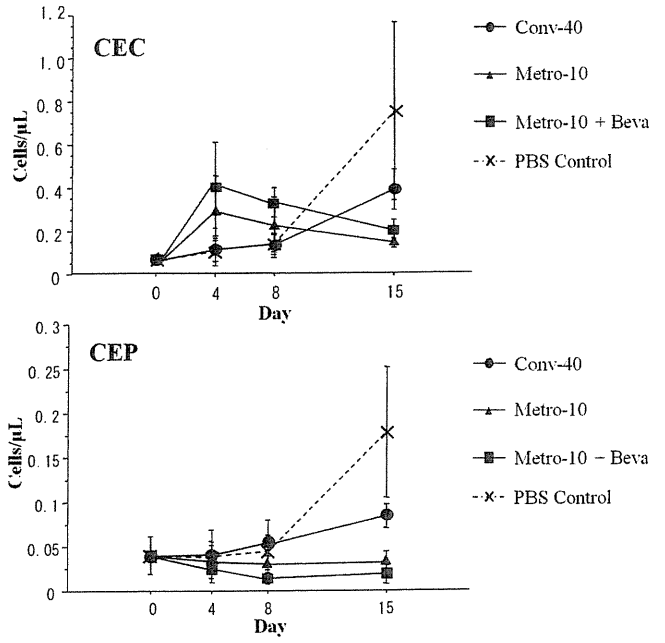

Figure 4. CEC and CEP kinetics before and after treatment in BALB/c/nu/nu mice implanted with KM12SM cell tumors.

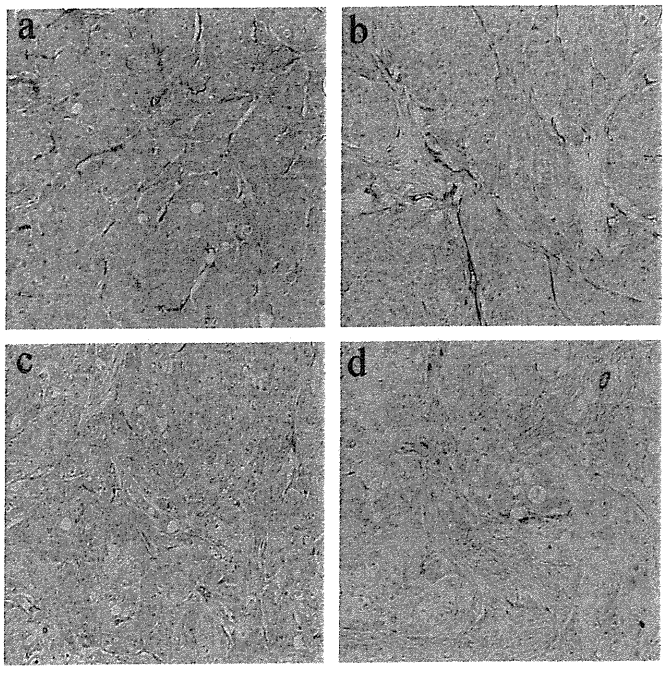

Figure 5. Immunohistochemical staining for CD31 of subcutaneously implanted tumors: (a) PBS control, (b) Conv-40, (c) Metro-10, (d) Metro-10 + Beva.

increase in the metronomic therapy (Metro-10 ± Beva) groups. While the numbers of CECs increased in the control group and the conventional (Conv-40) group on day 15, the numbers of CECs on day 15 in the metronomic therapy groups tended to decrease compared to the numbers on day 4 and 8, but did not reach significance.

There was no significant difference in the number of CEPs between each group on day 4 and 8. However, the numbers of CEPs tended to decrease in the metronomic therapy groups on day 8 compared to those on day 0. Although a statistically

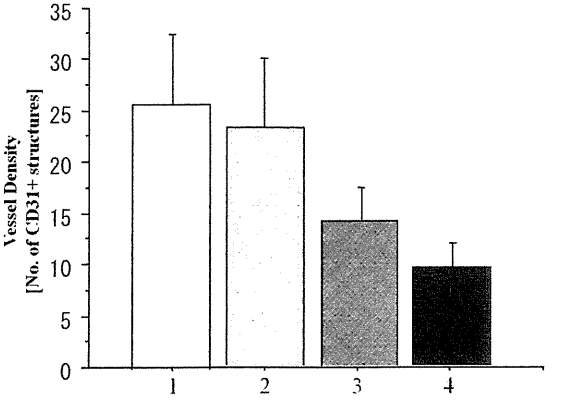

Figure 6. Quantification of the microvessel density in the implanted KM12SM cell tumors on day 15: 1, PBS control; 2, Conv-40; 3, Metro-10; 4, Metro-10 + Beva.

significant increase in the numbers of CEPs in the control and conventional (Conv-40) group on day 15 was noted compared to those on day 0, 4 and 8 (P=0.028), there was no increase in numbers of CEPs in the metronomic therapy groups (n=5 in each group) even on day 15 (Fig. 4).

Analysis of MVD. To investigate the antitumor mechanism of the metronomic CPT-11 treatment combined with or without bevacizumab, we evaluated the MVD in the implanted colon cancer tumors in the subcutis on day 15 after the beginning of drug administration (Fig. 5). The MVD values on day 15 in the metronomic treatment (Metro-10 ± Beva) groups were significantly lower than that in the conventional (Conv-40) group (P<0.001), although there was no significant difference between the conventional group and the PBS control group (P=0.173). Additive effects of the inhibition of vascularization were found when bevacizumab was combined with metronomic treatment of CPT-11 (Metro-10 + Beva vs. the Metro-10; P<0.001) (n=7 in each group) (Fig. 6).

Discussion

The purpose of the present study was to clarify the efficacy of metronomic chemotherapy using CPT-11 and its combination with bevacizumab, a specific anti-angiogenic agent, and the significance of CECs and CEPs as a surrogate marker for efficacy in metronomic chemotherapy/anti-angiogenic therapy for colon cancer. The concept of metronomic chemotherapy was summarized by Kerbel and Kamen (8) and Klement *et al* (21) as follows. (i) Conventional cytotoxic anticancer drugs have anti-angiogenic effects which could contribute to their efficacy. (ii) The anti-angiogenic effects of chemotherapy appear to be optimized by administering such drugs 'metronomically', in other words in small dosages using a frequent schedule (daily, several times a week or weekly) in an uninterrupted manner, over a relatively long period. (iii) Conventional chemotherapy, which is administered at a more toxic MTD, requires 2- to 3-week rest periods between successive cycles of therapy (which counteracts the potential for sustained therapeutically effective anti-angiogenic effects). (iv) In preclinical models, metronomic chemotherapy can be effective in treating tumors in which cancer cells have developed resistance to the same chemo-

therapeutics in an MTD administration (which also has the advantage of being less acutely toxic, therefore making a more extended treatment possible). (v) The efficacy of metronomic chemotherapy can be significantly increased when administered in combination with anti-angiogenic drugs, such as antibodies against VEGF or VEGF receptor 2. Finally, (vi) some metronomic chemotherapy regimens induce sustained suppression in CEPs and increase the levels of the endogenous angiogenesis inhibitor thrombospondin-1, both of which can suppress neovascularization.

In our experiment, the metronomic dispensing method of CPT-11 showed a higher tumor proliferation-controlling effect associated with reduced tumor MVD in nude mice transplanted with KM12SM colon carcinoma cells when compared with the conventional dispensing method. Moreover, the tumor proliferation-controlling effect of metronomic administration of CPT-11 was significantly increased when combined with bevacizumab, an anti-angiogenic agent. In addition, in the metronomic administration groups weight loss as an adverse effect was milder compared with that in the conventional MTD administration group. These results from our colon cancer model also support the concept of low-dosage metronomic chemotherapy suggesting the ability of long-term administration and tumor proliferation control.

It has been reported that, although the numbers of CEPs markedly increase during rest periods between MTD administrations of a chemotherapeutic agent to tumor-bearing mice, CEPs are absent during the metronomic administration and the development of tumors was not noted (18). We also investigated the serial changes in CECs/CEPs and their relationship with tumor vasculature (MVD) after treatment with CPT-11 and the vascular-targeting agent bevacizumab. Our data provide evidence that metronomic administration of CPT-11 and its combination with bevacizumab can have opposing effects in the early phase on days 4 and 8 and then similar effects in the late phase on day 15 on the number of CEPs and mature CECs just prior to the next MTD administration. Namely, the metronomic chemotherapy tended to increase the numbers of mature CECs and to decrease the numbers of CEPs in the early phase after the beginning of treatment (day 4 and 8), and tended to decrease both CECs and CEPs in the late phase after the beginning of treatment (day 15) in the KM12SM cell tumor-bearing mice. In particular, the difference in the numbers of CEPs in the late phase between the metronomic chemotherapy and conventional MTD chemotherapy was statistical significant. The small numbers of CEPs was associated with a concomitant inhibition in tumor vasculature and in tumor growth, suggesting that continuous suppression of CEPs may be a marker for anti-angiogenic activity, including metronomic chemotherapy in a clinical situation.

Our results support the conclusion that the antitumor effects of low dosage metronomic chemotherapy are attributable, at least in part, to a mechanism involving inhibition of tumor blood vessel formation. In addition to anti-angiogenic mechanisms in which fully differentiated endothelial cells are growth-inhibited and/or sacrificed by metronomic low-dosage chemotherapy (6), an anti-vasculogenic process may also be involved which is mediated by reduced CEP mobilization and viability. It is also interesting to consider whether MTD chemotherapy may sometimes accelerate tumor (re)growth and drug resistance by increased mobilization of CEPs. This may also help explain the robust reversal of the damage inflicted by MTD chemotherapy on tumor blood vessel endothelial cells as noted by Browder *et al* (22). An influx of mobilized CEPs during the rest periods between cycles of MTD therapy may replace damaged or sacrificed endothelial cells. In this regard, evaluating the mobilization, viability, and levels of CEPs detected in cancer patients treated with low-dosage metronomic chemotherapy regimens, (e.g., daily low-dosage oral chemotherapy and twice weekly oral methotrexate for breast cancer (23) or leukeran for lymphoma) (24) may be of considerable interest. Such studies and our data may provide a surrogate marker with which to monitor the anti-vasculogenic effects of metronomic chemotherapy protocols. In murine studies, the anti-angiogenic agent endostatin decreased the number of viable CEPs (25), whereas cyclophosphamide either induced or inhibited CEPs depending on whether it was administered in a conventional (every 21 days) or metronomic (every 6 days) dosing schedule (18).

With regard to the increase in the number of CECs early after the start of metronomic chemotherapy, it was found that mature CECs increased after 3 days of treatment with ZD6474 targeting the tumor vasculature in tumor-bearing mice but not in non-tumor-bearing mice (16), suggesting that the increase in mature CECs was due, at least in part, to the presence of the tumor and that ZD6474 or metronomic chemotherapy has at least some degree of selectivity for tumor endothelial cells rather than endothelial cells from normal vasculature. On the other hand, metronomic chemotherapy or anti-angiogenic therapy decreased the number of CECs on day 15 as well as the number of CEPs, while the CECs increased on day 15 in the control group and the MTD conventional chemotherapy group. The changes in number of CECs were similar to the changes of CEPs on day 15 after each treatment and in the control. These data suggest that mature CECs may originate from differentiation of CEPs in addition to the sloughing of tumor endothelial cells. Thus metronomic chemotherapy can consistently inhibit an increase in CEPs for a long time, while the number of CECs may be dependent on various factors such as anti-angiogenic efficacy, tumor volume, the status of tumor vasculature and time after chemotherapy, resulting in large individual variations in the number of CECs.

Recently, oral daily fluoropyrimidines such as capecitabine and UFT/LV have not been proven inferior to bolus and/or infusion MTD chemotherapy using 5-FU in randomized control studies for colon cancer (26,27). Also combination therapies of oral fluoropyrimidine and oxaliplatin/CPT-11 have been developed for colorectal cancer (28,29). Oral fluoropyrimidine would be a typical agent for metronomic chemotherapy (30). We previously reported the safety and efficacy of metronomic chemotherapy using low-dosage weekly CPT-11 and daily 5'-deoxy-5-fluorouridine, an intermediate metabolite of capecitabine, for advanced colorectal cancer (31). However, one of the major problems is a definition of the optimal dosage based on the concept of metronomic chemotherapy. This is a key reason why metronomic chemotherapy has not been widely adopted in clinical trials. Our data suggests that one possible means of determining the recommended dosage for metronomic chemotherapy is to monitor the serial change of CEPs rather than that of unstable

CECs. The optimal dosage for metronomic chemotherapy can be established as the lowest level which is associated with no increase or decrease in the number of CEPs for an individual patient.

We conclude that metronomic chemotherapy using CPT-11 against colon cancer was more effective than conventional therapy, via an anti-angiogenic effect. The combination with the specific anti-angiogenic agent, bevacizumab, may realize the advantage of metronomic chemotherapy. Measurement of CEPs may be a consistent predictive factor for metronomic chemotherapy in colon cancer. The assessment of serial changes in CEP values is recommended in clinical trials of metronomic chemotherapy.

Acknowledgements

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切除不能大腸癌に対する2nd-lineとしてのオキサリプラチン+レボホリナート+5-フルオロウラシル併用化学療法の多施設共同第II相臨床試験：日本人における結果

A Multicenter Phase II Clinical Study of Oxaliplatin, Folinic Acid, and 5-Fluorouracil Combination Chemotherapy as Second-Line Treatment for Advanced Colorectal Cancer: A Japanese Experience

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切除不能大腸癌に対する2nd-lineとしての オキサリプラチン+レボホリナート+5-フルオロウラシル併用化学療法の 多施設共同第II相臨床試験：日本人における結果

抄　録

目　的

本試験は、日本人における切除不能大腸癌を対象とした2nd-lineとしてのオキサリプラチン+レボホリナート+5-フルオロウラシル併用化学療法（FOLFOX4法）を施行した際の有効性および忍容性を明らかにするために計画された。

方　法

1st-lineの化学療法施行後に腫瘍の増悪を認めた53例が本試験に登録された。治療は、腫瘍の増悪、忍容不能な毒性の発現または患者の中止希望のいずれかまで2週間ごとに繰り返された。

結　果

不適格が4例、プロトコール治療未施行が1例であった。したがって、奏効率、全生存期間（OS）、無増悪生存期間（PFS）の評価対象は48例、毒性の評価対象は、プロトコール治療未施行例を除く52例となった。PRは10例で、奏効率は20.8%（95%信頼区間［CI］10.5～35.0%）であった。PFS中央値は5.6カ月（95%CI 4.1～7.0カ月）であり、OS中央値は19.6カ月（95% CI 11.4～24.3カ月）であった。最も高頻度に発現したGrade 3/4の血液毒性は好中球減少であった（43.1%）。毒性プロファイルは全体的に予測可能かつ管理可能であった。

結　論

切除不能大腸癌に対する2nd-lineとして、FOLFOX4法は良好な忍容性および有効性を示した。以上より、日本人における切除不能大腸癌に対する2nd-lineとしてのFOLFOX4法は有望であることが示された。

●監修者コメント

FOLFOX法は、海外のエビデンスをもとに2005年に本邦で承認されたため、当時、本邦のエビデンスは皆無であった。そのため、海外では大腸癌治療において良好な成績が報告されていたにもかかわらず、国内での使用は困難であると考えられていた。

このような背景のもと、本試験は2nd-lineとしてのFOLFOX法のエビデンス創出を目的として九州消化器癌化学療法研究会（KSCC）により実施されたプロスペクティブな多施設共同臨床試験である。その成績は、GERCOR（V308）[1]試験における成績（奏効率15%、PFS中央値4.2カ月）と同等以上であった。また、同グループは1st-lineとしてのFOLFOX法についても検討を行っており、現在、FOLFOX法が本邦でも標準的治療として使用できるのは、これら質の高い臨床試験に寄与するところが大きい。

KSCCは大腸癌臨床研究の中心的な役割を担ってきた研究グループの一つである。これらの研究の他にも、分子標的治療薬を取り入れた治療戦略の開発、術前・術後補助化学療法の検討、さらには治療期間の延長を図るべくCa/Mgを用いたオキサリプラチン特有の神経毒性の緩和などにも取り組んでいる。癌治療の進歩のためにも本邦のエビデンスを発信していくことは非常に有意義であり、日本を代表する臨床研究グループとしてKSCCのさらなる発展を期待する。

1) Tournigand C, et al. J Clin Oncol 22:229-37, 2004