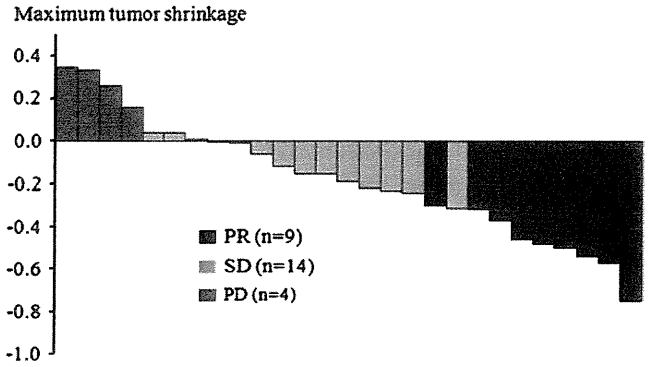

Fig. 1 Maximum tumor shrinkage from baseline. The objective response rate was 30.0%, and the disease control rate was 76.7%. Among the 14 patients with stable disease, 8 patients experienced >10% tumor shrinkage. Three patients were not evaluable for treatment response. Abbreviations: *PR* partial response; *SD* stable disease; *PD* progressive disease

survival was 10.8 months (95% CI; 6.8-not reached) with fourteen patients still alive (Fig. 2).

Toxicity

Grade 3–4 neutropenia was observed in 9 patients (30.0%), 3 patients experienced grade 3–4 anemia, and one patient experienced grade 3–4 thrombocytopenia (Table 2). Febrile neutropenia was observed in 2 patients (6.7%), which were successfully managed by treatment with granulocyte-colony stimulating factor and antibiotics. Skin toxicity including acne, rash, dry skin, pruritus, acneiform dermatitis, and papular rash, was observed in 27 patients (90.0%); the majority of these (n=15) were grade 2. Three patients (10.0%) experienced grade 3 skin toxicity. One patient died from pneumonia. This patient experienced fever and dyspnea 10 days after the fourth cycle of treatment. CT scan showed diffuse gland glass opacity with consolidations. Culture of blood and sputum was negative for any pathogen including *Pneumocystis jiroveci*. Although antibiotics and high doses of steroids were administered, the patient did not improve. Definitive cause of pneumonia could not be determined since autopsy was denied. Other grade 3–4 non-hematological toxicities included diarrhea (16.7%) and anorexia (10.0%).

Table 2 Toxicity

Toxicity	Grade 1–4 (%)	Grade 3–4 (%)
Leucopenia	15 (50)	5 (17)
Neutropenia	16 (53)	9 (30)
Febrile neutropenia	2 (7)	2 (7)
Anemia	14 (47)	3 (10)
Thrombocytopenia	2 (7)	1 (0.3)
Fever	7 (23)	0 (0)
Diarrhea	14 (47)	5 (17)
Skin toxicity	26 (87)	3 (10)
Nausea	15 (50)	1 (0.3)
Vomiting	7 (23)	1 (0.3)
Fatigue	14 (47)	3 (10)
Stomatitis	10 (33)	1 (0.3)
Anorexia	19 (63)	3 (10)
Hypomagnesia	16 (53)	1 (0.3)

Results of PK analysis

The mean of Cmax was 195.20 ug/mL on day 1 and 230.80 ug/mL on day 15, and the mean of trough concentrations was 22.14 ug/mL on Day 15 and 38.34 ug/mL on day 29 (Fig. 3). The both Cmax and trough were increasing. However; this was not shown in all the patients of multiple administrations due to the large variation in each case and the small patients number. The trough on day

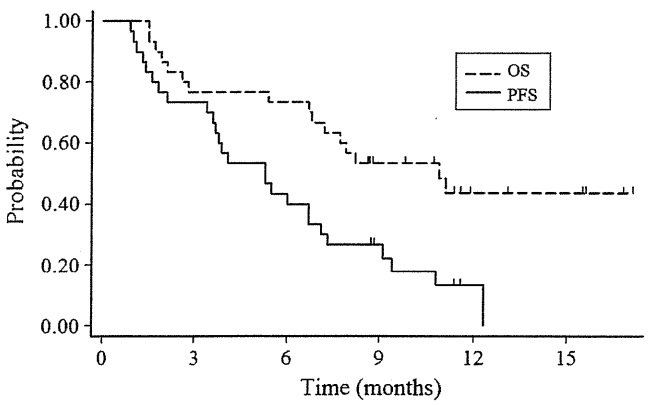

Fig. 2 Progression-free survival and overall survival time. The median progression-free survival was 5.3 months and median overall survival was 10.8 months. Abbreviations: *PFS* progression-free survival; *OS* overall survival

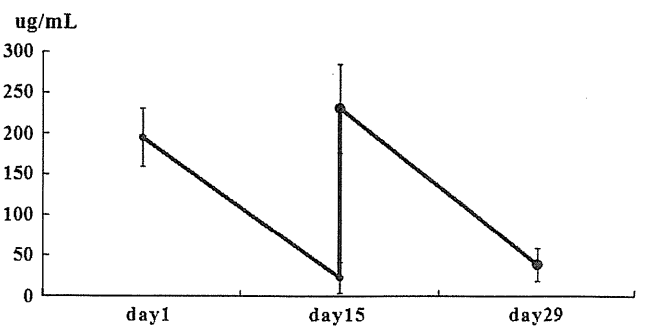

Fig. 3 Mean (±S.D.) peak and trough cetuximab serum concentrations day 1–day 29. The mean of Cmax was 195.20 ug/mL on day 1 and 230.80 ug/mL on day 15, and the mean of trough concentrations was 22.14 ug/mL on Day 15 and 38.34 ug/mL on day 29

15 and day 29 of Cetuximab 500 mg/m^2 administration were similar to the results from other studies [11, 12].

Discussion

In this study, we evaluated the efficacy and safety of combination chemotherapy with biweekly cetuximab plus irinotecan in patients with wild-type *KRAS* colorectal cancer who failed prior chemotherapy including irinotecan, oxaliplatin, and fluoropyrimidine. To our knowledge, this was the first report to evaluate biweekly cetuximab in prospectively recruit patients after assessing *KRAS* mutation status.

To our knowledge, there were three published reports that evaluated biweekly administration of cetuximab. Tabernero et al. conducted a phase I study of cetuximab monotherapy followed by a combination with a FOLFIRI regimen and reported that a cetuximab dose of 500 mg/m^2 every 2 weeks exhibited predictable pharmacokinetics, which were similar to those of the approved weekly dosing regimen [11]. Although most patients in the Tabernero study were chemo naïve patients, our results supported the assumption that 500 mg/m^2 might be optimal even in heavily pretreated patients with active serum concentrations of cetuximab maintained throughout the 2-week dosing period with this regimen. The other two reports in similarly pretreated settings showed almost consistent efficacy of biweekly use of cetuximab with irinotecan with a response rate of 22.5%–25% and 3.4–5.4 months [12, 13] , although these studies did not evaluate *KRAS* status (Table 3).

The response rate of 30% in the present study was relatively higher than those of previous prospective studies in a similarly pretreated setting, such as the BOND-1 study (22.9%, irinotecan plus cetuximab; 10.8%, cetuximab monotherapy) or the MABEL study, considering a study population with and without *KRAS* mutant tumors [2, 16]. The present disease control rate (76.7%) and progression free survival (5.3 months) was also relatively higher than that of the BOND-1 study (55.5% and 4.2 months in the combination arm) or the MABEL study (45.2% and 3.2 months) [2], although these indirect comparisons should be cautiously interpreted. The efficacy data in this study were almost similar to our previous phase II study using weekly cetuximab plus irinotecan for patients with *KRAS* wild-type metastatic colorectal cancer [9]. These results highlight the usefulness of biweekly administration of cetuximab.

Toxicity in our study and previous biweekly studies was almost compatible to those of weekly regimens (Table 3), although we experienced one possible treatment related death due to pneumonia. In this study, although 2 patients discontinued treatment due to toxicity, other toxicities were generally well tolerated and expected. Therefore biweekly administration may be a potentially convenient alternative to the approved weekly dosing regimen considering most chemotherapy regimens in colorectal cancer were based on biweekly administration, although cautions for toxicity are still required.

In conclusion, the results of this phase II study demonstrated that combination of biweekly cetuximab and irinotecan chemotherapy was active and tolerated in patients with wild-type *KRAS* colorectal cancer who failed prior chemotherapy including irinotecan, oxaliplatin, and fluoropyrimidine. Although the small number of patients in the single arm study was the major limitation to this study, our results suggested that the biweekly administration of cetuximab combined with irinotecan was feasible and active in patients heavily pretreated with MCRC. Further

Table 3 Results of prospective study of cetuximab plus irinotecan for MCRC refractory to irinotecan

Author	Weekly cetuximab plus irinotecan				Biweekly cetuximab plus irinotecan			
	Cunningham [2]	Wilke [16]	Pfeiffer [12]	Tahara [10]	Shitara [9]	Pfeiffer [12]	Martin-Martorell [13]	This study
Number of patients	329	1147	65	39	30	71	40	30
KRAS status	NR	NR	NR	NR	Wild	NR	NR	Wild
Previous oxaliplatin (%)	62.6	69	95	100	100	100	97.5	100
Response rate (%)	22.9	20.1	20	30.8	30	25	22.5	30
Disease control (%)	55.5	45.2	66	64.1	80	77	60	76.7
median PFS (months)	4.1	3.2	5.4	4.1	5.8	5.4	3.4	5.3
median OS (months)	8.6	9.2	10.4	8.8	12.5	8.9	8	10.8
Skin toxicity(G3-4)	9	13.3	11	5.1	0	5	7.5	10.0
Diarrhea (G3-4)	21	19	10	17.9	13.3	9	10	16.7
Neutropenia (G3-4)	9	9.9	4	23.1	33.3	7	7.5	30.0

NR not reported; *PFS* progression free survival; *OS* overall survival; *G* grade

randomized studies that compared biweekly administration of cetuximab with weekly administration might be warranted.

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Conflict of interest statement None declared.

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Characteristics and Outcomes of Patients With Advanced Gastric Cancer Who Declined to Participate in a Randomized Clinical Chemotherapy Trial

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Abstract

Purpose: There is insufficient data to verify whether participation in clinical trials in itself can lead to better clinical outcomes. We have analyzed the characteristics and outcomes of patients who declined to participate in a randomized trial in comparison with those who participated in the trial.

Patients and Methods: A randomized trial for naive advanced gastric cancer was offered to 286 patients. The trial investigated the superiority of irinotecan plus cisplatin and the noninferiority of S-1 compared with continuous fluorouracil infusion. We retrospectively reviewed the characteristics and outcomes for both participants and nonparticipants in this trial.

Results: Of the 286 patients, 98 (34%) declined to participate in the trial. The rate of declining was significantly higher among younger patients ($P = .003$), and it varied significantly between attending physicians (range, 23% to 58%; $P = .004$). There were no other significant correlations between rate of declining and patient characteristics. No significant differences were observed in the clinical outcomes between the participants and nonparticipants, for whom the median survival times were 367 versus 347 days, respectively. The hazard ratio for overall survival, adjusted for other confounding variables, was 1.21 (95% CI, 0.91 to 1.60). No interaction was observed between participation and the various regimens.

Conclusion: There was no difference in clinical outcomes between participants and nonparticipants. However, the patient's age and the doctor-patient relationship may have an effect on patient accrual to randomized trials.

Introduction

A randomized clinical trial (RCT) is the definitive method for comparing the efficacy of treatments, and an RCT is a crucial step in the development of any new cancer treatment. Nevertheless, there is a consistent problem in that low accrual rates limit the progress of RCTs.[1-3]

Several factors that act as barriers to participation in trials have been documented,[1-6] and some have been successfully targeted for improvement.[4-5] Major barriers include a lack of availability of appropriate trials, limitations of eligibility criteria, socioeconomic factors (including insufficient awareness of clinical trials, lack of medical insurance, and geographical limitations), physician triage, and patient decision making. Insufficient data are available on the actual outcomes for nonparticipants in RCTs in comparison with those for participants.[7-11]

We have previously analyzed the characteristics and outcomes of patients who had been referred and were eligible for, but declined to participate in, RCTs and compared them with those of participants, with the aim of developing an approach to improve patient accrual to RCTs.[12] We found no evidence to suggest any significant differences in the characteristics or clinical outcomes between participants and nonparticipants. We also reported that the trial design and the doctor-patient relationship might have an effect on patient accrual to RCTs.

In the present study, we reviewed the characteristics and clinical outcomes of patients who met the eligibility criteria of an RCT designed to compare three different types of therapy, including both injection and oral agents, the levels of toxicity of which were estimated to be quite different. Our analysis was designed to test our previous findings. We also analyzed whether participation in an RCT that compared several arms with different efficacies affected patient outcomes.

Patients and Methods

All the patients who were recruited into this study fulfilled the entry criteria for the Japan Clinical Oncology Group RCT on unresectable or recurrent gastric cancer (JCOG 9912). The patients were informed of all aspects of the trial and were invited to participate. Irrespective of their participation or nonparticipation in the RCT, all received first-line chemotherapy at the National Cancer Center Hospital, Tokyo, Japan, between November 2000 and January 2006. Signed informed consent was obtained from the patients to permit future statistical analysis of data from their clinical courses and outcomes, even if they were treated outside the clinical trials.

The RCT was a three-arm, phase III trial conducted by JCOG to investigate the superiority of irinotecan (CPT-11) plus cisplatin (CDDP) combination chemotherapy and the

noninferiority of *S*-1 compared with continuous fluorouracil (FU) infusion.[13]

The criteria for inclusion of patients were as follows: histologically documented unresectable or recurrent gastric cancer; no prior systematic chemotherapy or radiation therapy except for adjuvant chemotherapy with one oral fluoropyrimidine agent other than *S*-1, completed 6 months earlier; age 20 to 75 years; Eastern Cooperative Oncology Group performance status (PS) of 0 to 2; no history of chemotherapy or radiation therapy for malignant disease other than gastric cancer; and adequate hematologic, hepatic, and renal functions. Those with severe peritoneal dissemination resulting in impaired bowel passage, ascites beyond the pelvic cavity, or wall deformity detected by barium enema were excluded. A measurable lesion was not mandatory. Each patient was required to submit written informed consent before taking part in the RCT.

The treatment schedule of each arm was as follows: (1) Continuous FU infusion: FU was infused continuously over 120 hours; this required hospitalization for 7 days. (2) CPT-11 plus CDDP combination chemotherapy: CPT-11 was infused on days 1 and 15, and CDDP was infused on day 1; this required hospitalization for 5 days. (3) *S*-1 monotherapy: *S*-1 was administered orally on days 1 through 28 and repeated every 6 weeks. Patients were required to undergo a medical examination every 2 weeks. Patients who declined to participate ultimately selected their treatment regimen after discussions with their families and physicians. We provided the selected therapies after confirming that patients fully understood that the standard therapy at that time was FU infusion and that the CPT-11 plus CDDP combination therapy and the *S*-1 monotherapy were still under evaluation.

In the RCT, CPT-11 plus CDDP therapy resulted in a longer survival rate, and *S*-1 showed significant noninferiority compared with FU.[13] The hazard ratio (HR) of CPT-11 plus CDDP versus FU was 0.82 (95% CI, 0.68 to 0.99; $P = .019$). The HR of *S*-1 versus FU was 0.83 (95% CI, 0.68 to 1.00, P for noninferiority $< .001$).

Six male physicians participated in the trial. At the start of the trial (November 2000), physicians A, B, C, D, E, and F had 8, 10, 11, 17, 19, and 19 years of experience, respectively, as gastrointestinal oncologists. One of these six attending staff physicians, together with one, two, or three residents or trainees, attended each consultation. They explained to the patients that this was a JCOG study, that standard therapy was continuous FU infusion, and that we could not tell which arm was superior, but the treatment schedule, toxicities, and required lengths of hospitalization were expected to be different among the various arms. If patients chose not to participate in the study, we recommended the standard therapy, but they could choose other, off-protocol regimens.

We reviewed all the medical records of patients who underwent chemotherapy for unresectable or recurrent gastric cancer between November 2000 and January 2006, and we selected 286 patients who were documented as having been offered the opportunity to participate in the RCT. During the study period, some other patients were judged to be ineligible for the study and were offered other treatments, as clinically indicated, but the number of such patients is not available. Paper and/or electronic medical records from the initial visit to our center to the end of follow-up were reviewed retrospectively. Demographic data (age and sex), medical information (tumor histology, clinical stage, PS, peritoneal dissemination, and therapy characteristics), and clinical outcomes (response rate [RR], follow-up time, overall survival [OS] time, and 1- and 2-year survival rates) were abstracted and analyzed. Response was evaluated by the attending physicians according to the Response Evaluation Criteria in Solid Tumors (RECIST).[14] It is our policy to assess clinical responses to RECIST, even in routine practice. The follow-up time at our institution was defined as the period from the first day of initial therapy to the last visit or the last day of hospitalization at our institution (including death during follow-up). Data on the survival of the patients who left our institution were collected through inquiries to the Japanese official agency for family registries.

The χ^2 test and logistic regression analysis were used to assess associations between patient characteristics and the rate of declining to participate. OS curves were prepared by using the Kaplan-Meier method and were compared with the results of the log-rank test. All participants (those who agreed to be enrolled onto the RCT), including two who were later found to be ineligible after random assignment, and all nonparticipants (those who declined to participate in the RCT), including one who was lost to follow-up, were included in the OS analysis. A Cox proportional hazards model was used to adjust for other potential confounding factors (ie, age, sex, histology, clinical stage, PS, nonsevere peritoneal dissemination, and treatment regimen) in comparing the OS of participants and nonparticipants. Interaction between participation and regimen was tested with an α level of 0.2; $P < .05$ was regarded as significant. Collected data were analyzed by using an SPSS II statistical package (SPSS, Chicago, IL). This study was approved by the institutional review board at the National Cancer Center and was conducted in accordance with the ethical principles stated in Japanese ethics guidelines for clinical and epidemiological studies. No patient explicitly refused to be analyzed for his or her outcome during this study period. The institutional review board approved the use of such clinical data for the study objective.

Results

Table 1 shows the patient characteristics and the rates of declining. A total of 190 patients accepted, and 96 patients (34%) declined, entry into the RCT. There was no significant correlation between the declining rate and sex, clinical stage, PS, tumor histology, or peritoneal dissemination. Patients younger than 60 years declined to participate at a significantly higher frequency ($P = .003$). There were also significant differences in the declining rates between the various attending physicians who informed the patients about the trial and asked for their participation ($P = .004$). The patients were divided equally among the offering physicians by characteristic.

Table 1. Patient Characteristics and Rate of Declining to Participate in Randomized Clinical Trials

	Participants		Non-participants			Participants			Nonparticipants		
Characteristic	No.	%	No.	%	ROD (%)	OR	95% CI	*P*	OR	95% CI	*P*
No.	190		96		16						
Sex											
Male	146	77	64	67	30	1.66	0.97 to 2.85	.07	0.49	0.26 to 0.90	.02
Female	44	23	32	33	42						
Age, years											
< 60	48	25	41	43	46	0.45	0.27 to 0.76	.003	2.54	1.44 to 4.47	.01
≥ 60	142	75	55	57	28						
Clinical stage											
III	1	1	0	0	0						
IV	146	77	70	73	32	1.30	0.74 to 2.26	.36	0.55	0.29 to 1.04	.06
Recurrent	43	23	26	27	38						
PS											
0	104	55	51	53	30						
1	84	44	44	46	34	0.96	0.58 to 1.58	.87	0.85	0.49 to 1.47	.56
2	2	1	1	1	33	0.98	0.09 to 11.07	.99	0.51	0.03 to 7.04	.61
Histology											
Well differentiated	75	39	34	35	31	0.85	0.51 to 1.42	.55	1.05	0.59 to 1.89	.86
Poorly differentiated	115	61	61	64	35						
Undifferentiated	0	0	1	1	100						
Peritoneal dissemination											
Yes	85	45	51	53	38	0.71	0.44 to 1.17	.18	1.54	0.89 to 2.69	.13
No	105	55	45	47	30						
Physicians											
A	31	16	19	20	38			.04			< .01
B	27	14	10	10	27						
C	35	18	13	14	27						
D	25	13	27	28	52						
E	67	35	20	21	23						
F	5	3	7	7	58						

NOTE. Univariate analysis was performed with Pearson's χ^2 test; multivariate analysis was logistic regression analysis.
Abbreviations: ROD, rate of declining; OR, odds ratio; PS, performance status.

Table 2 shows the treatment options of patients who declined to participate in the RCT. Nearly 60% of all those who declined to participate selected *S*-1 monotherapy. Moreover, approximately 70% of nonparticipants who were under 60 years of age selected *S*-1 monotherapy. The proportion of those who selected CPT-11 plus CDDP, which was expected to be more beneficial but showed more severe toxicity and required hospitalization, was not necessarily higher among nonparticipants younger than 60 years than among older nonparticipants. No specific tendency was shown in selection of regimen in relation to the attending physician.

Post-therapy was analyzed in 188 of the participants. This group excluded all 96 nonparticipants, as well as two patients found to be ineligible after random assignment: one patient who developed gastrointestinal bleeding several hours after entry, and another who was later diagnosed with adenosquamous cell carcinoma. Survival was analyzed in the 190 participants and the 96 nonparticipants. There were no treatment-related deaths among either the participants or the nonparticipants. There was no difference in the number of cycles of first-line chemotherapy received by participants or nonparticipants: 53% of the participants and 58% of the nonparticipants received fewer than three cycles ($P = .406$). A total of 85% of the participants and 70% of the nonparticipants were given more than two chemotherapy regimens. Statistically, more participants than nonparticipants were given chemotherapy after the initial therapy ($P = .003$). A total of 14 (7%) of the participants and 6 (6%) of the nonparticipants in the RCT participated later in early-phase clinical trials of experimental therapies.

There were no major differences in clinical outcome between participants and nonparticipants (Figure 1). Clinical response to the initial therapy was analyzed in all 190 participants and 96 nonparticipants. The RR was 30.5% for the participants and 21.9% for the nonparticipants ($P = .121$). The median follow-up time at our hospital was not significantly different between the participants (317 days) and the nonparticipants (292 days). The median survival time (MST) was 367 days for the participants and

Table 2. Characteristics and First Treatment Regimen of Nonparticipants

Characteristic	FU		CPT-11 Plus CDDP		S-1		P*
	No.	%	No.	%	No.	%	
No.	31		8		57		
Sex							
Male	22	34	5	8	37	58	.819
Female	9	28	3	9	20	63	
Age, years							
< 60	10	24	3	7	28	68	.297
≥ 60	21	38	5	9	29	53	
Clinical stage							
IV	20	29	6	9	44	63	.438
Recurrent	11	42	2	8	13	50	
PS							
0	15	29	6	12	30	59	.641
1	16	36	2	5	26	59	
2	0	0	0	0	1	100	
Histology							
Well differentiated	10	29	4	12	20	59	.814
Poorly differentiated	21	34	4	7	36	59	
Undifferentiated	0	0	0	0	1	100	
Peritoneal dissemination							
Yes	16	31	1	2	34	67	.043
No	15	33	7	16	23	52	
Physicians							
A	5	26	1	5	13	68	.363
B	4	40	3	30	3	30	
C	4	31	0	0	9	69	
D	8	30	2	7	17	63	
E	8	40	2	10	10	50	
F	2	29	0	0	5	71	

Abbreviations: FU, fluorouracil; CPT-11, irinotecan; CDDP, cisplatin; PS, performance status.
* Pearson's χ^2 test.

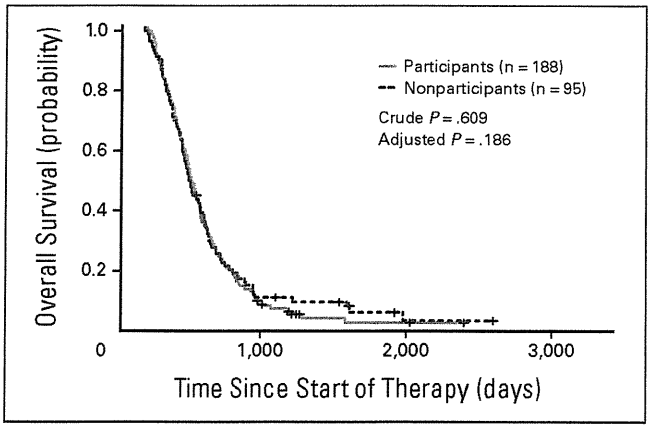

Figure 1. Overall survival of nonparticipants in randomized trials compared with that of participants. No significant difference were observed.

347 days for the nonparticipants. There were no significant difference in OS between the participants and the nonparticipants (Figure 1), and the HR was 1.07 (participants *v* nonparticipants; 95% CI, 0.83 to 1.38). With the Cox proportional hazards model adjusted for sex, age, tumor histology, clinical stage, PS, peritoneal dissemination, and treatment regimen, the HR of participants versus nonparticipants was 1.21 (95% CI, 0.91 to 1.60; $P = .19$). Furthermore, the RR and OS were not significantly different between the participants and the nonparticipants for each regimen. The RR in participants versus nonparticipants was 9.5% versus 6.5% for FU ($P = .646$), 54.0% versus 62.5% for CPT-11 plus CDDP ($P = .648$), and 28.1% versus 24.6% for *S*-1 ($P = .657$). MST in participants versus nonparticipants was 358 days versus 335 days for FU, 435 days versus 458 days for CPT-11 plus CDDP, and 338 days versus 345 days for *S*-1. The HR values for OS were 0.91 (95% CI, 0.57 to 1.44; $P = .679$) for FU, 0.99 (95% CI, 0.38 to 2.56; $P = .981$) for CPT-11 plus CDDP, and 1.22 (95% CI, 0.81 to 1.83; $P = .333$) for *S*-1 (Appendix Figures A1-A3, online only).

We analyzed the interaction between participation and regimen. The *P* value for the interaction term was greater than the α level of 0.2; it was 0.75 for participants and CPT-11 plus CDDP, and 0.28 for participants and *S*-1 (Appendix Table A1, online only).

Discussion

We previously analyzed the characteristics and outcomes of patients who had been referred and were eligible for, but declined to participate in, two RCTs for naive, advanced, non–small-cell lung cancer and compared them with those of participants.[12] Trial 1 was a comparison of four similar combinations of injection therapies (cisplatin-irinotecan, carboplatin-paclitaxel, cisplatin-gemcitabine and cisplatin-vinorelbine), and Trial 2 compared two sequences of injection and oral therapies (four courses of carboplatin-paclitaxel followed by gefitinib or gefitinib until disease progression, followed by carboplatin-paclitaxel). We found that the rate of declining to participate in a trial in which similar injection therapies were compared was lower than that in a trial in which injection and oral therapies were compared (16% *v* 37%). We also reported that there was no evidence to suggest any difference, except for that of the attending physician, in the characteristics and clinical outcomes between participants and nonparticipants.

In the present study, we compared three different regimens, two of which were given by injection and the other as an oral agent. The rate of declining in the present study was 34%, which was as high as that of Trial 2 in our previous study. It is easy to understand that more difficulty is experienced in accepting the randomization of different types of therapy.[8,15] The therapy arms of the present study used different methods of administration; moreover, the estimated toxicities and the need for hospitalization were quite different among the various arms. We thus confirmed our previous finding that trial design influences trial accrual.

Nearly 60% of those who declined entry into the trial selected *S*-1 monotherapy, which may reflect the patients' desire for convenience and a higher quality of life. Younger patients, in particular, preferred this oral agent. We speculate that they may attach greater importance to avoiding hospitalization than to uncertain efficacy. This difference between age groups was a new finding of the present study.

As noted in our previous report, the rate of declining also appeared to be greatly affected by the attending physician. No record was available of which person actually took the initiative and offered the trial at each consultation; however, even when a resident or trainee offered the trial, the attending physician would have taken the responsibility for the consultation. No relationship was found between the length of experience of the physician as a gastrointestinal oncologist and the rate of declining. Each attending physician attempted to present the three regimens equally without showing favor toward any particular regimen; this suggests that individual consultations were not the source of bias. Physicians' clinical communications have been noted as affecting patients' decision making regarding participation in clinical trials.[16] Improved communications and more frequent interventions by clinical research coordinators and other medical staff members for all eligible patients might improve the accrual rate.[17-19] This study did not clarify whether differences in communication skills between physicians led to differences in rates of declining; further investigations of this effect are warranted.

On the other hand, inadequate data are available on the actual outcomes for RCT nonparticipants compared with those of participants.[7-11] Although several reports and a review[7] have suggested the existence of a "trial effect" in which participants enjoy more favorable outcomes, other studies, especially those that attempted to exclude confounding factors, have refuted this finding.[8-11] Our study revealed that the outcomes for participants were no better than those of nonparticipants. Furthermore, our results showing that interactions between participants or nonparticipants and the treatment regimen were not significant (Table 3) may suggest that the conclusion of this RCT could be generalized. The HR for OS between participants and nonparticipants was very close to 1 (0.91; 95% CI, 0.57 to 1.44) in the FU arm, which was the control arm in the trial, and numerically favorable for nonparticipants in the CPT-11 plus CDDP arm and the *S*-1 arm (CPT-11/CDDP: 0.99; 95% CI, 0.38 to 2.56; *S*-1: 1.22; 95% CI, 0.81 to 1.83), which were the testing arms in the trial. This suggests the possibility of a self-selection bias.

Our study has several limitations. First, we selected the participants and nonparticipants retrospectively among those who underwent chemotherapy for advanced gastric cancer during the period in which we conducted the RCT. The fact that all the patients accepted treatment of some sort is, in itself, a selection process, and information on patients who declined all active treatments at our institution remains elusive. There may have been some patients who did not want to continue active treatment and who instead opted for supportive care only, or other patients who declined to participate in the RCT and went to other hospitals. We did not review this population, and if there were any such patients, this may have affected the survival analysis.

Second, the present study was conducted at a single academic institution, and there was an insufficient number of patients. As a result, the numbers of patients in the various subsets were quite small, and it is difficult to rule out significant differences in some of these because of a lack of statistical power. Our investigation should therefore be interpreted as exploratory and hypothesis generating. Our results require further validation at other institutions, preferably on a multi-institutional basis, because the situation may well be different at other institutions.

Third, no data were available regarding the reasons for participation or nonparticipation. Such information would be useful for analyzing factors that affect consent or refusal to participate and would help in improving the accrual rate. However, so that patients are not coerced into participating in the study, reasons for their participation or refusal need to be collected by independent investigators.

In conclusion, we confirmed that the rate of declining to participate in RCTs was influenced by the design of the trial and by the referring physician. The age of the patients also had an effect on the rate of declining, suggesting that some patients may attach a greater importance to not having their normal schedule disrupted than to expectations of efficacy. There was no evidence of any difference in the RRs and survival times between participants and nonparticipants, and the interaction between participants or nonparticipants and the treatment regimen was not significant.

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Authors' Disclosures of Potential Conflicts of Interest

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Commentary: Clinical Trials Represent the Best Cancer Care. Or Do They?

By Charles D. Blanke

The Mayo clinic Web site states "it's not uncommon for your cancer doctor....to discuss the option of a clinical trial as the *best treatment* [emphasis mine]...for your cancer.[1] In fact, it has long been argued that trial participants have better outcomes than those not enrolled onto such studies.[2] Many possible explanations for such a phenomenon exist: patients treated on study are likely to be closely monitored (allowing for early dose adjustments, including escalations, as well as prompt treatment of toxic events); study patients may be more health conscious in general than those not electing to participate; perhaps newer treatments do tend to be better than older standards; and, although it would certainly be hard to definitively prove, it has even been argued clinicians who recruit to trials are in general superior physicians. Of course, reports that attempt to compare trial participants with those treated off-study often attempt to match up different populations with various underlying

imbalances, automatically leading to biases that can skew long-term results.[3]

In this issue of *Journal of Oncology Practice*, Tanai et al[4] describe characteristics and outcomes of patients with gastric cancer who declined to participate in a chemotherapy randomized clinical trial (RCT). In brief, The Japan Clinical Oncology Group recently conducted a three-arm, phase III trial testing irinotecan plus cisplatin versus *S*-1 versus continuous fluorouracil infusion in patients with incurable gastric cancer. Tanai et al actually reviewed medical records of all patients undergoing chemotherapy for advanced stomach cancer between November 2000 and January 2006, and selected 286 patients who were eligible for and had been offered participation in that trial. A variety of information was retrospectively gathered (demographics, performance status, clinical stage, etc), and response and survival outcomes were abstracted. Standard statistical analyses were used in comparing patient characteristics in the groups who participated in the RCT and those who declined, as well as in matching up clinical outcomes. The authors sought to determine whether trial participation itself affected patient outcome, and to confirm whether participants and nonparticipants shared the same characteristics.

Approximately one-third (34%) of patients declined to participate in the RCT. Although FU was recommended to this group, they were allowed to select their own chemotherapy regimen, and approximately 60% elected to take single-agent *S*-1. The RCT itself reported that combination chemotherapy effected longer survival and that *S*-1 was noninferior compared with FU. No significant correlations between rate of declining and sex, stage, or performance status were found; younger patients (< 60 years) refused to participate at a much higher frequency. Rates among each of the six physicians offering the trial also differed significantly. There were no major differences in outcome between participants and nonparticipants. Response rate was 9% lower ($P = .121$) and median survival approximately 5% worse for nonparticipants. Interestingly but probably not surprisingly, given the limited treatment options, similar percentages of participants and nonparticipants went on to participate in early-phase experimental trials. The authors concluded patients may have had difficulty in accepting random allocation to study arms expected to have markedly different toxicity (and perhaps efficacy) rates, not to mention different routes of administration for the included drugs. They also suggested the rate was affected by who was offering the trial, though this did not correlate with the physicians' years of experience as a GI oncologist. Finally, they concluded outcomes for participants in the RCT were no better.

This article has several limitations, many acknowledged by the authors themselves. All patients accepted treatment of some kind, and the authors had no information on the characteristics of patients who elected best supportive care alone. That group very well might differ from those who accepted active chemotherapy, whether given as part of an RCT or not. Patients included in this article still signed informed consent allowing statistical analysis of their clinical course and outcome; those willing to do so might also differ from patients who refused to participate in a trial of any kind. Numbers were very small, so the numerically different outcomes might have become significant with a larger patient pool, particularly calling into question whether those treated off trial truly do as well as those participating in a study. No data were available regarding the reasons underlying refusal to participate; that information could possibly have been useful in overcoming patient resistance and increasing accrual to future studies. Information garnered might not be generalizable because of the nondiverse patient population, with the situation worsened by the fact the study was limited to a single academic institution.

The authors state their data are exploratory, and they do not make any highly controversial conclusions. However, the interesting questions of whether those participating in a trial are different than the overall nonparticipants with the same disease and whether care on a trial is the best care remain unanswered.

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FOLFIRI Plus Bevacizumab 5 mg/kg Versus 10 mg/kg as Second-line Therapy in Patients with Metastatic Colorectal Cancer Who Have Failed First-line Bevacizumab Plus Oxaliplatin-based Therapy: A Randomized Phase III Study (EAGLE Study)

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We planned a multicenter randomized phase III study to evaluate the efficacy of appropriate dose of bevacizumab (5 or 10 mg/kg) with FOLFIRI in patients with advanced/metastatic colorectal cancer who have failed prior bevacizumab plus oxaliplatin-based therapy. The primary endpoint is progression-free survival. The secondary endpoints are the toxicity, response rate, time to treatment failure, overall survival, overall survival from the start of the first-line treatment and second progression-free survival (time duration from the initiation of the first-line treatment until progression after the protocol treatment). A total of 370 patients were considered to be appropriate for this trial.

Key words: bevacizumab – FOLIRI – irinotecan – beyond progression – advanced/metastatic colorectal cancer

INTRODUCTION

Age-adjusted prevalence of colorectal cancer (CRC) is the second largest percentage after that of gastric cancer in males and breast cancer in females in Japan (1). According to the CONCORD study, it is reported that Japanese men attain the first place and Japanese women attain sixth for a 5-year survival rate with CRC in the world (2). Japanese patient's clinical registered data from 1991 to 1994 by the Japanese Society for Cancer of the Colon and Rectum is superior to the same period's data from Survival Epidemiology and End Results and National Cancer Data Base for each of Stage I, II, III CRC, at most 20%.

It is estimated that the number of CRC patients will be 480 396 in 2015 and 512 225 in 2020 (1). It is also expected that the incidence of CRC will overtake that of breast cancer after 2010. Although CRC screening rates were improved, considerably large number of patients had a locally advanced or metastatic disease at the time of diagnosis. For patients with metastatic CRC, recommended first-line regimens by guidelines are FOLFOX or FOLFIRI (3,4) plus biological agents.

Bevacizumab (Avastin; Genentec, Inc., South San Fran cisco, CA), a recombinant, humanized monoclonal antibody that binds to and neutralizes vascular endothelial growth factor (VEGF) is one of the biological agents and was proved to improve overall survival (OS) and progression-free survival (PFS) in bevacizumab-naïve patients with metastatic CRC when administered to first- and second-line chemotherapy.

For patients with previously treated metastatic CRC, treatment results of FOLFIRI or FOLFOX as a second-line therapy were reported from the phase III study. PFS was 2.5 and 4.2 months, respectively (5). Treatment results of FOLFIRI plus bevacizumab at 5 mg/kg and FOLFOX plus bevacizumab at 5 mg/kg as a second-line treatment were reported from the phase II study. PFS was 7.8 and 5.3 months, respectively (6). In addition, the treatment result of FOLFOX4 plus bevacizumab at 10 mg/kg as a second-line therapy was reported from a randomized phase III study. OS as the primary objective was 12.9 months compared with 10.8 months of FOLFOX4 alone (HR, 0.66; $P < 0.0011$). PFS was 7.3 months, which is also significantly improved compared with 4.7 months of FOLFOX4 alone (HR, 0.61; $P < 0.0001$) (7). However, all of these treatments were examined for previously bevacizumab-naïve patients.

A key element of continuous administration of bevacizumab beyond progression is as shown below. In basic research, regrowth of tumor vessels are often observed soon after cessation of bevacizumab administration (8–10) and VEGF expression is identified across the board from the initial period of the tumor lifecycle (11). Several experimental studies have examined that the muMAb 4.6.1 antibody, mouse monoclonal precursor of VEGF inhibitors in CRC xenograft models prevents growth of tumor cells at metastatic sites dose dependently (12). In addition, the BRiTE study (13), one of the observational cohort studies in the USA provides supportive clinical data about the foregoing. Median OS were 12.6, 19.9 and 31.8 months in the no post-progressive disease (PD) treatment, chemotherapy without bevacizumab and chemotherapy with bevacizumab groups, respectively.

After adjustment for other prognostic factors, bevacizumab treatment beyond progression maintained a statistically significant effect on survival after PD, compared with no post-PD bevacizumab (HR, 0.49; 95% CI, 0.41–0.58; $P < 0.001$). In this study, the proportion of bevacizumab doses administered as the second-line therapy were 90.7% (5 mg/kg), 3.6% (7.5 mg/kg) and 2.3% (10 mg/kg). These results from the BRiTE study suggest that continuous VEGF inhibition with bevacizumab beyond initial PD could play an important role for prolonging survival of patients with metastatic CRC.

There are three major clinical questions to be solved about second-line biological agents in metastatic colorectal cancer. The first clinical question about the continuation of bevacizumab after exposure to bevacizumab treatment will be revealed from the results of the on-going trial 'AIO 0504'. The second clinical question about the drug selection between bevacizumab and anti-epidermal growth factor receptor antibodies with KRAS wild type after a first-line bevacizumab-containing regimen will also be answered by the on-going trial 'SPIRITT'.

On the other hand, the third clinical question about the optimal doses of bevacizumab as second-line treatment followed by a bevacizumab-containing regimen is still remains unsolved. The verified data indicates the efficacy of bevacizumab at 5 mg/kg/weekly (=10 mg/kg/biweekly) in the second-line setting followed by bevacizumab-naïve treatment (7). The recommended dose of bevacizumab is 5 mg/kg/weekly (=10 mg/kg/biweekly) in non-small cell lung cancer, breast cancer, renal cell cancer and second-line colorectal cancer (14–19), but 2.5 mg/kg/weekly (=5 mg/kg/biweekly) in the first-line CRC treatment. The dose of bevacizumab 2.5 mg/kg/weekly (=5 mg/kg/biweekly) could be lower than the recommended dose in the second-line CRC treatment.

Thus, it is necessary for us to investigate the effectiveness of high-dose bevacizumab for metastatic CRC.

Accordingly, we have conducted a randomized phase III study of FOLFIRI plus bevacizumab 5 mg/kg versus 10 mg/kg as second-line therapy in patients with metastatic CRC who have failed first-line bevacizumab plus oxaliplatin-based therapy (EAGLE study).

The study protocol was approved by the institutional review boards of each participating institution. The study met the ethical guidelines for clinical studies of the Health, Labor and Welfare Ministry in Japan, and was conducted in compliance with the Declaration of Helsinki. All patients provided written informed consent.

PROTOCOL DESIGN FOR EAGLE STUDY

Objective

A multicenter randomized phase III study of adding bevacizumab 5 or 10 mg/kg to FOLFIRI in advanced/metastatic CRC who have failed prior bevacizumab plus oxaliplatin-based first-line therapy.

Endpoint

The primary endpoint is PFS. The secondary endpoints are the toxicity, response rate, time to treatment failure, OS, OS from the start of the first-line treatment and second PFS (time duration from the initiation of the first-line treatment until progression after the protocol treatment). The progression will be evaluated on the basis of response evaluation criteria in solid tumors (RECIST) ver. 1.1.

Eligibility Criteria

Inclusion Criteria

(i) PD after chemotherapy with bevacizumab plus oxaliplatin-based therapy as the first-line treatment

(with measurable lesions in the RECIST criteria) or difficult to continue the first-line therapy due to the other reasons.
(ii) Oxaliplatin and bevacizumab were administered for more than four times in the first-line treatment.
(iii) Cytologically and/or histologically proven CRC.
(iv) Written informed consent.
(v) Aged 20 years old and above.
(vi) Eastern Cooperative Oncology Group performance status (ECOG PS) 0 or 1.
(vii) Life expectancy estimated $\geq$3 months.
(viii) Sufficient organ functions.

Exclusion Criteria

(i) Previous irinotecan treatment.
(ii) Administration of transfusion/hematopoietic factor or antithrombotic drug within 14 days.
(iii) Serious renal dysfunction.
(iv) Serious drug hypersensitivity or a history of drug allergy.
(v) Active concomitant malignancy.
(vi) Active infections.
(vii) Symptomatic or asymptomatic heart disease that is being treated at the time of registration to the trial.
(viii) History of thrombosis, interstitial pneumonia, pulmonary fibrosis or high-grade pulmonary emphysema.
(ix) Fresh hemorrhage from the digestive tube, intestinal tube paralysis, intestinal obstruction and peptic ulcer.
(x) Pleural effusion, peritoneal fluid and pericardial fluid.
(xi) Symptomatic brain metastasis.
(xii) History of mental disturbances or cerebrovascular accident.
(xiii) High blood pressure and diabetes that cannot be controlled.
(xiv) Uncontrolled diarrhea.
(xv) Serious non-healing wound and/or major surgical procedure within 4 weeks prior to enrolling in this trial.
(xvi) Traumatic fracture that has not been headed at the time of enrollment.
(xvii) Bleeding tendency and anti-platelet therapy (including aspirin and non-steroidal anti-inflammatory drugs).
(xviii) Pregnant women, possibly pregnant women, wishing to become pregnant and nursing mothers.
(xix) Needing treatment with atazanavir sulfate.
(xx) Paralyzed bowel.

Registration

Any medical institution that would like to participate could contact a secretariat at Epidemiological and Clinical Research Information Network (ECRIN) or publicly contact: Hideyuki Mishima at the Department of Surgery, National Hospital Organization Osaka National Hospital, Osaka, Japan.

Registration forms are sent from the ECRIN to the medical institution for registration.

Registered patients are allocated randomly into the FOLFIRI + 5 mg of bevacizumab arm (arm A) or the FOLFIRI + 10 mg of bevacizumab arm (arm B) at the data-center. For randomization, a minimization method or dynamic randomization is used with five balancing factors: baseline ECOG PS, number of metastasis ($2>$, $2\leq$), reason for a change in therapy to second-line treatment (PD in first-line treatment/non-PD), early recurrence within 6 months (during/after adjuvant treatment) and institutions.

Treatment Methods

FOLFIRI plus bevacizumab consists of bevacizumab at 5 mg/kg (or 10 mg/kg) as a 30-min infusion and *l*-leucovorin 200 mg/m^2 as a 2-h infusion, and concurrently irinotecan 150 mg/m^2 as an over 90-min infusion, followed by bolus fluorouracil (5-FU) 400 mg/m^2 within 15 min and 46-h infusion of 5-FU 2400 mg/m^2. Patients randomly assigned to arm A receive FOLFIRI plus bevacizumab 5 mg/kg. FOLFIRI plus bevacizumab 10 mg/kg is administered to patients randomly assigned to arm B. These treatments are repeated every 2 weeks until disease progression, unacceptable toxicity or patient choice.

Follow-Up

Disease progression and occurrence of new diseases are monitored by using abdominal radiography, abdominal computed tomography (CT) or magnetic resonance imaging, and thoracic CT, and by measuring levels of the tumor markers CEA and CA19–9 at the baseline and every 8 weeks during the treatment period (tumor marker levels are measured every 4 weeks). Blood tests and symptom checks (collecting adverse events) will be carried out throughout the treatment period. In case of dyspnea, arterial blood gases will be tested and chest X-ray test will be carried out. In case of arrhythmia, a 12 lead electrocardiogram will be carried out. The follow-up period is 1 year after the registration of the last patient.

Study Design and Statistical Analysis

The primary objective of this trial is to evaluate whether arm B (FOLFIRI plus 10 mg/kg of bevacizumab therapy) significantly improves PFS compared with arm A (FOLFIRI plus 5 mg/kg of bevacizumab therapy). The null hypothesis, if the PFS of both arms is equal, is tested by the stratified log-rank test with the balancing variables (except for the institutions) as the stratification factor. If arm B showed a statistically significant prolonging effect on PFS compared with the other arm, it is concluded that arm B is more

beneficial therapy. The overall significance level of the trial is set as 5% for the two-sided test.

PFS curves are depicted by the Kaplan–Meier method. Median PFS and the annual PFS rates are also estimated using the Kaplan–Meier method with the two-sided 95% confidence interval using the Greenwood formula (20). The stratified Cox proportional hazards model is used to assess the hazard ratio with Wald-type 95% confidence intervals for the treatment effect between both arms.

Median PFS of arm A in this trial is assumed to be 5.0 months based on previous studies (6,7) and it is considered as a clinically relevant prolongation if the median PFS of arm B is 7.0 months (risk reduction 30%). At the start of this trial, the planned sample size was 280 patients to detect 30% risk reduction with 80% power for a log-rank test comparing two survival curves with a two-sided significance level of 0.05, assuming an accrual time of 2 years and a follow-up time of 1 year (21). This calculation was carried out by employing nQuery Advisor 7.0 software (Statistical Solutions, Saugus, MA, USA). On 8 April 2011, an independent data monitoring committee of the EAGLE trial recommended that the statistical power be amended from 80 to 90% with the consideration of the promising enrollment of patients. As a result, 358 patients (330 events) will be needed to detect 90% power under the same assumption. Taking some dropouts into account, the sample size to be accrued was set at 370 patients in total.

THE EAGLE TRIAL GROUP

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Participating institutions: Approximately 150 Japanese institutions and hospitals are participating in this trial.

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Conflict of interest statement

None declared.

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Cediranib in combination with mFOLFOX6 in Japanese patients with metastatic colorectal cancer: results from the randomised phase II part of a phase I/II study

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Background: Colorectal cancer (CRC) is the second most common malignancy in Japan. Treatment with inhibitors of the vascular endothelial growth factor (VEGF) signalling pathway has proven benefit in metastatic CRC. Cediranib is an oral highly potent VEGF signalling inhibitor that inhibits all three VEGF receptors.

Patients and methods: In this phase II, double-blind, placebo-controlled study, 172 patients with metastatic CRC were randomised to receive once-daily cediranib (20 or 30 mg) or placebo, each combined with modified FOLFOX6 (mFOLFOX6). The primary objective was comparison of progression-free survival (PFS).

Results: The comparison of cediranib 20 mg versus placebo met the primary objective of PFS prolongation [hazard ratio = 0.70 (95% confidence interval 0.44–1.11), $P = 0.167$], which met the protocol-defined criterion of $P < 0.2$. Median PFS was 10.2 versus 8.3 months, respectively. The PFS comparison for cediranib 30 mg versus placebo did not meet the criterion. The most common adverse events (AEs) in the cediranib-containing groups were diarrhoea and hypertension.

Conclusions: Cediranib 20 mg plus mFOLFOX6 met the predefined criteria in terms of improved PFS compared with placebo plus mFOLFOX6. Cediranib 20 mg was generally well tolerated and the AE profile was consistent with previous studies.

Key words: cediranib, colorectal cancer, mFOLFOX6, placebo, progression-free survival

introduction

In Japan, the incidence of colorectal cancer (CRC) has increased nearly fivefold in the last 25 years, owing primarily to changing Japanese dietary habits, which are becoming increasingly similar to those of Western countries. In 2008, there were 101 656 new cases of CRC in Japan and 43 349 deaths attributed to this disease [1]. CRC is now the second most common malignancy in Japan and is predicted to become the most common by 2015. Fluorouracil (5-FU) was one of the first chemotherapies used for the treatment of CRC, and the combination of 5-FU with leucovorin and oxaliplatin (FOLFOX) has improved outcomes. Treatment with these components (plus irinotecan in some regimens) can provide a median overall survival (OS) of up to 20 months, compared with ~6 months with best supportive care [2]. Japanese clinical guidelines recommend FOLFOX as standard treatment of metastatic colorectal cancer (mCRC) [3]. To reduce toxicity associated with the FOLFOX regimen, a number of modifications have been tried [4, 5]; the current standard is modified FOLFOX6 (mFOLFOX6).

Inhibition of the vascular endothelial growth factor (VEGF) signalling pathway with bevacizumab has demonstrated additional clinical benefit in CRC when used with 5-FU-based regimens in the first-line setting in mCRC [6, 7]. Cediranib is an oral highly potent VEGF tyrosine kinase inhibitor (TKI) that inhibits all three VEGF receptors [8, 9]. Cediranib is suitable for once-daily dosing and has demonstrated antitumour activity during early phase clinical evaluation in patients with advanced cancer [10]. Further studies demonstrated that cediranib was generally well tolerated as monotherapy [11–15] and in combination with various anticancer agents at doses ≤30 mg/day [16–21].

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The efficacy of cediranib in combination with chemotherapy has been investigated in two phase III studies—HORIZON II [22] and HORIZON III [23]—in Western patients with previously untreated mCRC. Two cediranib doses were initially selected for investigation in the HORIZON programme: 20 (lowest biologically active dose) and 30 mg/day (maximum dose suitable for chronic dosing in combination with chemotherapy). The decision to investigate cediranib 20 and 30 mg/day doses in this study was taken before an end-of-phase II decision from the HORIZON programme to proceed with only the 20 mg/day dose. As such, this two-part phase I/II study, which mirrored HORIZON II, investigated cediranib, at the same doses used initially in the Western studies, plus mFOLFOX6 in Japanese patients with previously untreated mCRC (ClinicalTrials.gov identifier NCT00494221; AstraZeneca study code D8480C00039). The phase I part of this study demonstrated that both doses of cediranib were generally well tolerated in combination with mFOLFOX6 [24]. Here, we report the results of the randomised, double-blind, phase II part of this study, which assessed the efficacy of cediranib (20 or 30 mg/day) plus mFOLFOX6 compared with mFOLFOX6 alone.

patients and methods

eligibility

Eligible patients were aged ≥18 years with histological or cytological confirmation of carcinoma of the colon or rectum. Patients required chemotherapy for stage IV (metastatic) disease, had a World Health Organisation (WHO) performance status (PS) of zero or one, and one or more measurable lesions according to the RECIST (version 1.0). Any adjuvant oxaliplatin or 5-FU therapy must have been completed >12 and >6 months, respectively, before study entry. Patients with brain or meningeal metastases were considered eligible if they were clinically stable and had not required corticosteroid treatment of 10 days. Exclusion criteria included prior systemic therapy for metastatic disease and prior therapy with monoclonal antibodies or small molecule inhibitors against VEGF or VEGF receptors, including bevacizumab and cediranib.

study design

This phase II, randomised, double-blind, placebo-controlled study assessed the efficacy of first-line treatment with cediranib plus mFOLFOX6 compared with mFOLFOX6 alone. Patients were randomised 1 : 1 : 1 to receive once-daily cediranib (20 or 30 mg) or placebo, each in combination with 14-day treatment cycles of mFOLFOX6 (oxaliplatin 85 mg/m^2 IV, day 1; leucovorin 200 mg/m^2 IV, day 1; 5-FU 400 mg/m^2 IV bolus, day 1 and then 2400 mg/m^2 continuous IV infusion over 46 h). Patients were stratified at randomisation according to a two-level liver function covariate [based on baseline albumin and alkaline phosphatase (ALP) levels] and WHO PS (0 versus 1). Randomised treatment was continued until objective disease progression (as defined by RECIST) or until the occurrence of toxicity, death, withdrawal of patient consent or other discontinuation criteria. RECIST measurements were made using computed tomography or magnetic resonance imaging scans; clinical assessment of these scans was conducted by the study investigators.

The primary objective was to determine the efficacy of cediranib plus mFOLFOX6 compared with mFOLFOX6 alone by assessment of progression-free survival (PFS). Secondary objectives included comparison of OS, objective response rate (ORR: complete response + partial response), duration of response, change in tumour size and assessment of the safety and tolerability of cediranib plus mFOLFOX6. An exploratory end point was to investigate the effect of treatment on soluble markers of angiogenesis (VEGF and sVEGFR-2). VEGF and sVEGFR-2 were measured by enzyme-linked immunosorbent assay of plasma samples from patients who provided separate informed consent.

PFS and ORR were determined from objective tumour assessments (RECIST) carried out at weeks 6, 12, 18, 24 and then every 12 weeks until disease progression or death. Adverse events (AEs) were recorded and graded according to Common Terminology Criteria for Adverse Events version 3.0. The study was approved by each centre's institutional review board and was carried out in accordance with the Declaration of Helsinki, the International Conference on Harmonisation/Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics.

statistical analysis

Assuming a median PFS of 9 months in the placebo group, an 18-month accrual period and a minimum 12-month follow-up, a total of 55 patients per group was required to have 80% power to detect a true PFS hazard ratio (HR) of 0.6 at two-sided significance level of $P < 0.2$ (one-sided $P < 0.1$), which was considered appropriate evidence of activity for a randomised phase II study [25]. The primary PFS analysis was conducted using a log-rank test stratified by WHO PS (0 or 1) and a two-level baseline liver function covariate (covariate 1 for baseline albumin < 3.5 g/l or ALP > 320 U/l; covariate 0 for all other values). PFS and OS were summarised by treatment group using the Kaplan–Meier method. The formal analysis was conducted when ~105 progression events had occurred across the three groups. No formal statistical analysis was carried out on safety data.

The results in the present study were relatively immature (65% of PFS events versus 81% in HORIZON II) and the HR was favourable compared with HORIZON II (HR = 0.84). Furthermore, there was a higher proportion of patients with a PS of zero. Therefore, further analysis of efficacy and safety outcomes was carried out when 81% of progression events had occurred.

results

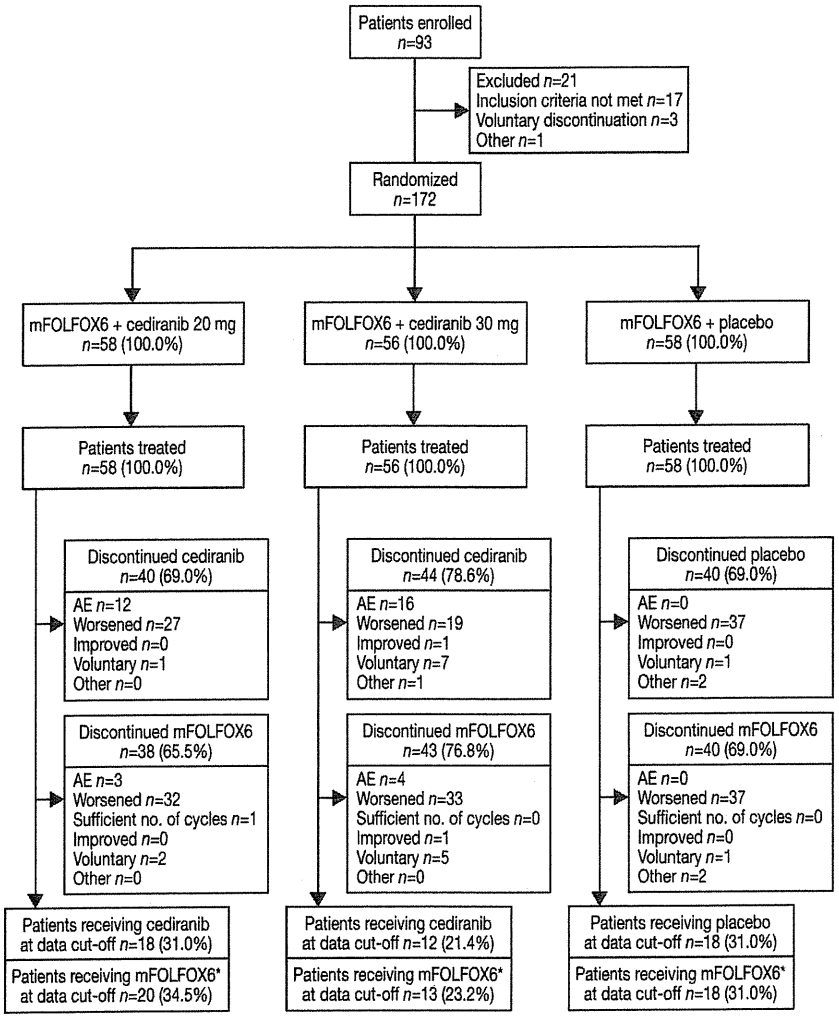
patients

Between January 2008 and January 2009, 172 Japanese patients were randomised to treatment with cediranib 20 mg plus mFOLFOX6 ($n = 58$), cediranib 30 mg plus mFOLFOX6 ($n = 56$) or placebo plus mFOLFOX6 ($n = 58$) (Figure 1). Patient characteristics were representative of the patient population (Table 1). All patients were Japanese and 20% were receiving antihypertensive treatment at baseline. Baseline characteristics were generally well balanced across the groups, although there were more female patients in the cediranib 30 mg group. Imbalances were noted in metastases at baseline, time from initial diagnosis to randomisation, tumour grading, baseline ALP and baseline liver function (Table 1).

At the protocolled data cut-off (13 October 2009), 65% (112) of patients had progressed and 22% (38) had died. The most common reason for discontinuation of placebo/cediranib was worsened condition. At the second data cut-off (11 June 2010), 81% of patients had progressed and median OS follow-up was 19.0 months with 74 OS events.

efficacy

For the PFS comparison of cediranib 20 mg versus placebo, the HR was 0.70 [95% confidence interval (CI) 0.44–1.11],



*Patients may be receiving either 5-FU/leucovorin or 5-FU/leucovorin/oxaliplatin.

Figure 1. CONSORT diagram.

two-sided $P = 0.167$ (Figure 2A), which met the protocol-defined criterion for evidence of activity ($P < 0.2$). Median PFS was 10.2 and 8.3 months, respectively. For the PFS comparison of cediranib 30 mg versus placebo, the HR was 0.82 (95% CI 0.54–1.31), two-sided $P = 0.261$ (Figure 2B), which did not meet the predefined criterion. Median PFS was 8.9 months in the cediranib 30 mg arm. Predefined subgroup analysis of PFS for both dose groups did not identify a particular patient population that derived a differential PFS benefit from cediranib versus placebo (supplemental Figure S1, available at *Annals of Oncology* online).

The ORR was 53.4%, 69.6% and 53.4% in the cediranib 20 mg, cediranib 30 mg and placebo arms, respectively; RECIST best response is summarised in Table 2. The median best percentage changes in tumour size were −37.3% (cediranib 20 mg), −43.4% (cediranib 30 mg) and −40.0% (placebo). The median duration of response was 9.2 (cediranib 20 mg), 6.7 (cediranib 30 mg) and 7.1 months (placebo) (Figure 3). At the primary analysis, there were insufficient deaths (total = 38; 15, 9 and 14 in the cediranib 20 mg, cediranib 30 mg and placebo arms, respectively) to draw conclusions on OS.

safety and tolerability

Overall, the most common AEs were diarrhoea and hypertension (Table 3); neither caused discontinuation of cediranib at the 20 mg dose. The incidence of AEs leading to discontinuation of cediranib/placebo was higher in the cediranib 30 mg group (27%) compared with the cediranib 20 mg (19%) or placebo (0%) groups; of these, only decreased appetite, diarrhoea and pneumonia (all $n = 2$) were reported in multiple patients.

The incidence of grade 3/4 AEs was 66%, 75% and 36% in the cediranib 20 mg, cediranib 30 mg and placebo groups, respectively. The most common grade 3/4 AEs are summarised in Table 4. The incidence of serious adverse events (SAEs) was 39.7%, 39.3% and 19.0% in the cediranib 20 mg, cediranib 30 mg and placebo groups, respectively. No AEs had an outcome of death.

Clinical laboratory evaluation showed that treatment with cediranib plus mFOLFOX6 caused decreases in leucocyte, neutrophil and platelet counts and an increase in thyroid-stimulating hormone, but no new clinically important trends were observed in either cediranib group.

Table 1. Patient demographics and baseline characteristics

Characteristic	Cediranib 20 mg + mFOLFOX6 (n = 58)	Cediranib 30 mg + mFOLFOX6 (n = 56)	Placebo + mFOLFOX6 (n = 58)
Median age (range), years	63.5 (33–79)	64.5 (40–82)	64.0 (36–80)
Sex, n (%)			
Male	38 (65.5)	30 (53.6)	39 (67.2)
Female	20 (34.5)	26 (46.4)	19 (32.8)
World Health Organisation performance status, n (%)			
0	44 (75.9)	43 (76.8)	47 (81.0)
1	14 (24.1)	13 (23.2)	11 (19.0)
Type of cancer, n (%)			
Colon	39 (67.2)	34 (60.7)	36 (62.1)
Rectal	19 (32.8)	22 (39.3)	22 (37.9)
Tumour grading, n (%)			
Well differentiated (G1)	11 (19.0)	14 (25.0)	16 (27.6)
Moderately differentiated (G2)	44 (75.9)	38 (67.9)	36 (62.1)
Poorly differentiated (G3)	2 (3.4)	3 (5.4)	4 (6.9)
Undifferentiated (G4)	1 (1.7)	1 (1.8)	1 (1.7)
Unassessable (GX)	0	0	1 (1.7)
Metastatic sites, n (%)			
1	32 (55.2)	29 (51.8)	28 (48.3)
>1	26 (44.8)	27 (48.2)	30 (51.7)
Metastases at baseline, n (%)			
Patients with liver only metastases at baseline	14 (24.1)	10 (17.9)	14 (24.1)
Patients with liver and other metastases at baseline	25 (43.1)	22 (39.3)	32 (55.2)
Patients with no liver involvement at baseline	19 (32.8)	24 (42.9)	12 (20.7)
Prior adjuvant therapy, n (%)			
Yes	13 (22.4)	9 (16.1)	8 (13.8)
No	45 (77.6)	47 (83.9)	50 (86.2)
Time from initial diagnosis to randomisation, n (%)			
<6 months	36 (62.1)	38 (67.9)	45 (77.6)
6 to <12 months	2 (3.4)	0	1 (1.7)
12 to <24 months	6 (10.3)	10 (17.9)	4 (6.9)
24 to <36 months	6 (10.3)	2 (3.6)	3 (5.2)
≥36 months	8 (13.8)	6 (10.7)	5 (8.6)
Baseline ALP, n (%)			
≤320 U/l	31 (53.4)	35 (62.5)	29 (50.0)
>320 U/l	27 (46.6)	21 (37.5)	29 (50.0)
Baseline liver function			
ALP > 320U/l or albumin < 35 g/l	29 (50.0)	22 (39.3)	30 (51.7)
Other	29 (50.0)	34 (60.7)	28 (48.3)
Baseline vascular endothelial growth factor			
n	36	37	38
Mean (standard deviation), pg/ml	146.5 (416.3)	74.3 (56.6)	96.9 (100.7)
Median (min, max), pg/ml	46.6 (31.2, 2520.5)	55.5 (31.2, 243.3)	54.6 (31.2, 508.1)

mFOLFOX6, modified FOLFOX6; ALP, alkaline phosphatase.

The median duration of exposure was 241.5, 213.0 and 223.5 days in the cediranib 20 mg, cediranib 30 mg and placebo groups, respectively. The proportion of patients experiencing a dose reduction/pause was highest in the cediranib 30 mg group (83.9%) versus the cediranib 20 mg (79.3%) and placebo (56.9%) groups (supplemental Figure S2, available at *Annals of Oncology* online). The dose intensity of cediranib/placebo was lower in the 30 mg group compared with the 20 mg and placebo groups; the mean daily dose of cediranib was 16.6 and 22.8 mg in the cediranib 20 and 30 mg groups, respectively. Exposure to mFOLFOX6 was similar in all arms; the median numbers of cycles of 5-FU, leucovorin and oxaliplatin were 17.0, 17.0 and 12.5, respectively, in the cediranib 20 mg group, 14.0, 14.0 and 11.0, respectively, in the cediranib 30 mg group and 15.0, 15.0 and 11.5, respectively, in the placebo group. However, more patients in the cediranib 30 mg group (33%) stopped oxaliplatin >12 weeks before progression compared with those in the cediranib 20 mg (14%) or placebo (8%) groups.

soluble biomarkers

Median VEGF levels ranged from 47 to 55 pg/ml at baseline; during treatment, levels remained similar to baseline in the placebo group but increased in cediranib-treated patients. In the cediranib 20 mg group, levels increased to 89 pg/ml by day 28

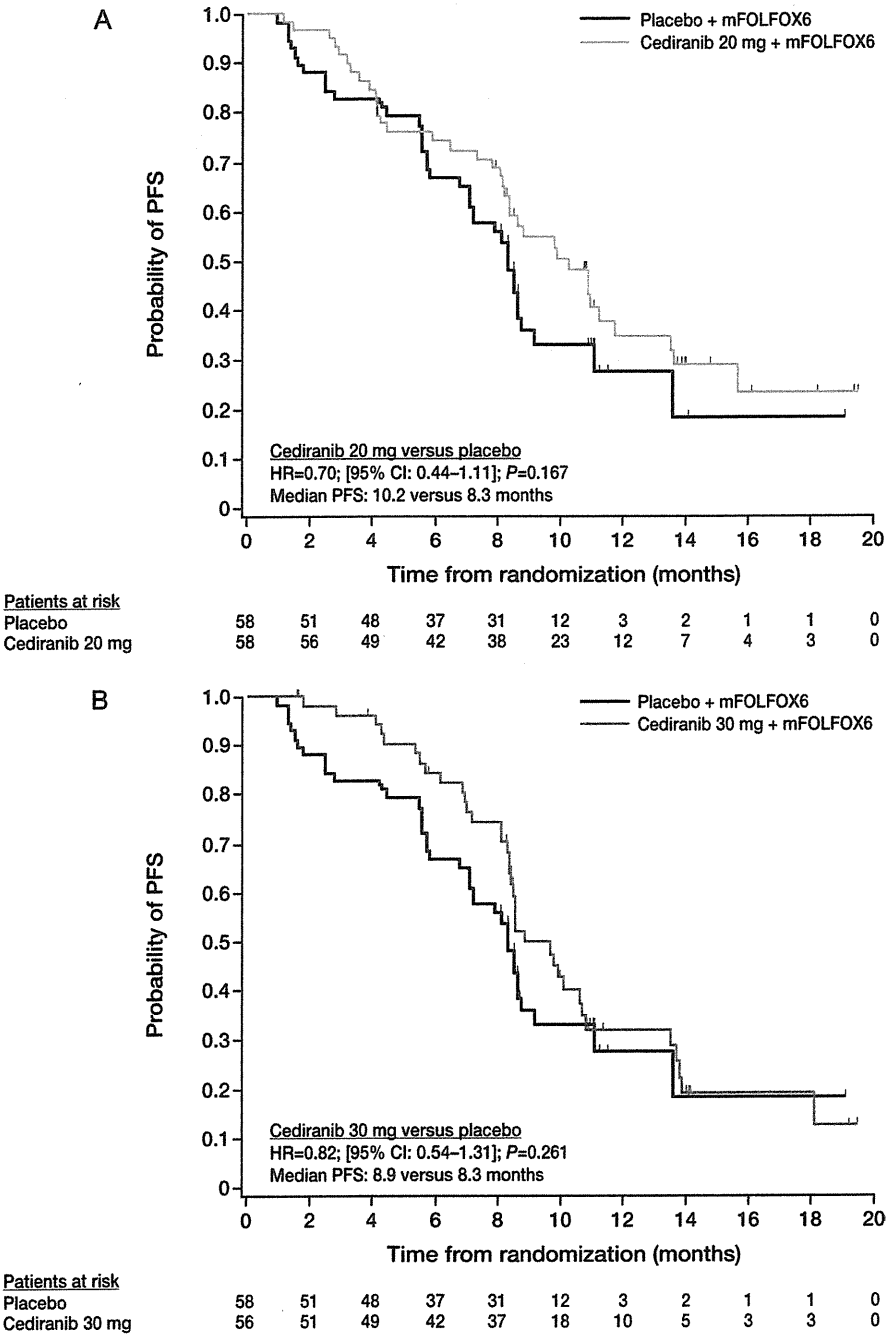


Figure 2. (A) Progression-free survival (PFS) for patients who received cediranib 20 mg + modified FOLFOX6 (mFOLFOX6) versus placebo + mFOLFOX6. (B) PFS for patients who received cediranib 30 mg + mFOLFOX6 versus placebo + mFOLFOX6.

Table 2. Best RECIST response

Best response, *n* (%)	Cediranib 20 mg + mFOLFOX6 (*n* = 58)	Cediranib 30 mg + mFOLFOX6 (*n* = 56)	Placebo + mFOLFOX6 (*n* = 58)
CR	0	0	2 (3.4)
PR	31 (53.4)	39 (69.6)	29 (50.0)
Stable disease ≥6 weeks	24 (41.4)	14 (25.0)	20 (34.5)
Progressive disease	3 (5.2)	1 (1.8)	7 (12.1)
Non-evaluable	0	2 (3.6)	0

mFOLFOX6, modified FOLFOX6; CR, complete response; PR, partial response.