Table 3 Patient incidence of motesanib-related adverse events occurring in more than 10% of patients

Adverse event	Motesanib dose cohort			All patients ($n = 15$)
	50 mg QD ($n = 3$)	100 mg QD ($n = 3$)	125 mg QD ($n = 9$)	
Incidence of motesanib-related adverse events, *n*	3	3	9	15
Proteinuria	3	2	5	10
Hypertension	0	3	6	9
Fatigue	2	1	4	7
Headache	0	2	4	6
Hematuria	1	2	2	5
Diarrhea	1	0	4	5
Alanine aminotransferase increased	0	1	2	3
Dry skin	0	1	2	3
Nausea	0	1	2	3
Stomach discomfort	2	0	1	3
Vomiting	1	1	1	3
White blood cell count decreased	0	1	2	3
Aspartate aminotransferase increased	0	1	1	2
Blood alkaline phosphatase increased	0	0	2	2
Blood creatinine phosphokinase MB increased	1	1	0	2
Blood triglycerides increased	0	1	1	2
Cough	0	1	1	2
Eosinophil count increased	0	0	2	2
Eyelid edema	0	1	1	2
Edema	0	0	2	2
Pleural effusion	0	1	1	2
Rash	0	0	2	2
Weight decreased	1	0	1	2

and antitumor activity in preclinical models of human cancer [17] and acceptable toxicity and promising clinical efficacy in a phase 1 study conducted in the US [18].

The aim of this study was to investigate the safety, pharmacokinetics, and antitumor efficacy of motesanib in Japanese patients with advanced solid tumors.

No DLTs occurred in this study and, therefore, the MTD was not reached. We confirmed the tolerance of the 125 mg QD dose recommended in the US [18].

The safety profile of motesanib in this population of Japanese patients was similar to that observed in the US study [18].

Adverse events were typically mild to moderate in severity, and all of toxicities were acceptable at all motesanib doses tested in this study.

The most frequently occurring non-hematologic toxicity in cycle 1 was hypertension. There were two patients with grade 3 hypertension in level 2. The median time to onset of hypertension was 9 days (cycle 1) after treatment initiation. Hypertension increased in frequency as well as in severity at high dose or with multiple doses of motesanib. However, hypertension was typically manageable with antihypertensive therapy medications including calcium blocker.

The incidence of hypertension in this study was similar to that observed in the motesanib phase 1 study conducted in the US [18] as well as the incidence rate noted in studies of other VEGF inhibitors [20, 21]. Hypertension has been observed during treatment with other VEGF inhibitors and is considered a class effect of these agents [22]. Hypertension appears to be induced possibly by increasing vascular resistance (due to decreased NO and prostacyclin production), vascular rarefaction, and increased arterial stiffness [23, 24].

No patients experienced thromboembolic events or cholecystitis in this study.

Motesanib was rapidly absorbed following oral administration.

Values for t_{max} and $t_{1/2,z}$ were similar to those observed at the same doses in the US study [18]. However, exposure

Table 4 Pharmacokinetic parameters for motesanib following single-dose (day 1) and multiple-dose (day 21) oral administration

	Motesanib dose cohort		
	50 mg QD	100 mg QD	125 mg QD
Day 1			
n	3	3	9
t_{max}, h	0.25 (0.25–0.25)	0.5 (0.5–1.0)	1.0 (0.25–2.0)
C_{max}, ng/ml	462 (322–695)	521 (468–696)	792 (285–2410)
$t_{1/2,z}$, h	5.96 (5.07–6.12)	7.26 (6.35–9.24)	6.54 (4.04–8.11)
AUC_{0-inf}, μg h/ml	1.84 (1.17–1.88)	3.50 (1.56–5.85)	3.08 (2.35–6.61)
AUC_{0-24}, μg h/ml	1.77 (1.12–1.78)	3.16 (1.52–5.08)	2.84 (2.23–6.51)
CL/F, l/h	27.2 (26.6–42.7)	28.6 (17.1–64.1)	40.6 (18.9–53.1)
C_{24}, ng/ml	8.49 (6.83–12.5)	29.4 (3.53–50.2)	14.6 (4.68–37.0)
C_{48}, ng/ml	0.347 (0.310–0.715)	3.66 (0.547–11.3)	1.63 (BQL–4.94)
Day 21			
n	3	3	9
t_{max}, h	0.5 (0.5–2.0)	1.0 (1.0–2.0)	1.0 (0.25–2.0)
C_{max}, ng/ml	561 (267–669)	390 (351–636)	639 (272–1350)
$t_{1/2,z}$, h	3.81 (3.38–5.24)	4.83 (4.20–5.92)	4.12 (2.81–5.29)
AUC_{0-inf}, μg h/ml	NR	NR	NR
AUC_{0-24}, μg h/ml	1.31 (0.932–1.43)	2.36 (1.06–4.94)	1.99 (0.862–5.68)
CL/F, l/h	38.1 (35.0–53.6)	42.3 (20.2–94.6)	62.8 (22.0–145)
C_{24}, ng/ml	2.22 (1.24–4.64)	12.2 (2.81–45.3)	6.32 (0.979–33.8)
C_{48}, ng/ml	NR	NR	NR

AUC_{0-inf} = area under the plasma concentration versus time curve from time 0 to infinite time; AUC_{0-24} = area under the plasma concentration versus time curve from time 0–24 h postdose; CL/F = apparent clearance; C_{max} = maximum observed concentration after dosing; C_{24} = observed concentration at 24 h postdose; C_{48} = observed concentration at 48 h postdose; NR = not reported; QD = daily dose; t_{max} = time of maximum observed plasma concentration; $t_{1/2,z}$ = estimated terminal elimination half-life; BQL = below quantitation limit (0.5 ng/ml); All values are reported as the median (range)

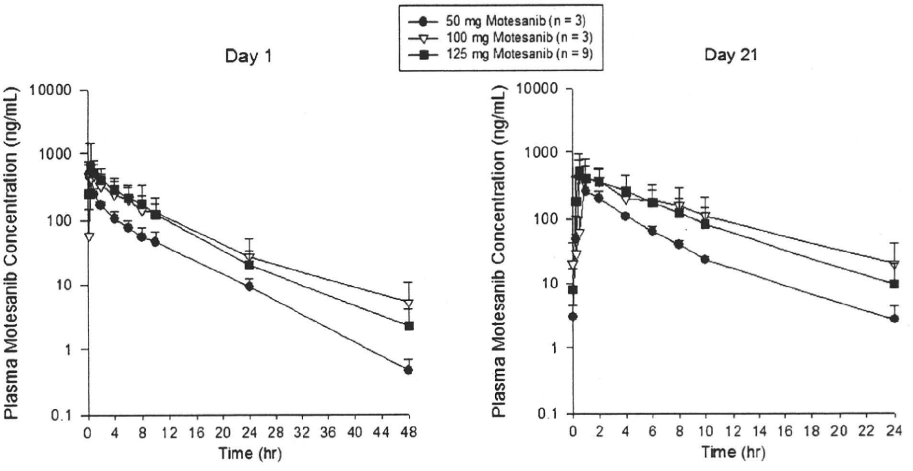

Fig. 1 Mean (+SD) plasma concentration–time profiles for motesanib after single-dose (day 1) and multiple-dose (day 21) administration in patients with advanced solid tumors

to motesanib was somewhat greater in this study than in previous motesanib studies. The reasons for this increased exposure are unclear.

Motesanib mean trough concentrations (C_{24}) were above the IC50 for human umbilical vein endothelial cell proliferation (4 ng/ml) [17] at dose ≥100 mg QD.

There was no evidence that motesanib accumulates in plasma following multiple-dose administration.

Motesanib exhibited encouraging antitumor activity in this study with all patients enrolled achieving a best response of stable disease. The duration of response in these patients seemed clinically meaningful. However,

Table 5 Tumor response per RECIST

	Motesanib dose cohort			All patients (n = 15)
	50 mg QD (n = 3)	100 mg QD (n = 3)	125 mg QD (n = 9)	
Patients with measurable/non-measurable disease at baseline, n	3	3	9	15
Response assessment, n				
Stable disease	3	3	9	15
Durable (>24 weeks) stable disease	0	0	5	5

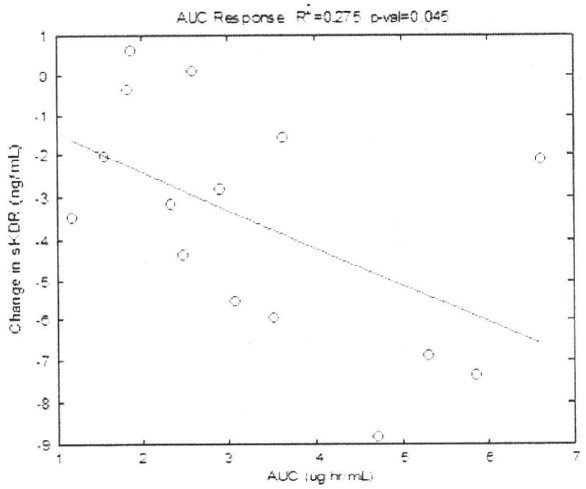

Fig. 2 Changes in serum sKDR compared to motesanib AUC

because of the small size of the study population, few firm conclusions can be drawn from this study regarding the clinical efficacy of motesanib. Bevacizumab, sunitinib malate, and sorafenib tosylate have demonstrated clinical efficacy, providing proof of concept that antiangiogenic agents can provide significant clinical benefit. In addition, multiple other small-molecule multikinase inhibitors including VEGFR as a target are currently under clinical development.

Adverse events generally reported to occur with increased incidence in patients receiving these investigational products include diarrhea, nausea, vomiting, hypertension, and fatigue [21, 25–27]. Some angiogenesis inhibitors have been associated with arterial and venous thrombosis [28, 29]. In this study, thrombosis was not observed.

The trends in the changes in the angiogenic cytokines follows patterns similar to those reported in the motesanib phase 1 study as reported in Rosen et al. [18]. These discrepancies could be associated with small sample size, and it should be taken the small sample size and paucity of decreased SLD measures into consideration at evaluation. The statistical analysis of the changes in the angiogenic factors in this study was limited by the small study size (15 patients). The results reported by Rosen et al. [18] were analyzed in larger study size of 69 patients.

Factors that may impact the comparison between the two studies are ethnicity, particular selection of tumor types, and the difference in when the tumor was assessed.

These results demonstrated that motesanib was tolerable in Japanese patients at doses up to 125 mg QD.

The safety profile of motesanib was similar to that observed in a US study.

These results, and the encouraging antitumor activity observed in this study, support the further development of motesanib for the treatment of patients with solid tumors.

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Phase II study of oxaliplatin plus S-1 as first-line treatment for advanced gastric cancer (G-SOX study)

W. Koizumi[1]*, H. Takiuchi[2], Y. Yamada[3], N. Boku[4], N. Fuse[5], K. Muro[6], Y. Komatsu[7] & A. Tsuburaya[8]

[1]*Department of Gastroenterology/Gastrointestinal Oncology, Kitasato University School of Medicine, Sagamihara;* [2]*Department of Gastroenterology, Osaka Medical College, Takatsuki;* [3]*Gastrointestinal Medical Oncology Division, National Cancer Center Hospital, Tokyo;* [4]*Division of Gastrointestinal Oncology, Shizuoka Cancer Center, Sunto-gun;* [5]*Division of Gastrointestinal Oncology and Digestive Endoscopy, National Cancer Center Hospital East, Kashiwa;* [6]*Department of Clinical Oncology, Aichi Cancer Center Hospital, Nagoya;* [7]*Department of Cancer Chemotherapy, Hokkaido University Hospital Cancer Center, Sapporo and* [8]*Department of Gastrointestinal Surgery, Kanagawa Cancer Center, Yokohama, Japan*

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Background: The efficacy and safety of oxaliplatin combined with S-1 (SOX regimen) for unresectable advanced or recurrent gastric cancer were investigated.

Patients and methods: Oxaliplatin was administered i.v. (100 mg/m^2) on day 1, while S-1 was administered orally (80 mg/m^2/day, b.i.d.) for 14 days followed by a 7-day rest. This schedule was repeated every 3 weeks.

Results: Among 55 patients enrolled, one patient received oxaliplatin for the other study, and three patients were considered unsuitable against the inclusion criteria. Accordingly, 51 patients were assessable for efficacy. The response rate was 59%, and the disease control rate was 84%. The median progression-free survival time was 6.5 months, the 1-year survival rate was 71%, and the median survival time was 16.5 months. In 54 patients assessed for safety, the major grade 3/4 toxic effects were neutropenia (22%), thrombocytopenia (13%), anemia (9%), anorexia (6%), fatigue (6%), and sensory neuropathy (4%).

Conclusion: These findings indicate that SOX regimen with oxaliplatin at a dose of 100 mg/m^2 is feasible and shows promising efficacy against advanced gastric cancer.

Key words: advanced gastric cancer, oxaliplatin, phase II, S-1, SOX

introduction

Chemotherapy for advanced gastric cancer was proven to be superior to best supportive care in terms of survival and quality of life [1–3]. Phase III studies have been carried out to compare epirubicin/cisplatin/5-fluorouracil (5-FU) with 5-FU/doxorubicin/methotrexate, cisplatin/5-FU with docetaxel/cisplatin/5-FU, and 5-FU/cisplatin with capecitabine/cisplatin [4–6]. On the basis of the results of these studies, advanced gastric cancer is mainly treated with combination chemotherapy that includes fluoropyrimidine derivatives and platinum compounds.

Oxaliplatin is a third-generation platinum compound that was developed to improve tolerability and ease of administration compared with cisplatin [7]. The non-inferiority of oxaliplatin-based regimens to cisplatin-based regimens was demonstrated in the Revised European-American Lymphoma (REAL)-2 phase III study [8]. In addition, the result of phase III study comparing 5-FU/leucovorin/cisplatin with 5-FU/leucovorin/oxaliplatin showed that oxaliplatin was at least as effective as cisplatin [9].

S-1 is an orally active prodrug of 5-FU that contains tegafur (which is continuously metabolized to 5-FU) blended with two modulators, gimeracil and potassium oxonate [10]. In Japan, advanced gastric cancer is mainly treated with S-1 alone or S-1 combined with other drugs. The SPIRITS phase III study demonstrated the superiority of S-1 plus cisplatin to S-1 alone [11]. The S-1 plus cisplatin regimen was also investigated by the FLAGS phase III study carried out in Western countries, which demonstrated that S-1 plus cisplatin was at least as effective as 5-FU plus cisplatin and less toxic [12].

We conducted a multicenter phase II study to evaluate the efficacy and safety of the combination regimen of S-1 and oxaliplatin (SOX regimen) in advanced gastric cancer as first-line therapy.

patients and methods

patients' eligibility

The following criteria were used to enroll patients for the present study. All patients had unresectable advanced or recurrent gastric cancer excluding the esophagus and gastroesophageal junction, confirmed by histological or

Correspondence to: Dr W. Koizumi, Department of Gastroenterology/Gastrointestinal Oncology, Kitasato University School of Medicine, 2-1-1 Asamizodai, Sagamihara, Kanagawa 228-8520, Japan. Tel: +81-42-748-9111; Fax: +81-42-748-5120; E-mail: koizumi@med.kitasato-u.ac.jp

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cytological examination. They had survived at least 4 weeks if extended or standard surgery had been carried out (or at least 2 weeks after minor surgery) and were able to take oral drugs. They were aged ≥20 years, had an Eastern Cooperative Oncology Group performance status (PS) of zero to two, and were expected to survive for at least 2 months. In general, they had not received prior chemotherapy, but those who had completed postoperative adjuvant therapy at least 180 days before enrollment were eligible. They had at least one measurable lesion according to RECIST guidelines [13]. They also had adequate bone marrow function (hemoglobin level ≥ 80 g/l, white blood cell count of 3–12 × 10^9/l, neutrophil count ≥ 1.5 × 10^9/l, and platelet count ≥ 100 × 10^9/l), liver function (total bilirubin ≤ 1.5 × the institutional upper limit of normal, aspartate aminotransferase/alanine aminotransferase ≤ 2.5 × the institutional upper limit of normal, and alkaline phosphatase ≤ 2.5 × the institutional upper limit of normal), and renal function (serum creatinine level ≤ 1.5 mg/dl and creatinine clearance ≥ 50 ml/min). All patients provided written informed consent.

This study was carried out in accordance with the Helsinki declaration and Good Clinical Practice guidelines and was approved by the institutional review boards of all participating medical institutions.

treatment plan

Oxaliplatin was administered i.v. at a dose of 100 mg/m^2 on day 1. S-1 was administered orally at a dose of 80 mg/m^2/day b.i.d. for 14 days (from the evening on day 1 until the morning on day 15), followed by a 7-day rest period in the 3-weekly schedule. Treatment was repeated until there was disease progression, unacceptable toxicity, or withdrawal of consent.

In the event of grade 4 neutropenia or febrile neutropenia or grade 3 diarrhea or stomatitis, the doses of oxaliplatin and S-1 were reduced by one dose level from the next cycle. If grade 2 sensory neuropathy not recovering by the end of the cycle or grade 3 sensory neuropathy occurred, the dose of oxaliplatin was reduced by one dose level from the next cycle after recovering to grade 2 or less. If grade 2 thrombocytopenia continued ≥8 days after the scheduled day for starting the next cycle or if platelet transfusion was required, oxaliplatin was reduced by one dose level from the next cycle. Oxaliplatin and S-1 could be reduced by two dose levels, but treatment was discontinued if subsequent reduction was indicated. The doses of oxaliplatin and S-1 could be reduced by 25 mg/m^2 and 10–30 mg/day, respectively, for each level. Treatment was discontinued if grade 4 diarrhea, stomatitis, or sensory neuropathy occurred, if grade 3 sensory neuropathy failed to recover by the time when the next cycle was scheduled, if grade 2 thrombocytopenia continued ≥15 days after the scheduled day for starting the next cycle, or if the rest period of S-1 was over 21 days.

evaluation

The data on the patients' characteristics, a 12-lead electrocardiogram, computed tomography (CT) scans, and tumor marker levels (CA19-9 and carcinoembryonic antigen) were obtained within 14 days of enrollment, while hematology tests, biochemistry tests, and assessment of symptoms and signs were carried out within 7 days before enrollment. During the study, hematology tests, biochemistry tests, and assessment of symptoms and signs were carried out every week until the end of the fourth cycle and subsequently every 3 weeks. CT scans were carried out and tumor markers were measured every 6 weeks (every 2 months after the best overall response was achieved).

Responses were evaluated according to the RECIST guidelines. To confirm partial response (PR) (30% or greater decrease in the sum of the longest diameter of target lesions, referenced against the baseline sum of the longest diameter of target lesions together with stabilization or decrease in size of nontarget lesions) or complete response (CR) (disappearance of all target and nontarget lesions together with normalization of tumor marker levels), tumor measurements were repeated no <4 weeks after objective response was firstly obtained. Responses were assessed by the independent review committee. Overall survival (OS) was defined as the time from treatment initiation to death from any cause. Progression-free survival (PFS) was the time from treatment initiation to first documentation of disease progression detected by the review committee or death from any cause (censored at second-line chemotherapy). Time-to-treatment failure (TTF) was the time from treatment initiation to discontinuation of treatment, first documentation of disease progression by the review committee, or death from any cause. Toxic effects were evaluated according to the Common Terminology Criteria for Adverse Events V3.0.

statistical analysis

The primary end point was the response rate (RR), while the secondary end points were OS, PFS, TTF, and safety. The required sample size was calculated to be at least 49 patients on the null hypothesis of the RR of ≤40% versus the alternative hypothesis of the RR of >60%, power 80%, and α 2.5% (one sided). The 95% confidence interval (CI) was calculated for the RR, PFS, and TTF. OS, PFS, and TTF were calculated by the Kaplan–Meier method. Safety was analyzed in all patients who received at least one dose of study medication.

The cut-off date for RR, PFS, TTF, and safety was 27 May 2008, while that for OS was 13 July 2009.

results

patients' characteristics

Fifty-five patients were enrolled from April to December in 2007. Among them, one patient who received oxaliplatin for the other study by mistake was excluded from all analyses. Three other patients were excluded from efficacy analysis because of prior chemotherapy (methotrexate), severe interstitial pneumonia, or absence of measurable lesions (one patient each). Accordingly, 51 patients formed the efficacy analysis set (Table 1), while 54 patients were analyzed for safety. The median age of the 51 patients was 63 years (range 30–77 years) and the PS was zero or one in 50 patients. Prior adjuvant chemotherapy with S-1 had been carried out in one patient, while 50 patients had received no prior chemotherapy.

treatment

At the data cut-off date, treatment was ongoing in eight patients. The major reasons for discontinuation of treatment in 46 patients were disease progression (63%), adverse events (28%), and withdrawal of consent (2%).

The median number of treatment cycles was 6.0 (range 1–16+). The median dose intensity was 88 mg/m^2/3 weeks for oxaliplatin and 867 mg/m^2/3 weeks for S-1, and the median relative dose intensity was 87.5% and 85.7%, respectively. The median total dose was 600 mg/m^2 for oxaliplatin and 5966 mg/m^2 for S-1.

efficacy

The response was assessed as PR, stable disease (SD) (less than a 30% reduction and less than a 20% increase in the sum of the longest diameter of target lesions, referenced against the baseline sum of the longest diameter of target lesions together with stabilization or decrease in size of nontarget lesions), and progressive disease (PD) in 30, 13, and 5, respectively, of the 51

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Table 1. Patients' profile (n = 51)

Characteristic	No. of patients	%
Median age, years (range)	63 (30–77)	
Sex		
Male	34	67
Female	17	33
ECOG PS		
0	32	63
1	18	35
2	1	2
Disease status		
Advanced	47	92
Recurrent	4	8
Primary tumor		
No	12	24
Yes	39	77
Prior adjuvant chemotherapy		
No	50	98
Yes	1	2
Histology		
Diffuse	35	69
Intestinal	16	31
Sites of metastasis		
Lymph nodes	41	80
Liver	23	45
Lung	9	18
Peritoneum	7	14
Other	9	18
No. of metastases		
1	22	43
≥2	29	57

ECOG PS, Eastern Cooperative Oncology Group performance status.

Table 2. Objective response to treatment (n = 51)

Response	No. of patients	% (95% CI)
CR	0	0
PR	30	59
SD	13	26
PD	5	10
Not evaluable	3	6
Overall response rate	30	59 (44.2–72.4)
Disease control rate (CR + PR + SD)	43	84 (71.4–93.0)

CI, confidence interval; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

patients in the efficacy analysis set (three were not assessable). The RR was 59% (95% CI 44.2% to 72.4%) and the disease control rate (CR + PR + SD) was 84% (95% CI 71.4% to 93.0%) (Table 2).

The median follow-up period was 16.5 months as of 13 July 2009. The median survival time (MST) was 16.5 months (95% CI 13.2–22.3 months) (Figure 1), median PFS was 6.5 months (95% CI 4.8–11.2 months) (Figure 2), and median TTF was 4.8 months (95% CI 4.0–5.6 months). The patients who received

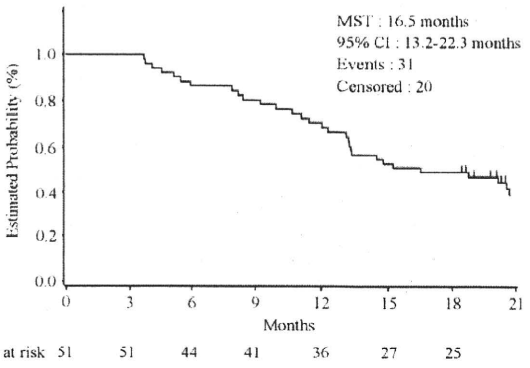

Figure 1. Kaplan–Meier estimates of overall survival (n = 51).

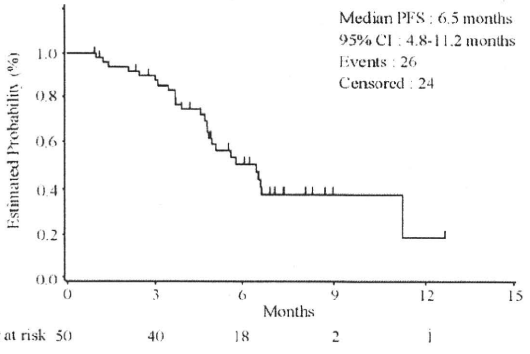

Figure 2. Kaplan–Meier estimates of progression-free survival (n = 50).

the second-line chemotherapy without PD were censored at the date of image examination immediately before the second-line chemotherapy in PFS analysis. The 1-year survival rate was 70.6% (95% CI 58.1% to 83.1%).

Forty-one of the 46 patients (89%) who discontinued treatment received second-line chemotherapy. One patient (2%) with PR underwent surgery and pathological CR was observed.

safety assessment

Grade 3/4 toxicity occurred in 33 of the 54 patients (61%) in the safety analysis set. Grade 3/4 leukopenia, neutropenia, thrombocytopenia, anemia, anorexia, and fatigue were noted in 2 (4%), 12 (22%), 7 (13%), 5 (9%), 3 (6%), and 3 patients (6%), respectively (Table 3). The median onset of thrombocytopenia in all grades was after 42 days and the nadir platelet count was seen at 113 days. The median time from the nadir to grade 0 or platelet count of treatment initiation was 15 days and the duration of thrombocytopenia in all grades was 21 days. Sensory neuropathy was observed in 48 patients (89%), but grade 3/4 neuropathy occurred only in two patients (4%). The median cumulative dose of oxaliplatin associated with sensory neuropathy of any grade was 150 mg/m^2 (grade 1: 150 mg/m^2, grade 2: 900 mg/m^2). There were no treatment-related deaths.

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Table 3. Toxicity of therapy (n = 54)

Toxicity (CTCAE)	No. of patients (%)					
	Grade 1	Grade 2	Grade 3	Grade 4	All grades	Grade 3/4
Hematological						
Leukopenia	15 (28)	16 (30)	2 (4)	0	33 (61)	2 (4)
Neutropenia	3 (6)	15 (28)	12 (22)	0	30 (56)	12 (22)
Thrombocytopenia	25 (46)	9 (17)	7 (13)	0	41 (76)	7 (13)
Anemia	14 (26)	14 (26)	4 (7)	1 (2)	33 (61)	5 (9)
Non-hematological						
Nausea	27 (50)	10 (19)	1 (2)	0	38 (70)	1 (2)
Vomiting	15 (28)	4 (7)	0	0	19 (35)	0
Diarrhea	17 (32)	4 (7)	1 (2)	0	22 (41)	1 (2)
Anorexia	21 (39)	16 (30)	2 (4)	1 (2)	40 (74)	3 (6)
Fatigue	24 (44)	14 (26)	2 (4)	1 (2)	41 (76)	3 (6)
Rash	13 (24)	2 (4)	0	0	15 (28)	0
Pigmentation	20 (37)	2 (4)	0	0	22 (41)	0
Hand–foot syndrome	12 (22)	2 (4)	0	0	14 (26)	0
Stomatitis	20 (37)	1 (2)	0	0	21 (39)	0
Increased creatinine	3 (6)	0	0	0	3 (6)	0
Febrile neutropenia	0	0	1 (2)	0	1 (2)	1 (2)
Sensory neuropathy	35 (65)	11 (20)	2 (4)	0	48 (89)	2 (4)

CTCAE, Common Terminology Criteria for Adverse Events V3.0.

discussion

Advanced gastric cancer is usually treated by combination chemotherapy with fluoropyrimidine derivatives and platinum compounds. Several recent large-scale phase III studies have shown that the RR ranges from 25% to 54%, median PFS from 2.9 to 7 months, and MST from 8.6 to 13 months [5, 6, 8, 9, 11, 14]. Unfortunately, these results are not satisfactory. In Japan, S-1 plus cisplatin is considered to be the standard treatment for advanced gastric cancer on the basis of the results of two phase III studies: the JCOG9912 study demonstrated non-inferiority of S-1 to i.v. infusion of 5-FU [14] and the SPIRITS study showed that S-1 plus cisplatin was superior to S-1 alone [11]. In the SPIRITS study, the RR, median PFS, and MST achieved with S-1 plus cisplatin were 54%, 6.0 months, and 13 months, respectively. However, more frequent incidences of grade 3/4 adverse events were reported as compared with S-1-alone group, and the combination regimens with improved safety are expected.

With the present SOX regimen, the RR was 59%, median PFS was 6.5 months, 1-year survival was 70.6%, and MST was 16.5 months, indicating similar efficacy to that of S-1 plus cisplatin. The excellent result of our SOX regimen in MST may be explicable by good PFS and feasible safety profile, which enabled patients to receive the second-line chemotherapy in the high proportion (89%). The efficacy of SOX regimen was also comparable with epirubicin and oxaliplatin plus capecitabine in the REAL-2 study (1-year survival rate of 47% and MST of 11.2 months) [8], which demonstrated that oxaliplatin was as effective as cisplatin combined with epirubicin and 5-FU or capecitabine.

Comparison of safety between the present SOX regimen and S-1 plus cisplatin that were reported previously [11] indicates a lower incidence of grade 3/4 toxicity with SOX regimen than S-1 plus cisplatin for leucopenia (4% versus 11%), neutropenia (22% versus 40%), anemia (9% versus 26%), anorexia (6% versus 30%), and nausea (2% versus 11%). The incidence of grade 3/4 thrombocytopenia was higher with SOX regimen (13% versus 5%). Sensory neuropathy is a characteristic toxicity of oxaliplatin, and 89% of the patients receiving SOX regimen had neuropathy, but only 4% had severe (grade 3/4) neuropathy. These results indicate that SOX regimen is more tolerable and tends to be superior to S-1 plus cisplatin in terms of safety.

Yamada et al. [15] reported that the treatment was discontinued at high frequency (28%) due to prolonged thrombocytopenia when metastatic colorectal cancer patients were treated with S-1 plus 130 mg/m^2 of oxaliplatin. This discontinuation was supposed to be caused by the geniality of dose reduction criteria which allowed the reduction of oxaliplatin only in case of occurrence of grade 3 or more toxicity in terms of thrombocytopenia. The incidence of thrombocytopenia was 93% in all grades and 28% in grade 3/4, resulting in low median relative dose intensity of S-1 74.6% and that of oxaliplatin 82.8%. Zang et al. [16] also reported the study of SOX regimen with 130 mg/m^2 of oxaliplatin in patients with metastatic colorectal cancer. In their study, the treatment was interrupted in cases of grade 2 or higher toxicity until the recovery to grade 0 or 1, and the doses of oxaliplatin and S-1 were reduced after a second occurrence of grade 2 toxicity. As a result, the incidence of thrombocytopenia was 13% in grade 3/4, and the median relative dose intensity of oxaliplatin and S-1 was 82% and 82%, respectively. In this study, we used 100 mg/m^2 dose of oxaliplatin as SOX regimen for advanced gastric cancer to decrease the incidence of thrombocytopenia considering the possible bleeding from the primary tumor and to maintain the dose intensity of S-1, which have been demonstrated to a key drug against advanced gastric cancer as a single agent. In this new regimen, the incidence of

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thrombocytopenia was 13% in grade 3/4 without reducing the antitumor activity. The median relative dose intensity of oxaliplatin and S-1 was 87.5% and 85.7%, respectively, indicating that the treatment was carried out as scheduled in most of patients in this study.

In conclusion, SOX regimen with oxaliplatin at a dose of 100 mg/m^2 was effective and well tolerated in patients with advanced gastric cancer. SOX regimen has the potential to replace current regimens such as S-1 plus cisplatin or 5-FU plus cisplatin because of similar efficacy with less toxicity and more convenient treatment. Further investigation of this SOX regimen is expected.

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disclosure

All authors declared no conflicts of interest.

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Adipocytokines as new promising markers of colorectal tumors: Adiponectin for colorectal adenoma, and resistin and visfatin for colorectal cancer

Takako Eguchi Nakajima,[1] Yasuhide Yamada,[1,6] Tetsutaro Hamano,[2] Koh Furuta,[3] Takahisa Matsuda,[4] Shin Fujita,[5] Ken Kato,[1] Tetsuya Hamaguchi[1] and Yasuhiro Shimada[1]

[1]Division of Gastrointestinal Oncology, National Cancer Center Hospital, Tokyo; [2]Hamano Statistical Analysis Ltd., Tokyo; Divisions of [3]Clinical Laboratory, [4]Endoscopy and [5]Colon Surgery, National Cancer Center Hospital, Tokyo, Japan

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Adipocytokines are adipocyte-secreted hormones associated with some malignancies such as colorectal, breast, and prostate cancer. We hypothesized that changes in the levels of adipocytokines may indicate the carcinogenesis and progression of colorectal cancer and adenoma, and investigated the association of the blood levels of several adipocytokines through a case-control study. Blood levels of adiponectin, leptin, resistin, visfatin, and C-peptide at diagnosis were measured in 115 colorectal cancer patients and 115 age-, sex-, and body mass index-matched controls. The same analysis was performed in 72 colorectal adenoma patients and 72 controls. Logistic regression models were used for estimating odds ratios and 95% confidence intervals, and one-way ANOVA was performed to determine the prevalence of each variable between two or more groups. Resistin and visfatin levels in cancer patients were significantly higher than those of controls on multivariate analysis ($P = 0.03$ and $P < 0.01$, respectively). Stage progression significantly correlated with resistin and visfatin levels ($P < 0.01$ for both). The adiponectin level in adenoma patients was significantly lower than that of controls on multivariate analysis ($P = 0.04$). Its level was inversely correlated with the number of adenoma ($P = 0.02$), but not correlated with the size of adenoma. Resistin and visfatin may be good biomarkers of colorectal malignant potential and stage progression. Adiponectin level may be a good biomarker of colorectal adenoma. (*Cancer Sci* 2010; 101: 1286–1291)

Adipocytokines, such as adiponectin, leptin, resistin, visfatin, tumour necrosis factor (TNF)-α, and interleukin (IL)-6 are cytokines secreted by visceral adipose tissue, and they have recently been suggested to be associated with obesity-related diseases.[1,2] Many epidemiologic studies have shown a positive correlation between obesity and increased risk of colorectal cancer and adenoma as well as other cancers at various sites (e.g. breast, prostate gland, and endometrium).[3–5]

In obesity mouse models, severe macrophage invasion was observed in the vascular/stromal compartment of adipose tissue, suggesting that excess adiposity is associated with chronic inflammation.[6,7] Other reports have shown that prostaglandin E2 stimulates leptin secretion from cultured human adipose tissue cells and that cyclooxygenase 2 inhibitors prevent an increase in leptin production.[8] In inflammation-associated colorectal cancers, such as those associated with inflammatory bowel diseases, non-genetic stimuli such as overexpression of IL-6 also enhance the survival and proliferation of preneoplastic cells.[9] Leptin was also reported to induce IL-6 production by $Apc^{Min/+}$ colon epithelial cells which leads to autocrine/paracrine trans IL-6 receptor signaling.[10] This results in the promotion and survival proliferation of preneoplastic cells. On the other hand, adiponectin reportedly inhibits inflammation and angiogenesis while leptin induces tumor angiogenesis.[11,12]

These findings in epidemiological and basic research suggest that adipocytokines may well contribute to the induction of carcinogenesis and tumor progression. Therefore, we hypothesized that changes in the levels of adipocytokines may indicate the carcinogenesis and progression of colorectal cancer and adenoma. To evaluate whether adipocytokines are stronger biomarkers of colorectal cancer and adenoma than body mass index (BMI), we performed a BMI-matched case-control study and investigated the association between the blood levels of several adipocytokines and colorectal cancer and adenoma.

Materials and Methods

Study population. After approval of the study protocol by the Institutional Review Board of the National Cancer Center, patients who underwent upper total colonoscopy at the hospital from February 1999 to February 2007, who were considered to have no active malignancies except colorectal cancer and no inflammatory bowel diseases, and whose blood samples at diagnosis before any treatments for colorectal cancer or adenoma could be obtained, were identified and invited to participate in the study. Patients who had been newly and pathologically diagnosed with colorectal cancer by biopsy using colonoscopy and treated at our hospital were identified as colorectal cancer patients among the enrolled patients. Age-, sex-, and BMI-matched controls (1:1) were identified among patients who had been diagnosed as free from colorectal cancer or adenoma by colonoscopy. Among the enrolled patients, we identified those patients who had been newly undergone hot-biopsy, polypectomy, or endoscopic mucosal resection and were pathologically diagnosed with colorectal adenoma at our hospital as colorectal adenoma patients. Age-, sex- and BMI-matched controls (1:1) were identified among patients who had been diagnosed as free from colorectal cancer or adenoma by colonoscopy. BMI at diagnosis was calculated based on the data in medical records as follows: weight (kg)/height $(m)^2$. All subjects (patients and controls) provided informed consent prior to the collection and analysis of blood samples. Clinical and pathological information for both groups was obtained from medical records.

Adipocytokines and C-peptide measurements. All blood samples were stored at −20°C until use. None of the samples were previously thawed. Blood levels of adiponectin, resistin,

[6]To whom correspondence should be addressed.
E-mail: yayamada@ncc.go.jp

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Table 1. Clinical characteristics of patients with colorectal cancer and controls

	Patients (n = 115)	Controls (n = 115)	P-values
Age (years)	63.7 ± 10.3	63.5 ± 10.5	0.99
Sex			
Female (%)	46 (40.0)	46 (40.0)	
Male (%)	69 (60.0)	69 (60.0)	1.00
Body mass index	22.9 ± 2.9	23.1 ± 2.7	0.897
Stage*			
0	23	–	–
I	23	–	–
II	19	–	–
III	23	–	–
IV	27	–	–
Location			
Right colon	55	–	–
Left colon	7	–	–
Rectum	53	–	–
Macroscopic type*			
0 – Ip	5	–	–
0 – Isp	6	–	–
0 – Is	10	–	–
0 – IIa	17	–	–
0 – IIb	0	–	–
0 – IIc	0	–	–
0 – III	0	–	–
1	1	–	–
2	73	–	–
3	1	–	–
4	1	–	–
5	1	–	–
Histological type*			
Well-differentiated adenocarcinoma	86	–	–
Moderately differentiated adenocarcinoma	21	–	–
Poorly differentiated adenocarcinoma	7	–	–
Mucinous adenocarcinoma	1	–	–

Data are presented as mean ± SD. *Japanese Classification of Colorectal Carcinoma 6th edition.

visfatin, and C-peptide at diagnosis were measured by SRL (Tokyo, Japan). Adiponectin was determined by enzyme-linked immunosorbent assay (ELISA) (Otsuka Pharmaceutical, Tokyo, Japan) with a sensitivity of 1.9 μg/mL, an intra-assay coefficient of variation of 3.5–5.1%, and an inter-assay coefficient of variation of 6.0–8.7%. Resistin was determined by ELISA (BioVender Laboratory Medicine, Brno, Czech Republic) with a sensitivity of 1.1 ng/mL, an intra-assay coefficient of variation of 2.8–3.4%, and an inter-assay coefficient of variation of 5.1–6.9%. Leptin was measured using radioimmunoassay kits (Linco Research, St. Charles, MO, USA) with a sensitivity of 0.5 ng/mL, an intra-assay coefficient of variation of 3.4–8.3%, and an inter-assay coefficient of variation of 3.0–6.2%. Visfatin was determined by ELISA (Adipo Gen, Seoul, Korea) with a sensitivity of 0.13 ng/mL, an intra-assay coefficient of variation of 4.4–10.4%, and an inter-assay coefficient of variation of 6.4–9.9%. C-peptide was determined by ELISA (Fujirebio, Tokyo, Japan) with a sensitivity of 0.04 ng/mL, an intra-assay coefficient of variation of 1.96–2.97%, and an inter-assay coefficient of variation of 1.06–2.60%. Duplicate measurements were performed in a single experiment.

Statistical analysis. The results of the comparison of clinical characteristics between patients and controls was evaluated by the χ^2-test for categorical variables and two-sample t-test for continuous variables. Conditional logistic regression models were used for estimating odds ratios and 95% confidence intervals to evaluate the association of each variable with colorectal cancer or adenoma. One-way ANOVA was performed to examine the prevalence of each variable between tumor stage groups. Log transformations were conducted on variables prior to analysis to achieve normal distribution. Differences with a P-value <0.05 were considered significant. All statistical analyses were carried out using the SAS system (version 9.1.3; SAS Institute, Cary, NC, USA).

Results

Adipocytokines and C-peptide, and colorectal cancer. The clinical characteristics and adipocytokine and C-peptide levels of the 115 colorectal cancer patients and 115 controls are shown in Tables 1 and 2. There was no significant difference in age, sex, and BMI between the two groups. Results of the univariate and multivariate logistic regression analyses are shown in Table 3. Resistin and visfatin levels were significantly higher in the colorectal cancer patients than in the controls on multivariate analysis (P = 0.03 and P < 0.01, respectively). Linear contrast analysis was conducted to evaluate the correlation between each variable and tumor stage defined by the Japanese Classification of Colorectal Carcinoma 6th edition (Table 4). Resistin and visfatin levels gradually increased with tumor stage progression (P < 0.01 and P < 0.01, respectively).

Adipocytokines and C-peptide, and colorectal adenoma. The clinical characteristics and adipocytokine and C-peptide levels of the 72 colorectal adenoma patients and 72 controls are shown in Tables 5 and 6. There was no significant difference in age, sex, and BMI between the two groups. Results of the univariate and multivariate logistic regression analyses are shown in Table 7. Multivariate analysis showed that adiponectin levels were significantly lower in the colorectal adenoma patients than in the control patients (P = 0.04). Linear contrast analysis was conducted to evaluate the correlation between each variable and the number of adenomas (Table 8a). Adiponectin level inversely correlated with the number of adenomas (P = 0.02). The size of the largest adenoma among all the adenomas of a patient showed no significant correlation with any variables (Table 8b).

Table 2. Blood adipocytokine levels in patients with colorectal cancer and controls

	Patients				Controls			
	n	Median value	25th quartile value	75th quartile value	n	Median value	25th quartile value	75th quartile value
Adiponectin (μg/mL)	115	8.9	6.6	13	115	8.9	5.7	12.9
Resistin (ng/mL)	115	4.5	3.1	6.4	115	3.1	2.2	4.7
Leptin (ng/mL)	115	3.7	2.4	5.7	114	4.2	2.3	6
Visfatin (ng/mL)	115	3.9	2.1	7.9	115	1.4	0.8	2.6
C-peptide (ng/mL)	114	0.2	0.1	0.4	111	0.3	0.1	0.6

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Table 3. Univariate and multivariate analysis of patients with colorectal cancer and controls

	Univariate analysis		Multivariate analysis	
	Odds ratios (95% confidence intervals)	*P*-values	Odds ratios (95% confidence intervals)	*P*-values
Adiponectin*	1.227 (0.653–2.307)	0.52	0.802 (0.321–2.003)	0.64
Resistin*	2.850 (1.700–4.777)	<0.01	2.067 (1.053–4.055)	0.03
Leptin*	0.799 (0.458–1.393)	0.43	1.057 (0.477–2.342)	0.89
Visfatin*	3.142 (2.064–4.783)	<0.01	2.985 (1.862–4.787)	<0.01
C-peptide*	0.711 (0.550–0.920)	0.01	0.983 (0.663–1.458)	0.93

*Log-transformed.

Table 4. Association between adipocytokine levels and stage progression of colorectal cancer

	Control		Stage 0		Stage 1		Stage 2		Stage 3		Stage 4		*P*-values
	n	mean ± SD	*n*	mean ± SD	*n*	mean ± SD	*n*	mean ± SD	*n*	mean ± SD	*n*	mean ± SD	
Adiponectin*	115	2.3 ± 0.5	23	2.3 ± 0.4	23	2.2 ± 0.6	19	2.3 ± 0.5	23	2.1 ± 0.5	27	2.3 ± 0.4	0.94
Resistin*	115	1.2 ± 0.5	23	1.3 ± 0.5	23	1.6 ± 0.5	19	1.5 ± 0.5	23	1.5 ± 0.6	27	1.7 ± 0.5	<0.01
Leptin*	114	1.4 ± 0.7	23	1.4 ± 0.7	23	1.4 ± 0.7	19	1.5 ± 0.8	23	1.3 ± 0.5	27	1.1 ± 0.6	0.11
Visfatin*	115	0.2 ± 1.1	23	0.8 ± 1.2	23	1.3 ± 1.1	19	1.0 ± 0.9	23	1.5 ± 1.0	27	1.8 ± 0.9	<0.01
C-peptide*	111	−1.4 ± 1.2	23	−1.6 ± 1.2	23	−1.6 ± 1.1	19	−1.9 ± 1.2	22	−1.8 ± 1.1	27	−1.6 ± 1.0	0.17

*Log-transformed. Data are presented as mean ± SD.

Linear contrast analysis was also conducted to evaluate the correlation between adiponectin and the adenoma-carcinoma sequence, and the result was not significant (data not shown).

Table 5. Clinical characteristics of patients with colorectal adenoma and controls

	Patients (*n* = 72)	Controls (*n* = 72)	*P*-values
Age (years)	66.8 ± 7.3	66.7 ± 7.1	0.99
Sex			
Female (%)	22 (30.6)	22 (30.6)	
Male (%)	50 (69.4)	50 (69.4)	1.00
Body mass index	23.0 ± 2.8	22.8 ± 2.8	0.74
Number of adenomas			
2>	44	–	–
≥3	28	–	–
Location			
Right colon	33	–	–
Left colon	27	–	–
Rectum	12	–	–
Macroscopic type*			
0 – Ip	4	–	–
0 – Isp	13	–	–
0 – Is	24	–	–
0 – IIa	31	–	–
0 – IIb	0	–	–
0 – IIc	0	–	–
0 – III	0	–	–
Histological atypia			
Moderate atypia	64	–	–
Severe atypia	78	–	–
Maximum size			
–5 mm	14	–	–
6–10 mm	24	–	–
11–20 mm	17	–	–
>20 mm	17	–	–

Data are presented as mean ± SD. *Japanese Classification of Colorectal Carcinoma 6th edition.

Discussion

The results of this case-control study suggest that resistin and visfatin may be good biomarkers of colorectal malignant potential independently from BMI, and also of stage progression of colorectal cancer. Adiponectin may be a good biomarker of colorectal adenoma independently from BMI. For gastric cancer, we have reported similar results, namely, resistin and visfatin levels in gastric cancer patients were significantly higher than those in controls, and gradually increased with tumor stage progression. Furthermore, adiponectin levels tended to be lower in early stage gastric cancer patients than in controls.[13]

Obesity is recognized as a strong risk factor for the development of several cancers.[3–5] However, many experimental and case-control studies have suggested that BMI is not the best and only marker for elucidating the physiology of obesity. Recently, adipocytokines produced by adipose tissue have been the subject of intense investigation as novel risk markers not only of metabolic syndrome but also of cancers, particularly those indicating a correlation between their risk of development and obesity such as colorectal cancer and adenoma.[14–20] To the best of our knowledge, however, the present study is the first report to evaluate a difference in visfatin level between colorectal cancer patients and controls, and the only one report has been reported for a difference in resistin level so far.[21]

Adiponectin suppresses the secretion of inflammatory cytokines such as TNF-α, and induces the secretion of anti-inflammatory cytokines such as IL-10 in the atherogenic process.[22–24] Furthermore, it has been reported to inhibit tumor growth by suppressing angiogenesis *in vitro* and *in vivo*.[25] In case-control studies, the correlation between adiponectin level and colorectal cancer remains controversial[19,26]. An inverse correlation between adiponectin level and colorectal adenoma has been also reported.[27] Our results showed an inverse correlation between adiponectin and colorectal adenoma. However, we had no information regarding body weight changes in the patients and controls before the sampling, and thus it was not possible to determine whether the decrease in adiponectin levels in the patients was caused by obesity before the sampling. It was also difficult to determine when the adiponectin level decreased, either before or after colorectal adenoma development. Instead

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Table 6. Blood adipocytokine levels in patients with colorectal adenoma and controls

	Patients				Controls			
	n	Median value	25th quartile value	75th quartile value	*n*	Median value	25th quartile value	75th quartile value
Adiponectin (μg/mL)	72	7.5	5.4	10.3	72	8.8	6.3	13.6
Resistin (ng/mL)	72	3.1	2.4	4.8	72	2.8	1.9	3.9
Leptin (ng/mL)	71	3.3	2.4	5.4	72	3.3	1.8	5.4
Visfatin (ng/mL)	72	1	0.6	2.8	72	1.6	0.7	2.8
C-peptide (ng/mL)	71	0.3	0.1	0.7	69	0.2	0.1	0.5

Table 7. Univariate and multivariate analysis of patients with colorectal adenoma and controls

	Univariate analysis		Multivariate analysis	
	Odds ratios (95% confidence intervals)	*P*-values	Odds ratios (95% confidence intervals)	*P*-values
Adiponectin*	0.363 (0.169–0.780)	0.01	0.422 (0.189–0.946)	0.04
Resistin*	1.293 (0.706–2.368)	0.41	1.200 (0.595–2.420)	0.61
Leptin*	1.497 (0.772–2.901)	0.23	1.331 (0.662–2.677)	0.42
Visfatin*	0.883 (0.661–1.180)	0.40	0.872 (0.604–1.260)	0.47
C-peptide*	1.208 (0.893–1.634)	0.22	1.023 (0.704–1.484)	0.91

*Log-transformed.

Table 8. Association between adipocytokine levels and clinical features of colorectal adenoma. (a) Association between adipocytokine levels and number of colorectal adenomas. (b) Association between adipocytokine levels and maximum size of colorectal adenomas

	Control		≤2		≥3		*P*-values
	n	mean ± SD	*n*	mean ± SD	*n*	mean ± SD	
(a)							
Adiponectin*	72	2.2 ± 0.5	44	2.0 ± 0.6	28	2.0 ± 0.4	0.02
Resistin*	72	1.1 ± 0.6	44	1.2 ± 0.5	28	1.1 ± 0.5	0.90
Leptin*	72	1.2 ± 0.6	43	1.2 ± 0.6	28	1.4 ± 0.5	0.15
Visfatin*	72	0.3 ± 1.2	44	0.2 ± 1.5	28	0.1 ± 1.1	0.40
C-peptide*	69	−1.5 ± 1.2	43	−1.2 ± 1.2	28	−1.2 ± 1.1	0.34

	Control		−5 mm		6–10 mm		11–20 mm		>20 mm		*P*-values
	n	mean ± SD	*n*	mean ± SD	*n*	mean ± SD	*n*	mean ± SD	*n*	mean ± SD	
(b)											
Adiponectin*	72	2.2 ± 0.5	14	1.9 ± 0.4	24	1.9 ± 0.4	17	1.9 ± 0.5	17	2.3 ± 0.6	0.48
Resistin*	72	1.1 ± 0.6	14	1.2 ± 0.4	24	1.2 ± 0.6	17	1.4 ± 0.5	17	1.0 ± 0.4	0.81
Leptin*	72	1.2 ± 0.6	13	1.6 ± 0.7	24	1.2 ± 0.5	17	1.1 ± 0.6	17	1.3 ± 0.6	0.53
Visfatin*	72	0.3 ± 1.2	14	0.0 ± 1.4	24	0.3 ± 1.2	17	0.6 ± 1.5	17	−0.4 ± 1.2	0.31
C-peptide*	69	−1.5 ± 1.2	13	−0.9 ± 0.8	24	−1.1 ± 1.2	17	−1.6 ± 1.2	17	−1.3 ± 1.2	0.64

*Log-transformed. Data are presented as mean ± SD.

of these limitations, we evaluated the correlation between the number of adenomas, the size of adenomas and adenoma-carcinoma sequence, and adiponectin to speculate the possibilities as "risk factors" for colorectal adenoma. The results showed that adiponectin level was inversely correlated with the number of adenoma. However, we could not elucidate why the adiponectin level was not correlated with the size of adenoma. If many more patients were enrolled in this study, a significant correlation between adiponectin levels and adenoma sizes may have been detected.

We have performed the above additional investigations into the relationship between adiponectin levels and colorectal carcinoma; however, our study has a few limitations. The BMI levels of the selected target group are very important and can affect the results of the study. The mean of BMI level of the patients in this study was 22.9, which was lower than that reported previously; this low BMI level may be attributed to the fact that all the patients were Japanese. Further, it is possible that variables other than those evaluated in this study may be correlated with adiposity and may influence the levels of adipocytokines. Therefore, the implications of our findings should be carefully evaluated considering these limitations.

Leptin primarily controls body fat stores and has also roles in promoting cellular proliferation, inhibiting cellular apoptosis, and inducing angiogenesis.[28] Over the years, the association between leptin levels and the risk of colorectal cancer or adenoma has remained controversial.[20,29] The expression of the leptin receptor in normal human colon mucosa, adenomas, and cancers suggests that a direct effect of leptin may be involved in carcinogenesis.[30] In the present study, however, the level of leptin was not significantly different between controls and patients with colorectal cancer or adenoma. In our previous

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studies on the correlation between adipocytokines levels and gastric or esophageal cancer, we have shown that a strong correlation exists between leptin level and BMI. In this study, however, the BMI levels of patients and controls were similar; therefore, the value of leptin as a biomarker for colorectal could not be evaluated.[13,31]

Resistin has been demonstrated to be involved in inflammatory states corresponding to its predominant expression in mononuclear cells, particularly in atherosclerosis.[32,33] As for its correlation with cancer, three case-control studies on the risk of myelodysplastic syndrome, multiple myeloma, or colorectal cancer have been reported.[21,34,35] Dalamaga *et al.* demonstrated a decreased resistin level in myelodysplastic syndrome (MDS) patients, and speculated that it was due to a compensatory response to the up-regulation of other inflammatory factors etiologically linked to myelodysplasia. They also reported a decreased level of resistin in patients with multiple myeloma. Kumor *et al.* reported that the resistin levels in colorectal cancer patients are higher than those in controls and that the resistin levels in colorectal adenoma patients and controls were also significantly different. Our results showed that resistin levels, particularly in colorectal cancer patients, were significantly higher than those in controls independent of the BMI, and these levels gradually increased with progression in tumor stage. This may imply that resistin is a biomarker of colorectal malignant potential and stage progression.

Visfatin is a new insulinmimetic adipocytokine, which directly interacts with the insulin receptor but as the insulin-like growth factor receptor, and can subsequently promote cancer cell proliferation[36]. It is more highly expressed in primary colorectal cancer than in non-neoplastic mucosa.[37] Although the clinical correlations of visfatin with cancer have been rarely reported, we demonstrated here that it may be a novel and promising biomarker of colorectal cancer as well as resistin.

Taken together, the results suggest that resistin and visfatin may be good biomarkers of colorectal malignant potential independently of BMI, and also of stage progression of colorectal cancer. Adiponectin level may be a good biomarker of colorectal adenoma independently of BMI. Further investigations as to whether the changes in adipocytokine levels are the result and/or effects of colorectal cancer or adenoma development are needed, and the elucidation of this causative association will undoubtedly clarify the correlation between obesity and cancer. Histological studies on the expression of adipocytokines in cancer tissues also should be conducted to determine whether adipocytokines derived from cancer tissues or those derived from adipose tissues are important for carcinogenesis and tumor progression.

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Disclosure Statement

The authors have no conflict of interest.

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ORIGINAL REPORT

Multicenter Phase II Study of Everolimus in Patients With Previously Treated Metastatic Gastric Cancer

Toshihiko Doi, Kei Muro, Narikazu Boku, Yasuhide Yamada, Tomohiro Nishina, Hiroya Takiuchi, Yoshito Komatsu, Yasuo Hamamoto, Nobutsugu Ohno, Yoshie Fujita, Matthew Robson, and Atsushi Ohtsu

From the National Cancer Center Hospital East, Chiba; Aichi Cancer Center, Aichi; Shizuoka Cancer Center, Shizuoka; National Cancer Center Hospital; Novartis K.K., Tokyo; Shikoku Cancer Center, Ehime; Osaka Medical College, Osaka; Hokkaido University Hospital, Hokkaido; Tochigi Cancer Center, Tochigi, Japan; and Novartis Pharmaceutical Corp, East Hanover, NJ.

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Corresponding author: Toshihiko Doi, MD, PhD, National Cancer Center Hospital East, 5-1, Kashiwanoha 6-chome, Kashiwa-shi, Chiba 277-8577, Japan; e-mail: tdoi@east.ncc.go.jp.

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A B S T R A C T

Purpose

Everolimus, an oral inhibitor of the mammalian target of rapamycin, has shown antitumor activity in gastric cancer in preclinical and phase I studies. This phase II study evaluated the efficacy and safety of everolimus in pretreated patients with advanced gastric cancer.

Patients and Methods

Patients with advanced gastric cancer who experienced progression despite prior chemotherapy received everolimus 10 mg orally daily until disease progression or study discontinuation. The primary end point was disease control rate (DCR; ie, complete response, partial response, or stable disease). Secondary end points included progression-free survival (PFS), overall survival (OS), and safety.

Results

Fifty-three patients were assessable (median age, 63 years; 51% and 49% received one or two prior chemotherapy regimens, respectively). Although no complete or partial response was obtained, a decrease in tumor size from baseline was observed in 45% of patients by central review. The DCR was 56.0% (95% CI, 41.3% to 70.0%); median PFS was 2.7 months (95% CI, 1.6 to 3.0 months). At a median follow-up time of 9.6 months, median OS was 10.1 months (95% CI, 6.5 to 12.1 months). Common grade 3 or 4 adverse events included anemia, hyponatremia, increased γ-glutamyltransferase, and lymphopenia. Grade 1 or 2 pneumonitis was reported in eight patients (15.1%).

Conclusion

Everolimus monotherapy resulted in a promising DCR in patients with previously treated advanced gastric cancer. Adverse events are consistent with the reported safety profile of everolimus. These results warrant further evaluation in patients with advanced gastric cancer.

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INTRODUCTION

Gastric cancer is the fourth most common cancer worldwide, with 603,003 and 330,290 new cases among men and women, respectively, reported annually between 1993 and 2001.[1,2] Globally, it is the second most common cause of cancer death, with an estimated 700,000 deaths annually.[1,2] In Japan, gastric cancer is the second leading cause of cancer death (50,415 deaths in 2006), accounting for 15.3% of all cancer deaths.[3]

Only surgical resection is curative; however, patients with gastric cancer commonly present with unresectable disease.[4] Even after curative surgical resection, 60% of these patients eventually experience relapse.[5] Systemic chemotherapy has been evaluated extensively in patients with unresectable and recurrent gastric cancer.[4,5] At present, although fluoropyrimidine-based therapy is used worldwide, there is no globally accepted standard first-line chemotherapy for advanced gastric cancer. In randomized studies, combination chemotherapy regimens including fluorouracil (FU) or its derivatives, taxanes, irinotecan, and platinum derivatives generally achieved median overall survival (OS) times of less than 1 year in the first-line setting.[6-12] In Japan, S-1 (tegafur + gimeracil + oteracil potassium) is an established first-line agent for advanced gastric cancer. A recent phase III trial demonstrated a median OS time of 13 months with the combination of S-1 plus cisplatin as first-line therapy for patients (n = 148) with advanced gastric cancer.[13]

The poor long-term outcomes associated with chemotherapies to date strongly suggest considerable unmet needs in gastric cancer and a need for new agents, particularly targeted agents that will confer a survival benefit with acceptable tolerability. This is especially true in the second- and third-line

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settings, in which to date there are no phase III studies demonstrating survival benefit for chemotherapy compared with best supportive care.

Inhibition of the mammalian target of rapamycin (mTOR) pathway represents a new therapeutic target in the treatment of various human cancers. mTOR, a key protein kinase that regulates cell growth and proliferation, cellular metabolism, and angiogenesis,[14] is mainly activated via the PI3 kinase pathway through Akt/PKB and tuberous sclerosis complex. Mutations in these components or in PTEN, a negative regulator of PI3 kinase, result in inappropriate mTOR activation.[14] The mTOR pathway has been shown to be frequently dysregulated in a variety of human cancers, including gastric cancer.[15] Oncogenic transformation maintained by a dysregulated mTOR pathway may sensitize tumor cells to mTOR inhibitors.[14] Overexpression of the mTOR downstream effectors[14] eIF4E and 4E binding protein 1 (4E-BP1) was shown in GI cancer cells. Everolimus reduced 4E-BP1 phosphorylation and attenuated production of the proangiogenic factors hypoxia-inducible factor 1α and vascular endothelial growth factor in these gastric cancer cell lines.[15]

Everolimus is an orally bioavailable mTOR inhibitor that binds with high affinity to its intracellular receptor FKBP12.[16] Everolimus has demonstrated antitumor activity in gastric cancer in preclinical studies[14,15,17] and a phase I study involving patients with advanced gastric cancer.[18] The current phase II study evaluated the efficacy and safety of everolimus monotherapy in patients with advanced gastric cancer who had experienced treatment failure with one or two prior chemotherapy regimens.

PATIENTS AND METHODS

Patient Eligibility

This open-label, single-arm, multicenter, proof-of-concept, phase II study was conducted in Japan and included patients $\geq$ 20 years of age with pathologically confirmed advanced gastric adenocarcinoma who had received one or two prior chemotherapy regimens (one regimen was required to contain any of the following: FU or its derivatives, platinum derivatives, taxanes, or irinotecan) and who had $\geq$ one measurable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST). Patients were required to have documented progressive disease (PD) based on imaging during or after last prior treatment. Before study entry, prior therapies had to be completed for $\geq$ 2 weeks for anticancer agents and for $\geq$ 4 weeks for surgery or radiotherapy, and patients had to recover from adverse reactions of prior therapy. Patients were required to have Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1 and adequate organ function (bone marrow function: neutrophils $\geq 1.5 \times 10^9$/L, platelets $\geq 100 \times 10^9$/L, hemoglobin $\geq$ 8.5 g/dL; liver function: serum bilirubin $\leq$ 1.5 mg/dL and ALT and AST $\leq$ 2.5 $\times$ upper limit of normal [ULN] if no evidence of liver metastasis or serum bilirubin $\leq$ 1.5 mg/dL and ALT and AST $\leq$ 5.0 $\times$ ULN with liver metastases; renal function: serum creatinine $\leq$ 2 $\times$ ULN). Exclusion criteria were CNS metastases already detected, malignant ascites requiring invasive treatment (eg, ascites drainage), or severe or uncontrolled medical conditions (eg, impaired heart and lung function, diabetes, active infections, or liver disease).

This study was conducted according to the ethical principles of the Declaration of Helsinki and approved by the institutional review board of each center. All patients provided written informed consent.

Study Treatment and Assessment

All patients were treated with everolimus 10 mg/d orally in continuous 28-day cycles until tumor progression, unacceptable toxicity, or study discontinuation for any other reason. Two levels of dose reduction were permitted (5 mg/d and then 5 mg every other day) for tolerability. For the baseline tumor assessment, radiographic assessments (computed tomography or magnetic resonance imaging scans of the chest, abdomen, and pelvis) were performed within 2 weeks before the first dose of everolimus. Tumor response was assessed every 4 weeks from cycle 2 to cycle 4 and then every two cycles until determination of disease progression and/or at the end of the study. Disease status was assessed by a local radiologist with the investigator and reviewed by central review of radiology using RECIST criteria.

Safety assessments consisted of continuous monitoring and recording of all adverse events (AEs) and regular monitoring of hematology, serum chemistry, vital signs, weight, ECOG PS, chest computed tomography scans, and physical condition. AEs were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3).

Statistical Considerations

The primary efficacy objective was to assess disease control rate (DCR), which was defined as the proportion of patients with complete response, partial response, or stable disease (SD) as the best overall response according to RECIST. DCR was summarized in terms of percentage, with a 95% CI. The DCR was calculated primarily based on the assessment of the central radiologic review. All results were analyzed in the full analysis set (FAS), which included all patients who received at least one dose of everolimus. DCR as primary end point was also analyzed in the per-protocol set (PPS), which consisted of patients from the FAS who completed a minimum exposure requirement (dose-intensity $\geq$ 0.5) or experienced progression before the minimum exposure requirement without any major protocol deviation and was defined as the primary analysis population. This study adopted a Simon two-stage design for sample size determination,[19] which required disease control in $\geq$ eight of the first 21 patients enrolled onto the first stage to proceed to the second stage, in which an additional 27 patients were planned to be enrolled. The null hypothesis was a DCR of $\leq$ 30%. DCRs of 30% (futility rate) and 50% (targeted antitumor activity rate) were used for power setting.[20,21] If $\geq$ 20 of 48 patients achieved disease control, the null hypothesis would be rejected, and everolimus would be considered to have antitumor activity in this population.

The secondary end points of the study were to assess objective response rate, progression-free survival (PFS), OS, and the safety profile of everolimus. PFS and OS curves were generated using the Kaplan-Meier product-limit method. Median PFS and OS were obtained with a 95% CI. Safety analysis was performed in the safety population, which consisted of all patients who received $\geq$ one dose of everolimus and had $\geq$ one postbaseline safety assessment.

As an exploratory end point, the influence of gastrectomy on the pharmacokinetics (PKs) of everolimus was investigated. Blood samples for PK analyses were collected from patients enrolled onto the first stage before dose and at 1, 2, 3, and 4 hours after dose on day 1 of cycles 1 and 2 and from all patients before dose on day 1 of cycles 1, 2, 3, and 4. Everolimus concentrations in whole blood were determined by liquid chromatography–mass spectrometry. The PK population consisted of all patients from the safety population who had PK samples available. Noncompartmental methods with WINNonlin Pro (Version 5.2; Pharsight, St Louis, MO) were used to determine the PK parameters of area under the concentration-time curve from 0 to 4 hours after drug administration [$AUC_{(0\text{-}4)}$], observed predose concentration (C_{min}), maximum blood drug concentration (C_{max}), and time to reach maximum concentration after drug administration (T_{max}).

RESULTS

Patient Disposition

A total of 26 patients were enrolled onto the first stage to ensure 21 patients in the PPS population at week 8. Central radiologic review confirmed that $\geq$ eight patients achieved disease control, and an additional 28 patients were enrolled onto stage 2 (Fig 1). The FAS population included 53 patients; the remaining patient did not receive study medication because of ineligibility. Three patients were not

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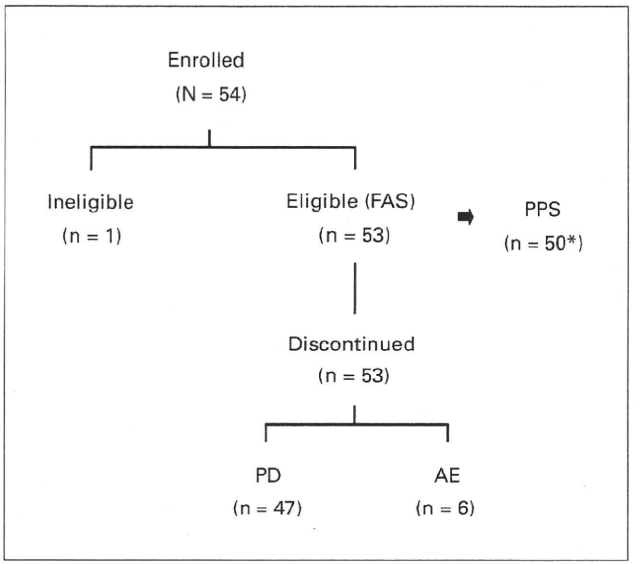

Fig 1. Patient disposition. (*) Three patients were excluded from the per-protocol set (PPS), two with unknown best response and one with dose intensity less than 50% during the first 8 weeks of treatment. FAS, full analysis set; PD, progressive disease; AE, adverse event.

included in the PPS population (n = 50); two patients were not assessable for best overall response, and one patient had a dose-intensity of less than 50% during the first 8 weeks of treatment. At study completion, 47 patients had discontinued treatment as a result of disease progression (Fig 1).

Patient Characteristics

Most patients were men (77%), and the median age was 63 years (Table 1). All treated patients had an ECOG PS of 0 or 1 (PS 0 = 60%; PS 1 = 40%). Most patients had moderately (47%) or poorly (42%) differentiated adenocarcinomas. Most patients had been previously treated; 25 of 53 patients had a gastrectomy, and all patients had received chemotherapy (51% with one prior line; 49% with two prior lines). The most commonly used prior chemotherapy agents in the study population were FU derivatives (S-1) as monotherapy (49%) and in combination with cisplatin (55%), and the most common second-line agents were paclitaxel (17%) or irinotecan (11%) as monotherapy (Table 1).

Efficacy

Best overall responses per central radiology review are listed in Table 2; 28 (56.0%) and 22 patients (44.0%) in the PPS population and 29 (54.7%) and 22 patients (41.5%) in the FAS population had SD and PD, respectively. Disease control was observed in more than 20 patients in the first 48 patients (out of 50 patients) in the PPS population, and the null hypothesis (DCR ≤ 30%) was rejected at the one-sided $\alpha = .05$. At the final analysis, disease control was observed in 28 patients (56.0%; 95% CI, 41.3% to 70.0%) in the PPS population. The lower limit 95% CI value (41.3%) exceeded the threshold (30%) for futility. Results in the FAS population (DCR = 54.7%; 95% CI, 40.4% to 68.4%) were consistent with the results observed in the PPS population. Although no complete or partial response was obtained, a decrease in tumor size from baseline was observed in 45% of patients by central review. The maximum best change observed was a 34% decrease in sum of longest diameters when compared with baseline (Fig 2). Subgroup analysis by number of previous chemotherapies indicated that the effect of everolimus was consistent in the second- and third-line PPS populations, with the same proportions of patients with SD (56.0%) and PD (44.0%) observed in each group.

Table 1. Patient Demographic and Clinical Characteristics

Demographic or Clinical Characteristic	No. of Patients (N = 53)	%
Age, years		
Median	63	
Range	30-77	
Asian	53	100
Male	41	77
ECOG performance status (0/1)		
0	32	60
1	21	40
Degree of tumor differentiation		
Well	6	11
Moderate	25	47
Poor	22	42
Gastrectomy	25	47
No. of prior chemotherapy regimens		
1	27	51
2	26	49
Contents of prior chemotherapy regimens		
FU monotherapy*	26	48
FU plus cisplatin	29	55
Paclitaxel monotherapy	9	17
Irinotecan monotherapy	6	11
Other†	9	17
Site of measurable lesion		
Abdominal lymph node	26	49
Liver	25	47
Distant lymph node	11	21
Peritoneum	4	8
Lung	3	6
Ovary	3	6
Other‡	5	9

Abbreviations: ECOG, Eastern Cooperative Oncology Group; FU, fluorouracil.
*Including FU derivatives S-1, capecitabine, and so on.
†Other includes irinotecan plus cisplatin (n = 4), FU plus paclitaxel (n = 3), FU plus irinotecan (n = 1), and FU plus methotrexate (n = 1).
‡Other measurable lesion sites include abdominal mass, adrenals, thyroid gland, pleura, pulmonary lymphangitic spread (n = 1 each).

Table 2. Best Overall Response and DCR per Central Review

Best Overall Response and DCR	PPS (n = 50) No. of Patients	PPS (n = 50) %	FAS (N = 53) No. of Patients	FAS (N = 53) %
Best overall response				
CR	0	0	0	
PR	0	0	0	
SD	28	56.0	29	54.7
PD	22	44.0	22	41.5
Unknown	0	0	2	3.8
DCR (CR + PR + SD)	28	56.0	29	54.7
95% CI, %	41.3 to 70.0		40.4 to 68.4	

Abbreviations: DCR, disease control rate; PPS, per-protocol set; FAS, full analysis set; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

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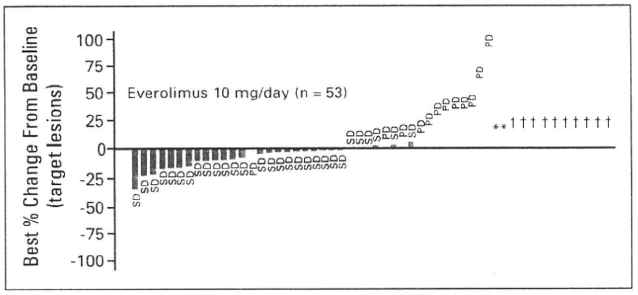

Fig 2. Maximum best change in tumor size from baseline. Decrease in best percent change from baseline = 45.28%; increase in best percent change or no percent change from baseline = 32.08%. (*) Percent change in target lesion was available but contradicted by overall lesion response = unknown 3.77%. (†) Percent change in target lesion was available but contradicted by overall lesion response = progressive disease (PD) 18.87%. SD, stable disease.

Median PFS was 2.7 months (95% CI, 1.6 to 3.0 months; Fig 3A). At 4 months, 28.3% (Kaplan-Meier estimate) of patients were progression free. Subgroup analysis did not reveal a difference in PFS stratified by number of prior chemotherapy regimens; in the second-line setting, median PFS was 2.6 months (95% CI, 1.0 to 3.0 months), and in the third-line setting, median PFS was 2.8 months (95% CI, 1.6 to 4.0 months). At a median follow-up time of 9.6 months, median OS was 10.1 months (95% CI, 6.5 to 12.1 months; Fig 3B); in the second-line setting, median OS was 9.8 months (95% CI, 6.2 to 12.3 months), and in the third-line setting, median OS was 10.7 months (95% CI, 6.3 months to not reached).

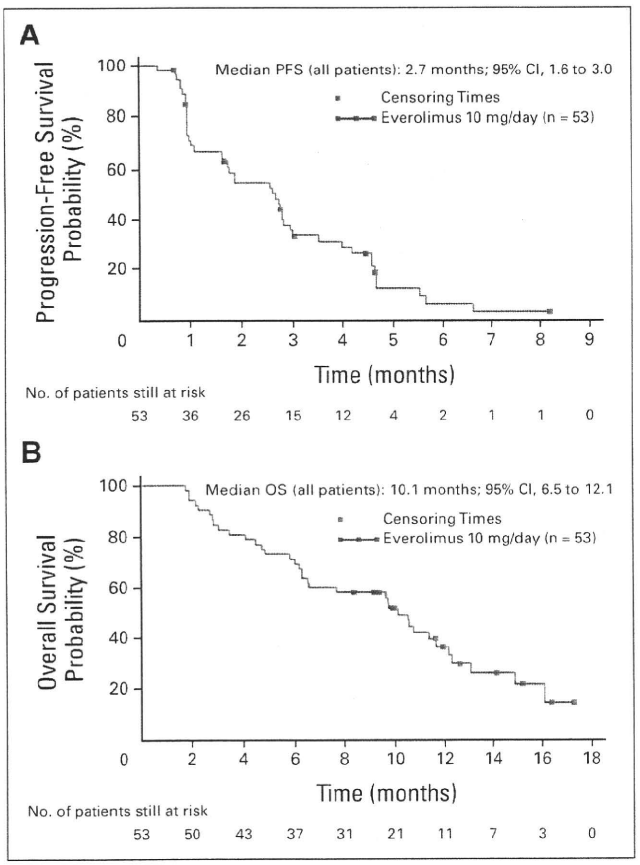

Fig 3. Kaplan-Meier plots of (A) median progression-free survival (PFS) and (B) median overall survival (OS) in all patients.

PK Analysis

On day 1 of cycle 1 and at steady-state (day 1 of cycle 2), slightly higher peak plasma concentrations (C_{max}) of everolimus were observed in patients who had undergone gastrectomy compared with patients who had not. In addition, T_{max}, C_{max}, and $AUC_{(0-4)}$ data on day 1 of cycle 1 and at steady-state also suggest that the rate of absorption of everolimus was faster in patients who had undergone gastrectomy [higher C_{max} and $AUC_{(0-4)}$ and shorter T_{max}] than in patients who had not (Table 3). However, mean C_{min} values on day 1 of cycles 1, 2, 3, and 4 were similar between patients with and without gastrectomy, as were AUC during dosing interval values at steady-state,

Table 3. PK Parameters of Everolimus

PK Parameter	No. of Patients	PK Value Mean	PK Value SD
Day 1 of cycle 1			
C_{max}, ng/mL			
No gastrectomy	14	78.3	39.7
Gastrectomy	12	122	33.2
T_{max}, hours			
No gastrectomy	14	1.5	0.92
Gastrectomy	12	1.1	0.29
$AUC_{(0-4)}$, h · ng/mL			
No gastrectomy	14	172	84
Gastrectomy	12	271	84
Day 29 (day 1 of cycle 2)			
C_{max}, ng/mL			
No gastrectomy	6	98.7	33.4
Gastrectomy	10	134	33.0
T_{max}, hours			
No gastrectomy	6	2.0	1.29
Gastrectomy	10	1.0	0.11
$AUC_{(0-4)}$, h · ng/mL			
No gastrectomy	6	254	101
Gastrectomy	10	324	94
C_{min}, ng/mL			
Day 1 (day 1 cycle 1)			
No gastrectomy	9	11.2	2.43
Gastrectomy	6	15.4	2.96
Day 29 (day 1 cycle 2)			
No gastrectomy	16	27.6	22.3
Gastrectomy	21	25.5	14.4
Day 57 (day 1 cycle 3)			
No gastrectomy	11	25.0	10.2
Gastrectomy	11	17.7	6.87
Day 85 (day 1 cycle 4)			
No gastrectomy	6	23.3	7.48
Gastrectomy	12	18.0	6.31
AUC0-τ on day 29 (day 1 of cycle 2), ng · h/mL			
No gastrectomy	6	1,080	744
Gastrectomy	10	1,100	417

Abbreviations: PK, pharmacokinetic; SD, standard deviation; C_{max}, maximum blood concentration; T_{max}, time to reach maximum plasma concentration; $AUC_{(0-4)}$, area under the concentration time curve during the first 4 hours after drug administration; C_{min}, minimum blood concentration; AUC0-τ, area under the concentration time curve during the dosing interval.

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suggesting that the extent of oral absorption was similar between the two groups (Table 3).

Safety

The median duration of everolimus therapy was 57.0 days (range, 11 to 249 days), with a median cumulative dose of 540 mg (range, 110 to 1,960 mg). Although 23 patients (43.4%) had a dose reduction or interruption, the mean relative dose-intensity was 0.9.

The major AEs observed with everolimus were grade 1 or 2 in severity. The most common AEs were stomatitis (73.6%), anorexia (52.8%), fatigue (50.9%), rash (45.3%), nausea (32.1%), peripheral edema (22.6%), diarrhea (20.8%), and pruritus (18.9%). Grade 3 or 4 AEs observed during the study are listed in Table 4. Grade 3 AEs occurred in 20 patients (37.7%), including anemia (11.3%), hyponatremia (9.4%), increased γ-glutamyltransferase (7.5%), lymphopenia (7.5%), fatigue (5.7%), stomatitis (5.7%), anorexia (5.7%), abnormal hepatic function (5.7%), hyperglycemia (3.8%), hypophosphatemia (3.8%), and ileus (3.8%). Grade 4 AEs suspected to be related to treatment were reported in four patients; one patient each had tumor hemorrhage, increased γ-glutamyltransferase, lymphopenia, and cerebral infarction. Six patients discontinued the protocol treatment as a result of AEs; five of these patients had AEs suspected to be related to everolimus (grade 2 pneumonitis, n = 2; grade 3 stomatitis, n = 1; liver dysfunction, n = 1; and tumor hemorrhage, n = 1). Pneumonitis related to everolimus was observed in eight patients (15.1%); the maximum severity was grade 2.

At the time of this analysis, 36 (67.9%) of 53 patients had died; 33 of these patients died of gastric cancer, two patients died of aspiration pneumonia (not suspected to be related to everolimus), and one patient died 313 days after last dose of study drug with the cause of death unknown.

DISCUSSION

Everolimus monotherapy demonstrated a promising DCR of 56% in pretreated patients with advanced gastric cancer. In addition, 45% of patients demonstrated tumor shrinkage from baseline, the median PFS was 2.7 months, and the median OS was 10.1 months. All efficacy data except survival were judged by an independent central radiologic review committee.

The choice of DCR as the primary end point in this study was considered appropriate because it reflects clinical practice where progression usually necessitates a change of treatment; its use is also appropriate in a proof-of-concept study in the second- and third-line settings. Patients in this study were previously treated; nearly half (49%) received everolimus as a third-line therapy. The reasons for the choice of this population were the recent establishment of S-1 plus cisplatin as a standard first-line regimen in Japan and the lack of any evidence, at the time of the study, to support a survival benefit of chemotherapy over best supportive care in the second- or third-line setting in advanced gastric cancer.

The clinical evaluation of everolimus in patients with gastric cancer is supported by research regarding the mTOR pathway in preclinical models[14,15,17,22,23]; blockade of PI3 kinase signaling via mTOR inhibition has shown antitumor activity in experimental models of gastric cancer.[22,23] It is noteworthy that the efficacy results were similar in patients who had received one or two prior chemotherapy regimens. A number of other agents and combinations have been evaluated as second-line therapy in patients with advanced gastric cancer, including docetaxel, paclitaxel, irinotecan/cisplatin, paclitaxel/doxifluridine, paclitaxel/cisplatin, and S-1/mitomycin.[20,24-29] Median OS ranged from 3.5 months[24] to 7.2 months[30] in the single-agent trials and from 6 months[28] to 10.5 months[29] in the combination therapy trials. In this trial, median OS was 10.1 months (9.8 months in the second-line setting and 10.7 months in the third-line setting). These results seem to compare favorably with those observed in the other trials evaluating single-agent and combination therapy in the second-line setting. Although the number of patients in the third-line setting in this study is small, their median OS of more than 10 months is encouraging when compared with other studies in this patient population.

In earlier studies comparing FU monotherapy with FU plus cisplatin, uracil/tegafur plus mitomycin,[31] or irinotecan plus cisplatin,[32] the combinations had no survival advantage over FU monotherapy. One potential explanation for this observation is that therapy with a single agent preserved the patients' PS, allowing them to receive additional lines of chemotherapy. The same effect may have been seen in this study, where the majority of patients (n = 45) received additional chemotherapy after discontinuation of everolimus, again potentially implying that the single-agent therapy with everolimus preserved the patients' PS, making them suitable candidates for further line(s) of therapy. At the time of study discontinuation, 85% of patients (45 of 53 patients) had PS of 0 to 1, and 92% of patients (49 of 53 patients) had PS of 0 to 2.

Everolimus was generally well tolerated, and no new safety concerns were identified in the study. Grade 3 stomatitis was reported in three patients. Other major grade 3 or 4 AEs included anemia (11.3%), hyponatremia (9.4%), increased γ-glutamyltransferase (7.5%), and lymphopenia (7.5%). Pneumonitis related to everolimus was observed in eight patients (15.1%), with no grade 3 or 4 pneumonitis observed. There were no treatment-related deaths and no deaths within 28 days after discontinuation of study drug. The frequency and severity of AEs in this study, including pneumonitis, seem to be consistent with those in a large phase III placebo-controlled trial in patients with advanced renal cell carcinoma.[33] Compared with other

Table 4. Grade 3 or 4 Adverse Events > 3% Regardless of Relationship to Study Drug (N = 53)

Adverse Event	No. of Patients: Grade 3	No. of Patients: Grade 4	Total Grade 3 or 4: No. of Patients	Total Grade 3 or 4: %
Anemia	4	1	5	9.4
Hyponatremia	5	0	5	9.4
Increased GGT	2	2	4	7.5
Lymphopenia	2	2	4	7.5
Fatigue	3	0	3	5.7
Stomatitis	3	0	3	5.7
Anorexia	3	0	3	5.7
Abnormal hepatic function	2	1	3	5.7
Hyperglycemia	2	0	2	3.8
Hypophosphatemia	2	0	2	3.8
Ileus	2	0	2	3.8

Abbreviation: GGT, γ-glutamyltransferase.

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