Table 2 Treatment discontinuation

Category	*N*	%
Progressive disease (PD)	61	77
Ascites	20	
Gastrointestinal stenosis	17	
Obstructive jaundice	4	
Hydronephrosis	4	
Pleural effusion	3	
Lymphangitis	1	
Bone metastasis	1	
Target lesions	5	
Clinical PD	6	
Unacceptable toxicity	5	6
Treatment-related death	2	3
Others[a]	11	14

[a] Ten patients transferred to other hospitals and 1 provided no follow-up

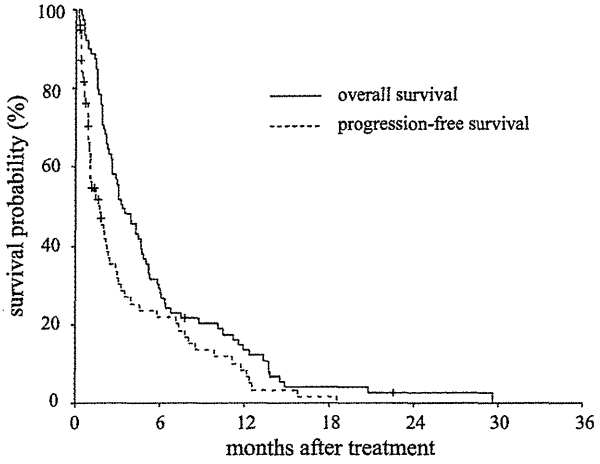

Fig. 2 Overall survival (*continuous line*) and progression-free survival (*dotted line*) in the 79 patients. The *marks on the curves* indicate censored cases

with stable disease (13%), unacceptable toxicity (6%), treatment-related death (3%), and loss of follow-up (1%) (Table 2). Among the 61 patients with disease progression, only 17 patients received second-line chemotherapy treatment, which consisted of a regimen of taxanes for 12 patients, MTX/5-FU for 2 patients, 5-FU ci for 2 patients, and mitomycin for 1 patient.

Seventy-seven patients had died at a median follow-up time of 3.3 months (range, 0.4–29.7 months). Twenty (25%) patients died within 30 days after the last administration of first-line chemotherapy. Of these 20 patients, 17 patients died of disease progression, 2 patients died of treatment-related causes, and 1 patient died of aspiration pneumonia. As to treatment-related death, both patients developed septic shock with febrile neutropenia. Median PFS and median OS for all patients were 1.7 months (95% CI, 0.9–2.4 months) and 3.3 months (95% CI, 2.1–4.5 months), respectively (Fig. 2).

Prognostic factors

In univariate analysis, five variables were identified as significantly associated with shorter survival time (Table 3A): serum CRP level of $\geq$2.0 mg/dl ($P < 0.001$), performance status of $\geq$3 ($P < 0.001$), serum albumin level of <3.0 g/dl ($P = 0.004$), massive ascites ($P = 0.004$), and number of metastatic sites of $\geq$2 ($P = 0.049$). The results of multivariate analysis are given in Table 3B. Elevated serum CRP level, low serum albumin level, poor performance status, and massive ascites were found to be significantly poor prognostic factors in multivariate analysis. The results of forward and backward stepwise regression procedures remained the same. The patients were then classified into three groups according to the prognostic index, as follows: good prognosis with none of the four prognostic factors (group 1, $n = 26$); intermediate prognosis with one or two of the poor prognostic factors (group 2, $n = 39$); or poor prognosis with three or four prognostic factors (group 3, $n = 14$). The survival curves for the three groups are shown in Fig. 3. The median survival time in the good, intermediate, and poor prognosis groups was 6.0, 3.1, and 1.4 months, respectively. There were significant differences in survival time among the three groups ($P < 0.015$).

Discussion

This study demonstrated that median OS of peritoneal disseminated gastric cancer patients with inadequate oral intake receiving first-line systemic chemotherapy was 3.3 months. Serum CRP level $\geq$2.0 mg/dl, serum albumin level <3.0 g/dl, massive ascites, and poor performance status (PS $\geq$ 3) were independent prognostic factors. To the best of our knowledge, this is the first study identifying the treatment outcome and prognostic factors in gastric cancer patients with inadequate oral intake resulting from peritoneal dissemination, treated by systemic chemotherapy.

Gastric cancer patients with peritoneal dissemination have been excluded from the eligibility criteria in most clinical trials because of the absence of measurable lesions and potential severe complications such as massive ascites, hydronephrosis, obstructive jaundice, and intestinal obstruction. Moreover, because peritoneal dissemination causes inadequate oral intake, it is difficult to continue chemotherapy using oral anticancer agents. Recent phase III trials demonstrated that chemotherapy using oral

Table 3 Pretreatment factors associated with the outcome

Variable	*N*	*P* value
(A) Univariate analysis		
Gender		
Male	43	0.06
Female	36	
Age		
≥65	18	0.08
<65	61	
ECOG PS		
0–2	60	<0.001
3	19	
Disease status		
Unresectable	20	0.52
Recurrent	59	
Histology		
Diffuse type	71	0.07
Non-diffuse type	8	
Primary tumor		
Present	46	0.81
Absent	33	
Number of metastatic sites		
1	49	0.049
≥2	30	
Ascites		
Non-massive	58	0.004
Massive	21	
Treatment regimen		
5-FU bolus	57	0.38
5-FU ci	22	
Albumin (g/dl)		
<3.0	31	0.004
≥3.0	48	
C-reactive protein (mg/dl)		
≥2.0	33	<0.001
<2.0	46	

Variable	*N*	Hazard ratio (95% CI)	*P* value
(B) Multivariate analysis			
ECOG PS			
0–2	60	1	0.05
3	19	1.78 (1.001–3.17)	
Number of metastatic sites			
1	49	1	0.14
≥2	30	1.32 (0.91–1.91)	
Ascites			
Non-massive	58	1	0.04
Massive	21	1.79 (1.04–3.08)	
Albumin (g/dl)			
≥3.0	48	1	0.03
<3.0	31	1.69 (1.05–2.73)	
C-reactive protein (mg/dl)			
<2.0	46	1	<0.01
≥2.0	33	2.03 (1.25–3.31)	

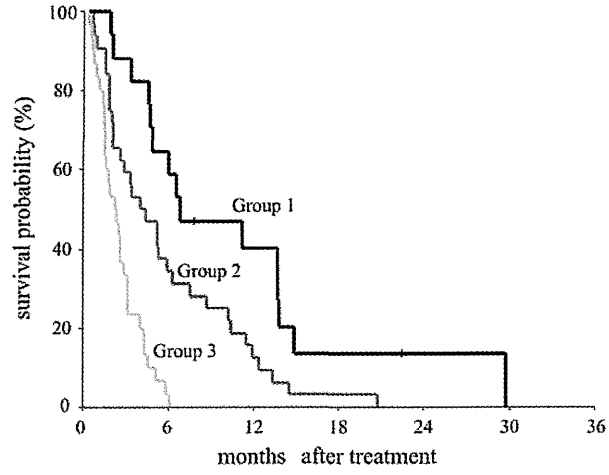

Fig. 3 Survival curves for the three groups determined by prognostic index: group 1, good prognosis (26 patients); group 2, intermediate prognosis (39 patients); group 3, poor prognosis (14 patients). The *marks on the curves* indicate censored cases

fluoropyrimidines, such as capecitabine or S-1, has efficacy results comparable to 5-fluorouracil-based chemotherapy [5, 7]. Patients with inadequate oral intake are subject to the exclusion criteria in the treatment protocol, and most of them must receive 5-FU-based chemotherapy as an intravenous administration. Although 5-FU is one of the most commonly used drugs in patients with gastrointestinal malignancies, systemic chemotherapy of 5-FU has a limited response rate. Therefore, we need to develop novel chemotherapeutic regimens to provide significant benefits at the initial stage of therapy to control the symptoms and improve the quality of life in gastric cancer patients who have severe peritoneal dissemination.

Regarding the host-related factors, good performance status, absence of ascites, serum CRP level <2.0 mg/dl, and serum albumin level ≥3.0 g/dl were found to be favorable prognostic factors by multivariate analysis. Presence of ascites and high serum CRP level were identified as being significantly associated with shorter survival times in the multivariate analysis, and these findings are compatible with previous reports [8, 9]. Moreover, performance status is one of the best known prognostic factors in most cancers beyond gastric cancer. For clinical application of these findings, we can directly predict the survival curve of each patient. These survival curves can be easily calculated because they are based on variables obtained during routine clinical examinations. These findings, therefore, can be used to stratify peritoneal disseminated gastric cancer patients with inadequate oral intake before systemic chemotherapy according to predicted survival. Accordingly, patients with a good prognosis may obtain sufficient treatment efficacy and survival with 5-FU-based chemotherapy as the first-line treatment. In contrast,

patients with a poor prognosis may be treated with palliative care only because of the extremely short median survival (1.4 months) expected, or may be treated with other, more intensive chemotherapy. Systemic chemotherapy for gastric cancer has recently become an important focus, because new anticancer agents, such as oxaliplatin and taxanes, have been proven to confer a survival benefit and to show promise as standard anticancer agents for patients with gastric cancer [6, 10, 11]. Especially in gastric cancer with peritoneal dissemination, paclitaxel is recognized as an effective agent because of its high molecular weight and bulky molecular structure, delaying its clearance from the peritoneal cavity [12–14]. A randomized phase II trial (JCOG 0407) comparing best available 5-FU versus weekly paclitaxel is now ongoing for fluoropyrimidine-resistant gastric cancer with peritoneal dissemination. Oxaliplatin tends to be selected as a substitute for cisplatin in cases of peritoneal dissemination with a certain amount of ascites because oxaliplatin does not require extensive hydration [15]. To improve treatment efficacy, further chemotherapy regimens, such as combination therapy comprising 5-FU and taxane or oxaliplatin, remain as challenges to be met by further detailed investigations for peritoneal disseminated gastric cancer patients with inadequate oral intake. These findings may be helpful in predicting the life expectancy in peritoneal disseminated gastric cancer patients with inadequate oral intake who are treated with 5-FU-based chemotherapy.

In conclusion, this study demonstrated that the efficacy of 5-FU-based chemotherapy as the first-line treatment against peritoneal disseminated gastric cancer with inadequate oral intake was unsatisfactory. Patients receiving chemotherapy safely could be selected depending on some prognostic markers: PS, amount of ascites, serum CRP, and serum albumin. Systemic chemotherapy should be recommended with caution to patients with poor prognostic factors considering the risk–benefit balance. Further development of new regimens without oral anticancer agents is necessary to improve the quality of life and prognosis in this patient population.

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Conflict of interest We have no conflicts of interest to declare.

References

1. Parkin DM, Bray F, Ferlay J et al (2005) Global cancer statistics, 2002. CA Cancer J Clin 55:74–108
2. Dupont JB Jr, Lee JR, Burton GR et al (1987) Adenocarcinoma of the stomach: review of 1497 cases. Cancer (Phila) 41:941–947
3. D'Angelica M, Gonen M, Brennan MF et al (2004) Patterns of initial recurrence in completely resected gastric adenocarcinoma. Ann Surg 240:808–816
4. Yoo CH, Noh SH, Shin DW et al (2000) Recurrence following curative resection for gastric carcinoma. Br J Surg 87:236–242
5. Boku N, Yamamoto S, Fukuda H et al (2009) Fluorouracil versus combination of irinotecan plus cisplatin versus S-1 in metastatic gastric cancer: a randomised phase 3 study. Lancet Oncol 10:1063–1069
6. Cunningham D, Starling N, Rao S et al (2008) Capecitabine and oxaliplatin for advanced esophagogastric cancer. N Engl J Med 358:36–46
7. Kang YK, Kang WK, Shin DB et al (2009) Capecitabine/cisplatin versus 5-fluorouracil/cisplatin as first-line therapy in patients with advanced gastric cancer: a randomized phase III noninferiority trial. Ann Oncol 20:666–673
8. Lee J, Lim T, Uhm JE et al (2007) Prognostic model to predict survival following first-line chemotherapy in patients with metastatic gastric adenocarcinoma. Ann Oncol 18:886–891
9. Elahi MM, McMillan DC, McArdle CS et al (2004) Score based on hypoalbuminemia and elevated C-reactive protein predicts survival in patients with advanced gastrointestinal cancer. Nutr Cancer 48:171–173
10. Al-Batran SE, Hartmann JT, Probst S et al (2008) Phase III trial in metastatic gastroesophageal adenocarcinoma with fluorouracil, leucovorin plus either oxaliplatin or cisplatin: a study of the Arbeitsgemeinschaft Internistische Onkologie. J Clin Oncol 26:1435–1442
11. Van Cutsem E, Moiseyenko VM, Tjulandin S et al (2006) Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. J Clin Oncol 24:4991–4997
12. Emi Y, Yamamoto M, Takahashi I et al (2008) Phase II study of weekly paclitaxel by one-hour infusion for advanced gastric cancer. Surg Today 38:1013–1020
13. Yamada Y, Shirao K, Ohtsu A et al (2001) Phase II trial of paclitaxel by three-hour infusion for advanced gastric cancer with short premedication for prophylaxis against paclitaxel-associated hypersensitivity reactions. Ann Oncol 12:1133–1137
14. Kobayashi M, Sakamoto J, Namikawa T et al (2006) Pharmacokinetic study of paclitaxel in malignant ascites from advanced gastric cancer patients. World J Gastroenterol 12:1412–1415
15. Oh SY, Kwon HC, Lee S et al (2007) A Phase II study of oxaliplatin with low-dose leucovorin and bolus and continuous infusion 5-fluorouracil (modified FOLFOX-4) for gastric cancer patients with malignant ascites. Jpn J Clin Oncol 37:930–935

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ORIGINAL ARTICLE

Management of adjuvant S-1 therapy after curative resection of gastric cancer: dose reduction and treatment schedule modification

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Abstract
Background The aim of this study was to determine the optimal management of adjuvant S-1 therapy for stage II or III gastric cancer, encompassing the details of dose reduction and treatment schedule modification.
Methods We retrospectively examined 97 patients with stage II or III gastric cancer who received S-1 chemotherapy following gastrectomy between January 2003 and December 2007. S-1 (80 mg/m^2 per day) was orally administered twice daily for 4 weeks, followed by a 2-week rest. As a rule, treatment was continued for 1 year after gastrectomy. Dose reduction or treatment schedule modification was performed according to toxicity profiles.
Results Among the 97 patients, 57 (59%) underwent dose reduction at least once and 39 (40%) received treatment schedule modification. Of the 57 patients who required dose reduction, 45 (79%) underwent reduction within 3 months of the beginning of treatment. The most common reasons for dose reduction were anorexia (47%), followed by diarrhea (32%), leukopenia (24%), and rash (16%), with the reasons overlapping. Although the difference in the requirement for dose reduction was not significant, patients with a low creatinine clearance level or those who underwent total gastrectomy had a greater tendency to require dose reduction. The duration of the S-1 treatment period was at least 3 months in 88% of the patients, at least 6 months in 82%, and the planned 1-year period in 73% of the patients.
Conclusions In most patients, the planned 1-year adjuvant S-1 therapy for stage II or III gastric cancer could be completed by modifying the dose reduction and treatment schedule.

Keywords S-1 · Adjuvant chemotherapy · Gastric cancer

Introduction

Gastric cancer remains one of the leading causes of cancer-related deaths, the mortality rate of which ranks second worldwide [1]. Although surgery remains the sole mainstay of any curative treatment, the relapse rate is high and survival remains low even after surgical resection with curative intent. To prevent relapse and increase the survival rate, several types of adjuvant treatments have been administered. The rationale for using adjuvant treatment after curative resection remains controversial worldwide. In the United States, adjuvant chemoradiotherapy has become a standard treatment [2], and in Europe, perioperative chemotherapy has been established as a standard treatment [3]. On the other hand, in Japan, oral anticancer agents have been investigated for decades as postoperative adjuvant chemotherapy without sufficiently robust evidence for their efficacy. The different approaches in Europe, the United States, and Japan regarding adjuvant chemotherapy for gastric cancer may be attributable to differences in surgical approaches. In Europe and the United States, the standard surgical treatment is gastrectomy plus D0 or D1 lymphadenectomy, and chemoradiotherapy appears to be effective for local control after curative resection. In Japan, however, the established standard surgical treatment for gastric cancer is gastrectomy plus D2

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lymphadenectomy [4]. The role of adjuvant chemotherapy is to control distant or peritoneal recurrences. Against this background, adjuvant chemotherapy using oral fluorinated pyrimidines has been most widely used in both clinical practice and clinical trials [5, 6], although it remains unclear which specific treatment is effective.

S-1 is an effective derivative of 5-fluorouracil (5-FU) that combines tegafur with two modulators of 5-FU metabolism; namely, 5-chloro-2,4-dihydroxypyridine (CDHP), a reversible inhibitor of dihydropyrimidine dehydrogenase (DPD), and potassium oxonate, in a molar ratio of 1:0.4:1 [7]. Tegafur, an oral prodrug of 5-FU, is gradually converted to 5-FU and rapidly metabolized by DPD in the liver. The maximum concentration (Cmax) and area under the concentration time curve (AUC) of 5-FU in plasma during S-1 treatment have been found to be higher than the steady-state concentration and AUC of 5-FU in plasma during protracted intravenous infusion of 5-FU at 250 mg/m^2 per day [8]. Recently, the Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer (ACTS-GC) was performed [9]. This was a large randomized controlled trial comparing surgery alone versus surgery plus adjuvant chemotherapy. Following the ACTS-GC trial, S-1 administration for 1 year after curative surgery increased both overall and relapse-free survival compared with surgery alone. Thus, S-1 has become widely used in Japan not only for unresectable recurrent or metastatic tumors but also for disease-free patients after curative surgery for gastric cancer.

In the ACTS-GC trial, even though the major grade 3/4 toxicities included only anorexia (6.0%), nausea (3.7%), and diarrhea (3.1%), the percentage of patients who completed the planned 1-year S-1 treatment was only 65.8%. In addition, dose modification was performed in 42.4% of the patients, although details of the reasons for such modification were not provided. We therefore retrospectively investigated the details of dose reduction and schedule modification in patients with adjuvant S-1 therapy after curative resection of gastric cancer.

Patients and methods

Between January 2003 and December 2007, we retrospectively analyzed a total of 97 patients with stage II or III gastric cancer who received S-1 therapy after gastrectomy at the National Cancer Center Hospital, Tokyo. The clinicopathologic findings were determined in accordance with the *Japanese classification of gastric carcinoma* [10]. We regarded S-1 administration that started within 90 days after surgery as an acceptable period because this was a retrospective study, and because oncologists should consider starting adjuvant chemotherapy as soon as possible after gastrectomy (within 6 weeks) in order to eliminate micrometastases. There is no clear evidence for this 90-day period, but it is approximately twice the starting limit of the ACTS-GC study. Moreover, because the period of adjuvant S-1 therapy was 1 year, this study was intended for patients who had started adjuvant S-1 therapy 1 year or more before the time of analysis. In principle, S-1 was administered orally at 40 mg (body surface area [BSA] < 1.25 m^2), 50 mg (BSA 1.25–1.50 m^2), and 60 mg (BSA > 1.50 m^2) twice daily for 4 weeks, followed by a 2-week rest. However, a reduction of the starting dose was allowed at the physician's discretion; for example, when patients had postoperative gastrointestinal symptoms, poor general condition, or myelosuppression. S-1 administration was continued until 1 year after gastrectomy if there was no evidence of tumor recurrence or unacceptable toxicity. The dose or treatment schedule was modified at the physician's discretion according to toxicity profiles. In principle, we recommended that the schedule be changed from a 4-week administration followed by a 2-week rest to a 2-week administration followed by a 1-week rest if patients could take S-1 twice per day completely without S-1 skip but had severe gastrointestinal symptoms or myelosuppression during the first 2 weeks, and the dose was reduced (1 level down) if sufficient S-1 could not be administered to the patients due to adverse events during first 2 weeks. Nevertheless, we recommended a further dose reduction of S-1 (2 levels down) or 2-week administration followed by a 1-week rest when patients could not continue S-1 by adjusting first step dose or schedule modification. Furthermore, we attempted a 2-week administration followed by a 2-week rest or a 3-week administration followed by a 2-week rest if the treatment was not successful. We also allowed low doses such as 60 mg/day when we could not manage adverse events with a reduction to 80 mg/day.

The cumulative incidence of dose reduction was calculated by the Kaplan–Meier method, censoring at the date of treatment discontinuation caused by postoperative recurrence or adverse events. Statistical analysis was performed using Dr SPSS II (SPSS Japan, Tokyo, Japan). All statistical comparisons were two-sided and $P \leq 0.05$ was considered significant. Treatment-related toxicities were assessed using the Common Terminology Criteria for Adverse Events version 3.0.

This study was approved by the institutional review board of the National Cancer Center and was conducted in accordance with the ethical principles stated in Japanese ethics guidelines for epidemiological studies.

Results

Patient characteristics

The characteristics of the patients are shown in Table 1. Forty patients underwent total gastrectomy, 54 had distal

Table 1 Patient characteristics ($n = 97$)

	n (%)
Age (years)	
Median	59
Range	35–80
Sex	
Male	63 (65)
Female	34 (35)
ECOG performance status	
0	60 (62)
1	37 (38)
Stage, Japanese classification	
II	50 (52)
IIIA	29 (30)
IIIB	18 (19)
Surgical procedure	
Total gastrectomy	40 (41)
Subtotal gastrectomy	57 (59)
Creatinine clearance (ml/min)	
<60	10 (10)
6–80	29 (30)
>80	58 (60)
Initial dose of S-1 (mg/body)	
80	11 (11)
100	35 (36)
120	51 (53)

Creatinine clearance was calculated using the Cockroft–Gault formula. Percentages might not add up to 100% due to rounding

ECOG Eastern Cooperative Oncology Group

Table 2 Adverse events ($n = 97$)

	No. of patients				%	%
	G1	G2	G3	G4	All G	G3/4
Hematological toxicity						
Leukopenia	35	35	1	0	73	1
Neutropenia	18	36	22	1	79	24
Anemia	66	20	1	0	90	1
Thrombocytopenia	18	2	0	0	21	0
Nonhematological toxicity						
Anorexia	67	11	3	0	84	3
Nausea	43	5	0	0	49	0
Vomiting	14	2	0	0	17	0
Mucositis	35	4	0	0	40	0
Diarrhea	53	10	2	0	67	2
Fatigue	65	4	1	0	72	1
Rash	27	3	1	0	32	1
Pigmentation	40	4	–	–	45	–
Hand-foot syndrome	11	2	1	–	14	1
Watery eyes	6	5	1	–	12	1
Taste alteration	13	5	–	–	19	–
Hypoalbuminemia	23	2	1	0	27	1
Hyperbilirubinemia	33	10	1	0	45	1
AST	27	3	2	0	33	2
ALT	22	2	2	0	27	2
ALP	16	0	0	0	17	0
Creatinine	6	1	0	0	7	0

G grade, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *ALP* alkaline phosphatase

gastrectomy, and the remaining 3 underwent pylorus-preserving gastrectomy. Of 19 patients receiving dose reduction at the initial administration, 6 showed inadequate food intake after gastrectomy, 5 had leucopenia and were judged unfit to start at the standard dose, 1 developed pancreatic fistula as a postsurgical complication, and 1 had borderline BSA (This patient had BSA of 1.51, so physician selected S-1 100 mg/day in consideration of postsurgical condition); the reasons for the dose reduction in the remaining 6 patients were unknown. Of the 97 patients enrolled, 62 patients exceeded the 6-week starting time limit of the ACTS-GC study. The reasons were pancreatic fistula in 6 patients, gastrointestinal symptoms in 5 patients, poor oral intake in 3 patients, poor general condition in 3 patients, another treatment in 2 patients (dental therapy in 1 and treatment for early bladder cancer in the other), anastomotic stenosis in 1 patient, ileus in 1 patient, colitis in 1 patient, delay of pathological confirmation in 1 patient, and by patient request for 1 patient; and the remaining 38 patients delayed seeking an examination at the outpatient clinic by about 1 or 2 weeks.

Safety

S-1 chemotherapy adverse events, which involved grade 1/2 intensity in the majority of cases, are summarized in Table 2. The most common hematological adverse event was neutropenia, occurring at grade 3/4 intensity in 23 patients (24%). Only 1 patient developed grade 3 febrile neutropenia. Nonhematological toxicity was frequent but rarely severe. Taste alteration and watery eyes, which occurred consistently with repeated courses of therapy, were experienced by 18 (19%) and 12 (12%) patients, respectively, and occasionally a few patients needed dose reduction or treatment discontinuation. There were no treatment-related deaths.

Treatment administration

The median follow-up period after gastrectomy was 43.0 months (range 5.3–73.4 months). Among the 97 patients analyzed, 57 (59%) received dose reduction at least once and 39 (40%) underwent schedule modification during the planned 1-year treatment. Of the 57 patients

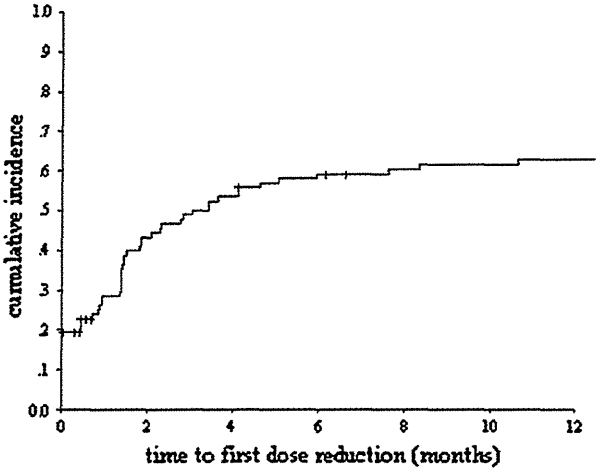

Fig. 1 Cumulative incidence of the time to first dose reduction

Table 3 Reasons for dose reduction ($n = 57$)

Pretreatment dose reduction	19 (33%)
Inadequate food intake	6
Leukopenia	5
Pancreatic fistula	1
Borderline BSA*	1
Unknown	6
Dose reduction during the treatment	38 (67%)
Gastrointestinal toxicities	
Anorexia	18
Diarrhea	12
Nausea/vomiting	5
Mucositis	2
Abdominal pain	1
Others	
Leukopenia/neutropenia	9
Rash	6
Fatigue	3
Taste alteration	3
Liver dysfunction	2
Watery eyes	1

The percentages and numbers do not balance because of overlapping reasons for dose reduction during the treatment

BSA body surface area

* 1 patient with borderline BSA had BSA of 1.51, so physician selected S-1 100 mg/day in consideration of postsurgical condition

who required dose reduction, 45 (79%) underwent the reduction within 3 months of starting the treatment. The median time to the first dose reduction was 1.4 months (range 0–10.6 months). The time to dose reduction is shown graphically in Fig. 1. The most common reasons for dose reduction during the treatment period were anorexia

Table 4 Reasons for treatment discontinuation ($n = 26$)

Adverse events	20 (77%)
Gastrointestinal toxicities	14
Anorexia	6
Diarrhea	3
Nausea/vomiting	3
Abdominal pain	1
Mucositis	1
Others	
Fatigue	3
Leukopenia/neutropenia	2
Watery eyes	2
Taste alteration	2
Rash	1
Hand–foot syndrome	1
Pigmentation	1
Liver function	1
Dyspnea	1
Recurrence	2 (8%)
Others	4 (15%)

The numbers do not balance because of overlapping reasons for treatment discontinuation

(47%), followed by diarrhea (32%), leukopenia (24%), and rash (16%) with reasons overlapping (Table 3). Of the 39 patients who required schedule modification, 22 patients underwent a 2-week administration followed by a 1-week rest, 19 patients had a 2-week administration followed by a 2-week rest, and 2 patients had a 3-week administration followed by a 2-week rest (including the 4 patients who underwent two modifications, i.e., a 2-week administration followed by a 1-week rest, and a 2-week administration followed by a 2-week rest in 3 patients, and a 3-week administration followed by a 2-week rest and a 2-week administration followed by a 2-week rest in 1 patient).

A total of 60 patients required dose reduction and/or schedule modification, and 32 patients underwent remodification after their initial modification (the number of modifications was 1 in 28 patients, 2 in 22 patients, 3 in 9 patients, and 4 in 1 patient). No patients were rechallenged with the initial dose after undergoing dose reduction due to adverse events during the adjuvant chemotherapy. The relative administration day, defined as the ratio of actual administration days to planned administration days, was 83.8%, and we regarded relative number of administration days assuming that was reckoned from the start date of actual S-1 administration, not within 6 weeks after surgery specified in ACTS-GC. The relative dose intensity, defined as the ratio of the actual cumulative dose to the planned cumulative dose, was 69.1%. The percentage of patients who continued treatment for at least 3 months was 88%, that of patients who continued treatment for at least 6 months was 82%, and that

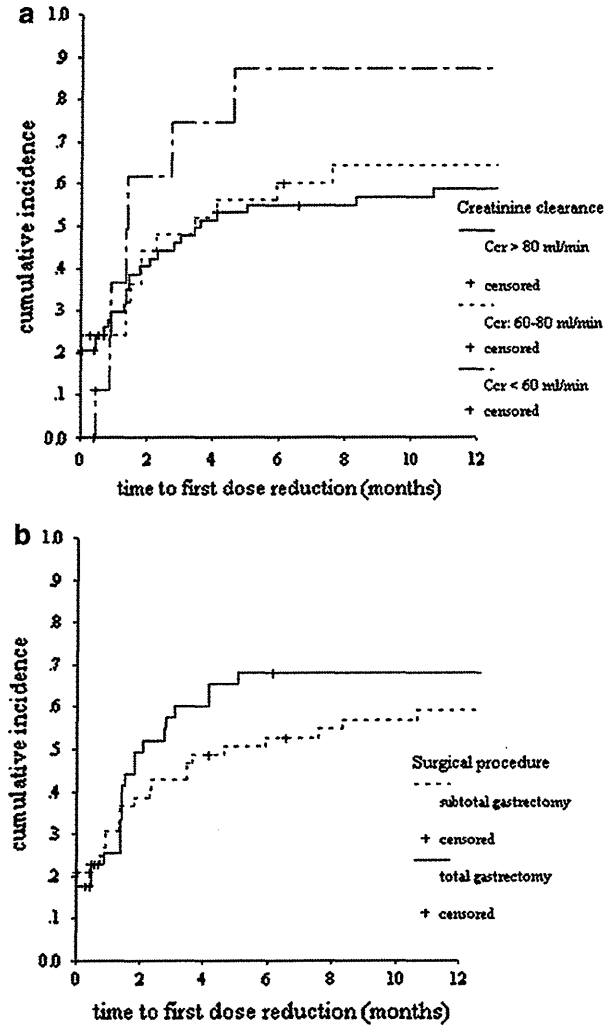

Fig. 2 Cumulative incidence of the first dose reduction. **a** By pretreatment creatinine clearance (*Ccr*) level; Ccr > 80 ml/min ($n = 58$), Ccr 60–80 ml/min ($n = 29$), Ccr < 60 ml/min ($n = 10$). Patients with a lower Ccr level had a greater tendency to require dose reduction ($P = 0.20$). **b** By surgical procedures; subtotal gastrectomy group ($n = 57$), total gastrectomy group ($n = 40$). Patients with total gastrectomy had a greater tendency to require dose reduction ($P = 0.36$)

of patients who continued treatment for the scheduled 12 months was 73%. Twenty-six patients (27%) discontinued treatment (Table 4). The reasons for treatment discontinuation were adverse events in 20 patients, recurrent disease in 2, and other reasons in 4. The median duration until treatment discontinuation was 4.0 months.

We performed univariate analyses using pretreatment patient profiles (sex, age, performance status, surgical procedure, creatinine clearance, and time interval between surgery and first S-1 administration) as the basis of dose reduction during the planned 1-year treatment. Although the univariate analyses revealed no significant predictive factors for dose reduction, the incidence of dose reduction tended to be higher in patients with a low creatinine clearance level and in those who underwent total gastrectomy (Fig. 2). Moreover, no significant difference in recurrence was found depending on the S-1 starting time (within 6 weeks vs. more than 6 weeks; data not shown).

Discussion

The present study demonstrated that in most patients, the planned 1-year adjuvant S-1 therapy for stage II or III gastric cancer could be completed by modifying the dose reduction and treatment schedule. Patients with a low creatinine clearance level at pretreatment and those starting the treatment after total gastrectomy may require careful observation for adverse events, particularly during the early period after treatment.

In the present study, patients with a low creatinine clearance level showed a trend to require dose reduction. Because CDHP, a biochemical modulator of 5-FU, is excreted mainly in the urine, renal function is critical for plasma CDHP clearance. Lower CDHP clearance leads to a prolonged high plasma CDHP concentration, which causes a sustained high plasma 5-FU concentration. This may lead to severe adverse events with an S-1 chemotherapeutic regimen for patients with a low creatinine clearance level. Post-marketing surveillance of S-1 in patients with advanced gastric cancer has demonstrated a close relationship between the incidence of grade 3 or worse hematological toxicities and renal function [11].

With regard to S-1 adverse events, gastrointestinal toxicity has become well recognized, particularly diarrhea, which was the identified dose-limiting toxicity of S-1 in phase I studies in Western countries [12–15]. In the adjuvant setting, these adverse events must be successfully managed to achieve the planned 1-year treatment with S-1. Of the 26 patients who discontinued treatment in the present study, 20 (77%) discontinued due to S-1 adverse events. Persistent gastrointestinal toxicities, even if the grade of adverse events was mild, were the major reasons for patients' refusal to undergo continuous treatment. Therefore, appropriate guidelines must be established for the proper management of adjuvant S-1 therapy in order that the planned 1-year treatment is completed. We recommended to the patients that they skip S-1 administration if they complained of uncomfortable gastrointestinal toxicities. Likewise, we explained to the patients to start taking S-1 again after the relief of symptoms.

Recently, S-1 pharmacokinetic data have demonstrated that the plasma Cmax and AUC of 5-FU after total gastrectomy were significantly higher with S-1 treatment than

these parameters were before surgery [16–18]. Moreover, statistically significant relationships were observed between the grade of S-1-induced diarrhea and AUC, as well as between the plasma Cmax and 5-FU concentration [12, 15]. Therefore, it is possible that S-1 toxicities might be enhanced by gastrectomy. In fact, the present study demonstrated that patients who had undergone total gastrectomy had a higher incidence of dose reduction than patients who had subtotal gastrectomy.

Post-hoc analyses of the ACTS-GC trial showed that patients who completed the planned 1-year S-1 treatment had a longer survival than patients who discontinued treatment [19]. Therefore, it is important to complete the planned 1-year treatment, if necessary by modifying the dose or treatment schedule. An appropriate strategy must be developed to achieve completion of treatment and appropriate management of adverse events. As an example, in our patients, when they could take the full 2-week S-1 treatment from the initial treatment but experienced uncomfortable gastrointestinal toxicities that prevented continuation of S-1 administration, we usually changed the treatment schedule from the original 4-week administration followed by a 2-week rest to 2-week administration followed by a 1-week rest. This change in the treatment schedule allows patients to have an earlier rest, which enables them to recover from the prolonged gastrointestinal toxicities or to discontinue treatment before symptoms develop. On the other hand, when patients had not taken the planned S-1 dosage at the time of examination 2 weeks from the initial treatment and had uncomfortable gastrointestinal toxicities that prevented continuation of S-1 administration, one dose-reduction level could be applied as follows: from 120 to 100 mg/day, from 100 to 80 mg/day, or from 80 to 60 mg/day. Thus, the greatest possible efforts to maintain dose intensity must be made.

As for the patients with dose reduction, there was a high probability of requiring dose reduction during the initial 3 months of the planned 1-year treatment. It is therefore deemed necessary that accurate examination and careful treatment must be carried out in light of the adverse events of S-1, particularly until 3 months after the initial S-1 treatment. Significant predictive factors of dose reduction were sought in the present study and in past studies of adjuvant S-1 treatment. We believe that clarification of the predictive factors of S-1 adverse events remains a major issue, because S-1 has been approved for the treatment of several cancers. In further large prospective trials, the exploration of predictive factors of adverse events, such as gene polymorphisms, is expected.

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References

1. Kelley JR, Duggan JM. Gastric cancer epidemiology and risk factors. J Clin Epidemiol. 2003;56:1–9.
2. Macdonald JS, Smalley SR, Benedetti J, Hundahl SA, Estes NC, Stemmermann GN, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med. 2001;345:725–30.
3. Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med. 2006;355:11–20.
4. Sasako M, Sano T, Yamamoto S, Kurokawa Y, Nashimoto A, Kurita A, et al. D2 lymphadenectomy alone or with para-aortic nodal dissection for gastric cancer. N Engl J Med. 2008; 359:453–62.
5. Kinoshita T, Nashimoto A, Yamamura Y, Okamura T, Sasako M, Sakamoto J, et al. Feasibility study of adjuvant chemotherapy with S-1 (TS-1; tegafur, gimeracil, oteracil potassium) for gastric cancer. Gastric Cancer. 2004;7:104–9.
6. Nakajima T, Kinoshita T, Nashimoto A, Sairenji M, Yamaguchi T, Sakamoto J, et al. Randomized controlled trial of adjuvant uracil-tegafur versus surgery alone for serosa-negative, locally advanced gastric cancer. Br J Surg. 2007;94:1468–76.
7. Kato T, Shimamoto Y, Uchida J, Ohshimo H, Abe M, Shirasaka T, et al. Possible regulation of 5-fluorouracil-induced neuro- and oral toxicities by two biochemical modulators consisting of S-1, a new oral formulation of 5-fluorouracil. Anticancer Res. 2001;21: 1705–12.
8. Yamada Y, Hamaguchi T, Goto M, Muro K, Matsumura Y, Shimada Y, et al. Plasma concentrations of 5-fluorouracil and F-beta-alanine following oral administration of S-1, a dihydropyrimidine dehydrogenase inhibitory fluoropyrimidine, as compared with protracted venous infusion of 5-fluorouracil. Br J Cancer. 2003;89:816–20.
9. Sakuramoto S, Sasako M, Yamaguchi T, Kinoshita T, Fujii M, Nashimoto A, et al. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. N Engl J Med. 2007;357:1810–20.
10. Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma-2nd English edition. Gastric Cancer. 1998;1: 10–24.
11. Yamanaka T, Matsumoto S, Teramukai S, Ishiwata R, Nagai Y, Fukushima M. Safety evaluation of oral fluoropyrimidine S-1 for short- and long-term delivery in advanced gastric cancer: analysis of 3758 patients. Cancer Chemother Pharmacol. 2008;61:335–43.
12. van Groeningen CJ, Peters GJ, Schornagel JH, Gall H, Noordhuis P, de Vries MJ, et al. Phase I clinical and pharmacokinetic study of oral S-1 in patients with advanced solid tumors. J Clin Oncol. 2000;18:2772–9.
13. Hoff PM, Saad ED, Ajani JA, Lassere Y, Wenske C, Medgyesy D, et al. Phase I study with pharmacokinetics of S-1 on an oral daily schedule for 28 days in patients with solid tumors. Clin Cancer Res. 2003;9:134–42.
14. Chu QS, Hammond LA, Schwartz G, Ochoa L, Rha SY, Denis L, et al. Phase I and pharmacokinetic study of the oral fluoropyrimidine S-1 on a once-daily-for-28-day schedule in patients with advanced malignancies. Clin Cancer Res. 2004;10:4913–21.
15. Cohen SJ, Leichman CG, Yeslow G, Beard M, Proefrock A, Roedig B, et al. Phase I and pharmacokinetic study of once daily oral administration of S-1 in patients with advanced cancer. Clin Cancer Res. 2002;8:2116–22.
16. Kochi M, Fujii M, Kanamori N, Kaiga T, Aizaki K, Takahashi T, et al. Effect of gastrectomy on the pharmacokinetics of S-1, an oral fluoropyrimidine, in resectable gastric cancer patients. Cancer Chemother Pharmacol. 2007;60:693–701.

17. Kim WY, Nakata B, Hirakawa K. Alternative pharmacokinetics of S-1 components, 5-fluorouracil, dihydrofluorouracil and alpha-fluoro-beta-alanine after oral administration of S-1 following total gastrectomy. Cancer Sci. 2007;98:1604–8.
18. Tsuruoka Y, Kamano T, Kitajima M, Kawai K, Watabe S, Ochiai T, et al. Effect of gastrectomy on the pharmacokinetics of 5-fluorouracil and gimeracil after oral administration of S-1. Anticancer Drugs. 2006;17:393–9.
19. Sakuramoto S, Kikuchi S, Watanabe M. Efficacy of S-1 (oral fluoropyrimidine) for gastric cancer. The Medical Frontline (Saishin Igaku). 2009;64:1075–80. (in Japanese).

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ORIGINAL ARTICLE

Neuroendocrine tumors of the stomach: chemotherapy with cisplatin plus irinotecan is effective for gastric poorly-differentiated neuroendocrine carcinoma

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Abstract
Background Neuroendocrine tumors (NETs) occur in various primary sites, but rarely in the stomach. NETs are classified into three types, carcinoids, malignant carcinoids and poorly differentiated neuroendocrine carcinomas (PNECs), whose clinical behavior is different. Currently, clinical outcomes and standard chemotherapy for NETs of the stomach remain unclear.
Methods We conducted a retrospective review of histopathologically confirmed NETs of the stomach at our hospital between January 2000 and August 2006.
Results Thirty-seven NETs were identified. Fifteen patients had carcinoids while 22 had PNECs. Among the carcinoid patients, 7 underwent endoscopic mucosal resection and 5 had gastrectomy as first-line treatment. Three patients were observed without intervention. All patients were alive after an average follow-up period of 27 months. Among the 22 PNEC patients, 3 had no metastasis, 11 had regional lymph node metastasis, and 8 had distant metastasis. Eight of 14 patients relapsed at a median of 177 days (range 120–1459 days) after curative surgery. Twelve patients with metastatic or recurrent disease received palliative cisplatin plus irinotecan chemotherapy. The response rate was 75%, the median progression-free survival time was 212 days, and median survival time was 679 days.
Conclusion Gastric PNEC patients with distant metastasis had poor outcomes. Regimens containing cisplatin plus irinotecan produced a good response in gastric PNEC.

Keywords Carcinoid tumor · Poorly differentiated neuroendocrine carcinoma · Cisplatin · Irinotecan · Stomach

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Introduction

Neuroendocrine tumors (NETs) occur in various primary sites, but rarely in the stomach. Gastric carcinoids account for only 3% of all carcinoid tumors [1]. The World Health Organization classifies endocrine tumors into the following categories: well-differentiated (neuro)endocrine tumors, well-differentiated (neuro)endocrine carcinomas, poorly differentiated (neuro)endocrine carcinomas (PNECs), and mixed exocrine-endocrine tumors [2]. Regarding NETs of the stomach, well-differentiated endocrine tumors and well-differentiated endocrine carcinomas are regarded as carcinoids and malignant carcinoids, respectively. PNEC is mainly regarded as small cell carcinoma.

Well-differentiated NETs and PNECs show different biological behaviors. Carcinoids demonstrate slow growth, whereas PNECs grow rapidly and carry a poor prognosis [3, 4]. Carcinoids are treated by endoscopic mucosal resection (EMR) or surgery, and most patients with carcinoids have localized tumor and a good prognosis, with the 5-year survival for localized gastric carcinoids reported to be 93% [1]. Gastric PNECs without distant metastasis are mainly treated by surgical intervention, whereas PNECs

with distant metastasis or recurrence are treated by chemotherapy. Various types of chemotherapy have been used to treat PNECs or extrapulmonary small cell carcinomas [4–7]; however, there is no standard regimen for metastatic or recurrent gastric PNECs.

Small cell lung cancer (SCLC) is a far more common disease than PNEC, but the two diseases share many clinicopathological features. In SCLC with extended disease, cisplatin plus irinotecan has been associated with better survival than cisplatin plus etoposide [8]. Here we report the clinical outcomes of primary NETs of the stomach and evaluate the efficacy of cisplatin plus irinotecan for gastric PNECs.

Patients and methods

This study was a retrospective analysis of histopathologically confirmed NETs primarily arising in the stomach in patients treated between January 2000 and August 2006 at the National Cancer Center Hospital in Tokyo, Japan. We extracted information on age, sex, disease stage, laboratory findings, radiological findings, pathological findings, therapy, effectiveness of therapy, and outcomes.

The cisplatin plus irinotecan regimen was administered as follows: on days 1 and 15 irinotecan (70 mg/m^2) was given as a 90-min intravenous infusion. Cisplatin (80 mg/m^2) was given via 120-min intravenous infusion on day 1. This regimen was repeated every 4 weeks until the occurrence of tumor progression or severe adverse reactions. The chemotherapy response was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) guideline version 1.0. Toxicity was graded according to the Common Terminology Criteria for Adverse Events version 3.0.

Statistical analysis was performed using SPSS version 11 software (SPSS Japan., Tokyo, Japan). Overall survival and progression-free survival curves were constructed by the Kaplan–Meier method.

Results

Thirty-seven patients [male, $n = 30$; female, $n = 7$; median age, 67 years (range 27–82 years)] had NETs arising in the stomach. Of these 37 patients, 15 had carcinoids and 22 had PNECs (16 small cell carcinomas, 4 small cell carcinomas with adenocarcinoma, and 2 large cell carcinomas). Among the carcinoid patients, EMR was performed in 7 patients, including 3 who later underwent surgery; surgery was performed in 5 patients, and 3 patients were observed, due to complication (other cancer) or tumor disappearance after biopsy. No patient had metastasis or carcinoid syndrome. All the patients with carcinoids were alive after an average follow-up period of 27 months (Fig. 1).

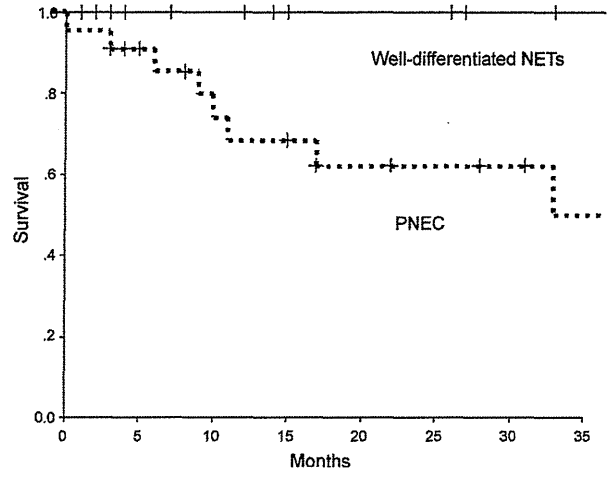

Fig. 1 Survival curves of patients with neuroendocrine tumors (*NETs*) primarily arising from the stomach. All patients with well-differentiated type ($n = 15$) were alive, and the median survival time of patients with poorly differentiated neuroendocrine carcinoma (*PNEC*) was 33 months ($n = 22$)

The clinical data regarding PNEC patients are summarized in Table 1. Among the 22 PNEC patients, 14 had local disease and 8 had distant metastasis. Serum carcinoembryonic antigen (CEA), neuron-specific enolase (NSE), and pro-gastrin-releasing peptide (GRP) were elevated in 23% (5/22), 38% (5/13), and 29% (4/14) of patients, respectively. Surgery was performed in 15 patients (14 patients with localized disease and 1 patient in whom peritoneal dissemination was detected by cytologic diagnosis during surgery). Among the 14 patients with localized disease, 2 patients received adjuvant S-1 chemotherapy after curative surgery. Of those who underwent surgery, only 4 (27%) were diagnosed with neuroendocrine carcinoma or small cell carcinoma from biopsy specimens prior to surgery.

Eight of 14 patients relapsed at a median of 177 days (range 120–1459 days) after curative surgery. A total of 14 patients (7 with unresectable disease at diagnosis, 7 with recurrent disease after surgery) received chemotherapy, and 1 relapsed patient received best supportive care.

The median survival time in the 22 PNEC patients was 33 months (Fig. 1), whereas in those with PNEC with distant metastasis the median survival time was 10.4 months. Twelve patients (5 with recurrent disease, 7 with unresectable disease) received chemotherapy with cisplatin plus irinotecan. The median number of treatment cycles was four. Six patients discontinued treatment because of disease progression, and 3 discontinued therapy because of adverse

Table 1 Clinical data of patients with poorly differentiated neuroendocrine carcinomas

Patient no.	Sex	Age (years)	Stage	CEA[a]	NSE[b]	GRP[c]	Treatment
1	M	61	1	3.7	NE	NE	Surgery, RF
2	M	82	2	3.8	NE	NE	Surgery, RC (liver), Palliation
3	M	71	2	1.1	8.5	13.9	Surgery, RF
4	M	74	2	2.1	14	19.5	Surgery, RC (liver), CX (IP)
5	M	72	2	2.5	33.6	44.6	Surgery, RC (LN), CX (IP)
6	M	61	2	1.5	12.8	42.5	Surgery, RC (liver), CX (IP)
7	F	67	3	4	NE	NE	Surgery, RF
8	M	75	3	2.7	NE	NE	Surgery, RF
9	F	70	3	8	NE	NE	Surgery, RC (LN), CX (S-1)
10	M	59	3	2	NE	NE	Surgery, AD (S-1), RF
11	M	69	3	6.7	NE	NE	Surgery, RC (LN), CX (S-1)
12	M	60	3	51.6	12.7	1039	Surgery, RC (liver), CX (IP)
13	M	75	3	4.5	9.7	21.2	Surgery, AD (S-1), RF
14	M	62	3	3	8.4	21.2	Surgery, RC (LN), CX (IP)
15	M	35	4	1.4	5.2	5.1	Surgery, CX (IP)
16	M	68	4	1.4	197	18	CX (IP)
17	M	62	4	7	89.6	5850	CX (IP)
18	M	27	4	3.2	NE	138	CX (IP)
19	F	61	4	2	3.5	43.5	CX (IP)
20	M	67	4	4.1	62.4	67.8	CX (IP)
21	M	73	4	2.1	181.2	23.6	CX (IP)
22	M	74	4	22.3	NE	NE	Palliation

NE not examined, *RF* relapse-free, *RC* recurrence (region), *CX* chemotherapy, *IP* irinotecan plus cisplatin, *AD* adjuvant chemotherapy, *LN* lymph node

[a] *CEA* carcinoembryonic antigen: normal range <5 ng/ml

[b] *NSE* neuron-specific enolase: normal range <15 ng/ml

[c] *GRP* pro-gastrin-releasing peptide: normal range <46 pg/ml

effects (neurotoxicity, febrile neutropenia, and diarrhea) at a median follow-up period of 29 months. The overall response rate was 75% (8/12) and 2 patients had stable disease. Rates of grade 3/4 neutropenia and diarrhea were 58% (7/12) and 17%, respectively, but there were no treatment-related deaths. The median progression-free survival (PFS) time was 212 days (95% confidence interval [CI] 121–302) and the median survival time was 679 days (95% CI 39–1319). No patient had brain metastasis during the time of observation.

Discussion

NETs arise from the widely distributed neuroendocrine cell system. Histologically, NET cells are argentophilic and express endocrine markers such as chromogranin or NSE. NETs of the stomach are classified into the following three categories; carcinoids, malignant carcinoids, and PNECs or small cell carcinomas, on the basis of clinical and pathological features [2, 9]. However, some confusion remains with regard to the histological classification.

Gastric carcinoids account for about 0.3% of all gastric tumors. Gastrointestinal small cell carcinomas account for about 0.1–1.0% of all gastrointestinal tumors, and gastric small cell carcinomas account for approximately 11% of gastrointestinal small cell carcinomas [4]. As for NETs of the stomach, Rindi et al. [10] reviewed the histology of 55 gastric endocrine tumors and reported 46 cases of well-differentiated tumors and 9 of neuroendocrine carcinomas. They further investigated 205 gastric endocrine tumors and reported 193 cases of well-differentiated and 12 of poorly differentiated tumors [11].

Well-differentiated NETs (carcinoids and malignant carcinoids) and PNECs have different biological behaviors. The 5-year survival rate of carcinoids without metastasis was reported to be 93–98% [1, 3]. In carcinoids with metastasis, the 5-year survival rate was reported to be 0–75%. The cumulative crude survival rate of PNEC was only 33.3% at 5 years after diagnosis. Carcinoid patients

have better survival than patients with PNEC. In our study, the difference in survival between carcinoid and PNEC was similar to that in previous studies.

Standard treatment of patients with localized gastric carcinoids involves endoscopic resection or surgical excision [9]. For functioning tumors (carcinoid syndrome) as well, surgery is the primary treatment option. For patients with metastasis, management is not well defined and thus they are treated using several strategies, including surgery, biotherapy, and chemotherapy. Rinke et al. [12] reported that a somatostatin analog retarded tumor progression in patients with functionally active and inactive metastatic midgut NETs. We had only patients with small and/or localized carcinoids; thus, resection or observation was performed and they showed a good prognosis.

There are no standard chemotherapy regimens for gastric PNEC. Surgery is performed to treat localized disease in patients with gastric PNEC. Matsui et al. [13] reported 17 patients with gastric small cell carcinoma who underwent surgery; 3 patients without metastasis survived for 6–20 months after the surgery and 14 patients with metastasis died 5–22 months after the surgery at the end of their observation. In a review of 54 patients with gastric small cell carcinoma [14], 3 patients without distant metastasis survived for more than 2 years after gastrectomy with dissection of regional lymph nodes. In our study, although the relapse rate was high, there were 2 long-term survivors who showed no relapse for more than 3 years after surgery. Although the effectiveness of surgery is limited, it remains one of the most important modalities for treating gastric PNEC.

For patients with gastric adenocarcinoma, adjuvant S-1 chemotherapy is effective [15], and chemoradiotherapy is effective for limited stages of SCLC [16]. Further studies that explore factors associated with relapse and assess the efficacy of adjuvant chemotherapy or chemoradiotherapy for gastric PNEC are needed. Prophylactic cranial irradiation is standard therapy in patients with limited SCLC, due to the high rate of brain metastasis [17]. In our study, no patients had brain recurrence; thus, it is unclear whether or not prophylactic cranial irradiation is effective for gastric PNEC.

There is no standard regimen for metastatic or recurrent gastric PNECs, which are typically treated according to the treatment guidelines for SCLC. The standard chemotherapy for SCLC is a combination regimen containing cisplatin. Noda et al. [8] reported that patients treated with cisplatin plus irinotecan had better outcomes than patients treated with cisplatin plus etoposide, with median survival times in the two groups of 12.8 and 9.4 months, respectively. On the other hand, there are few reports on chemotherapy for PNEC other than the chemotherapy used for SCLC. Moertel et al. [5] reported that a regimen containing cisplatin plus etoposide produced a good response rate (67%) in 18 patients with neuroendocrine carcinomas. Mitry et al. [6] obtained a response rate of 41.5% in 41 PNEC patients, with a PFS of 8.9 months and an overall survival of 15 months. These studies included only a few patients with gastric PNECs. A previous study showed good response of PNEC to combination chemotherapy with paclitaxel, carboplatin, and etoposide; however, the study included only 1 patient with gastric neuroendocrine carcinoma [7]. Kulke et al. [18] reported a very low response rate of 6.6% to cisplatin plus irinotecan for extrapulmonary NETs, although 78% (14/18) of their patients had well-differentiated NETs.

In our study, treatment with cisplatin plus irinotecan was effective against gastric PNECs, with an overall response rate of 75% and a PFS of 212 days. We consider the toxicity of this regimen tolerable. Of note, gastric PNECs often have components of adenocarcinoma [13], and cisplatin plus irinotecan has been shown to be effective against gastric adenocarcinoma [19]. Therefore, we consider this regimen suitable for gastric PNEC, although the present retrospective study has several limitations. We are now planning a prospective study of this cisplatin plus irinotecan regimen in PNEC patients.

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References

1. Godwin JD. Carcinoid tumors. Cancer. 1975;36:560–9.
2. Solcia E, Kloeppel G, Sobin LH. World Health Organization: International histological classification of tumours: histological typing of endocrine tumours. Berlin: Springer; 2000.
3. Botch K, Ahren B, Ahlman H, Falkmer S, Granerus G, Grimelius L. Gastric carcinoids. Biologic behavior and prognosis after differentiated treatment in relation to type. Ann Surg. 2005;242: 64–73.
4. Brenner B, Tang LH, Klimstra DS, Kelsen DP. Small-cell carcinomas of the gastrointestinal tract: a review. J Clin Oncol. 2004;22:2730–9.
5. Moertel CG, Kvols LK, O'Connell MJ, Rubin J. Treatment of neuroendocrine carcinomas with combined etoposide and cisplatin. Cancer. 1991;68:227–32.
6. Mitry E, Baudin E, Ducreux M, Sabourin JC, Rufle P, Aparicio T, et al. Treatment of poorly differentiated neuroendocrine tumours with etoposide and cisplatin. Br J Cancer. 1999;81:1351–5.
7. Hainsworth JD, Spigel DR, Litchy S, Greco FA. Phase II trial of paclitaxel, carboplatin and etoposide in advanced poorly differentiated neuroendocrine carcinoma: a Minnie Pearl Cancer Research Network study. J Clin Oncol. 2006;24:3548–54.
8. Noda K, Nishiwaki Y, Kawahara M, Negoro S, Sugiura T, Yokoyama A, et al. Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. N Engl J Med. 2002;346:85–91.
9. Arnold R. Endocrine tumours of the gastrointestinal tract. Introduction: definition, historical aspects, classification, staging, prognosis and therapeutic options. Best Pract Res Clin Gastroenterol. 2005;19:491–505.

10. Rindi G, Luinetti O, Cornaggia M, Capella C, Solcia E. Three subtypes of gastric argyrophil carcinoid and the gastric neuroendocrine carcinoma: a clinicopathologic study. Gastroenterology. 1993;104:994–1006.
11. Rindi G, Bordi C, Rappel S, Rosa ST, Stolte M, Solcia E. Gastric carcinoids and neuroendocrine carcinomas; pathogenesis, pathology and behavior. World J Surg. 1996;20:168–72.
12. Rinke A, Muller HH, Brittinger CS, Klose KJ, Barth P, Wied M, et al. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID study group. J Clin Oncol. 2009;27:4656–63.
13. Matsui K, Kitagawa M, Miwa A, Kuroda Y, Tsuji M. Small cell carcinoma of the stomach: a clinicopathologic study of 17 cases. Am J Gastroenterol. 1991;86:1167–75.
14. Arai K, Matsuda M. Gastric small-cell carcinoma in Japan: a case report and review of the literature. Am J Clin Oncol. 1998;21:458–61.
15. Sakuramoto S, Sasako M, Yamaguchi T, Kinoshita T, Fujii M, Nashimoto A, et al. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. N Engl J Med. 2007;357:1810–20.
16. Pignon JP, Arriagata R, Ihde DC, Johnson DH, Perry MC, Souhami RL, et al. A meta-analysis of thoracic radiotherapy for small-cell lung cancer. N Engl J Med. 1992;327:1618–24.
17. Auperin A, Arriagada R, Pignon JP, Le Péchoux C, Gregor A, Stephens RJ, et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. N Engl J Med. 1999;341:476–84.
18. Kulke MH, Wu B, Ryan D, Enzinger PC, Zhu AX, Clark JW, et al. A phase II trial of irinotecan and cisplatin in patients with metastatic neuroendocrine tumors. Dig Dis Sci. 2006;51:1033–8.
19. Boku N, Ohtsu A, Shimada Y, Shirao K, S Seki, Saito H, et al. Phase II study of a combination of irinotecan and cisplatin against metastatic gastric cancer. J Clin Oncol. 1999;17:319–23.

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ORIGINAL REPORT

Bevacizumab in Combination With Chemotherapy As First-Line Therapy in Advanced Gastric Cancer: A Randomized, Double-Blind, Placebo-Controlled Phase III Study

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Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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ABSTRACT

Purpose
The Avastin in Gastric Cancer (AVAGAST) trial was a multinational, randomized, placebo-controlled trial designed to evaluate the efficacy of adding bevacizumab to capecitabine-cisplatin in the first-line treatment of advanced gastric cancer.

Patients and Methods
Patients received bevacizumab 7.5 mg/kg or placebo followed by cisplatin 80 mg/m^2 on day 1 plus capecitabine 1,000 mg/m^2 twice daily for 14 days every 3 weeks. Fluorouracil was permitted in patients unable to take oral medications. Cisplatin was given for six cycles; capecitabine and bevacizumab were administered until disease progression or unacceptable toxicity. The primary end point was overall survival (OS). Log-rank test was used to test the OS difference.

Results
In all, 774 patients were enrolled; 387 were assigned to each treatment group (intention-to-treat population), and 517 deaths were observed. Median OS was 12.1 months with bevacizumab plus fluoropyrimidine-cisplatin and 10.1 months with placebo plus fluoropyrimidine-cisplatin (hazard ratio 0.87; 95% CI, 0.73 to 1.03; $P = .1002$). Both median progression-free survival (6.7 *v* 5.3 months; hazard ratio, 0.80; 95% CI, 0.68 to 0.93; $P = .0037$) and overall response rate (46.0% *v* 37.4%; $P = .0315$) were significantly improved with bevacizumab versus placebo. Preplanned subgroup analyses revealed regional differences in efficacy outcomes. The most common grade 3 to 5 adverse events were neutropenia (35%, bevacizumab plus fluoropyrimidine-cisplatin; 37%, placebo plus fluoropyrimidine-cisplatin), anemia (10% *v* 14%), and decreased appetite (8% *v* 11%). No new bevacizumab-related safety signals were identified.

Conclusion
Although AVAGAST did not reach its primary objective, adding bevacizumab to chemotherapy was associated with significant increases in progression-free survival and overall response rate in the first-line treatment of advanced gastric cancer.

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INTRODUCTION

Gastric cancer is a common malignancy and is associated with a high mortality rate. It is the fourth most prevalent cancer diagnosed in men worldwide (fifth in women), and the third most common cause of cancer-related deaths in men (fifth in women).[1] In the West, most patients with gastric adenocarcinoma present with advanced or metastatic disease, whereas in several Asian countries (eg, Korea and Japan), gastric cancer is usually identified early when cure rates remain high.[2] Other regional differences in gastric cancer are readily identifiable. For example, proximal gastric cancers are more prevalent in Europe and the Americas than in Asia.[3] Conversely, intestinal gastric cancer, characterized by chronic *Helicobacter pylori* infection, is more prevalent in high-incidence areas such as Japan, Korea, and Eastern Europe.[4] Although gastric cancer may be considered a heterogeneous disease with potential implications for disease biology,[5] patients are generally grouped together and treated irrespective of these differences. Prognosis is poor for most patients; only marginal improvements in patient outcomes have been achieved with chemotherapy despite extensive phase III testing.[6-8]

Targeted therapy may offer new possibilities for the treatment of gastric cancer, as illustrated by the Study of Herceptin (Trastuzumab) in Combination With Chemotherapy Compared

With Chemotherapy Alone in Patients With HER2-Positive Advanced Gastric Cancer (ToGA study),[9] which demonstrated a substantial increase in overall survival (OS) in HER2-positive patients with metastatic gastric cancer treated with trastuzumab plus chemotherapy versus chemotherapy alone.

Angiogenesis is recognized as an important aspect of tumorigenesis. Vascular endothelial growth factor A (VEGF-A) is a key mediator of physiologic and pathologic angiogenesis.[10] Activities of VEGF-A are mediated by two tyrosine kinase receptors, VEGFR-1 and VEGFR-2. Preclinical studies show that bevacizumab (Avastin, Genentech/Roche, San Francisco, CA/Basel, Switzerland), a monoclonal antibody targeting VEGF-A, results in tumor growth inhibition when given as monotherapy or in combination with cytotoxic agents.[11] Clinical trials have further demonstrated that bevacizumab in combination with chemotherapy has efficacy in several malignancies, including colon cancer,[12] breast cancer,[13] lung cancer,[14] and glioblastoma.[15] In patients with gastric cancer, VEGF expression has been linked to tumor aggressiveness[16] and poor prognosis.[17-19] Shah et al[20] showed that bevacizumab plus platinum-containing chemotherapy had promising efficacy in patients with metastatic gastric/gastroesophageal junction adenocarcinoma (median time to progression, 8.3 months; median OS, 12.3 months).

On the basis of the broad activity of antiangiogenic inhibition in epithelial malignancies and compelling results in metastatic gastric cancer, the Avastin in Gastric Cancer (AVAGAST) study was initiated. It was designed to demonstrate the benefit of bevacizumab in gastric cancer when added to a first-line chemotherapy doublet (cisplatin and capecitabine or fluorouracil [FU]). Capecitabine or FU was included in AVAGAST on the basis of the results of a randomized phase III study in which capecitabine-cisplatin and FU-cisplatin showed equal efficacy without any substantial change in safety profile.[21] This article reports the primary efficacy and safety analyses from AVAGAST. An additional objective was the mandatory sampling of tumor tissue and blood for analysis of predefined and exploratory biomarkers (presented elsewhere).[22]

PATIENTS AND METHODS

Study Design

AVAGAST was a prospective, random-assignment, double-blind, placebo-controlled phase III clinical trial. The protocol was approved at each participating site by an independent ethics committee or institutional review board (ClinicalTrials.gov identifier: NCT00548548). The trial was carried out in accordance with the Declaration of Helsinki. All patients provided written informed consent before study entry.

Patients were assigned (1:1 ratio) to treatment by using permuted-block randomization (see Appendix, online only), with geographic region (Asia-Pacific/Europe/Pan-America), fluoropyrimidine (capecitabine/FU), and disease status (metastatic/locally advanced) as stratification factors.

Patients

Patients age ≥ 18 years with previously untreated, histologically confirmed, unresectable locally advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction, with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 and life expectancy of ≥ 3 months were eligible. Measurable and nonmeasurable disease was allowed, but disease had to be evaluable according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria, version 1.0.[23] (Neo)adjuvant chemotherapy was permitted if completed ≥ 6 months before random assignment. Surgery or radiotherapy was permitted if completed ≥ 28 days before random assignment. Prior platinum or antiangiogenic therapy was not allowed. Patients were required to have adequate bone marrow, hepatic, and renal function (including proteinuria of ≤ 1 g/24 hours).

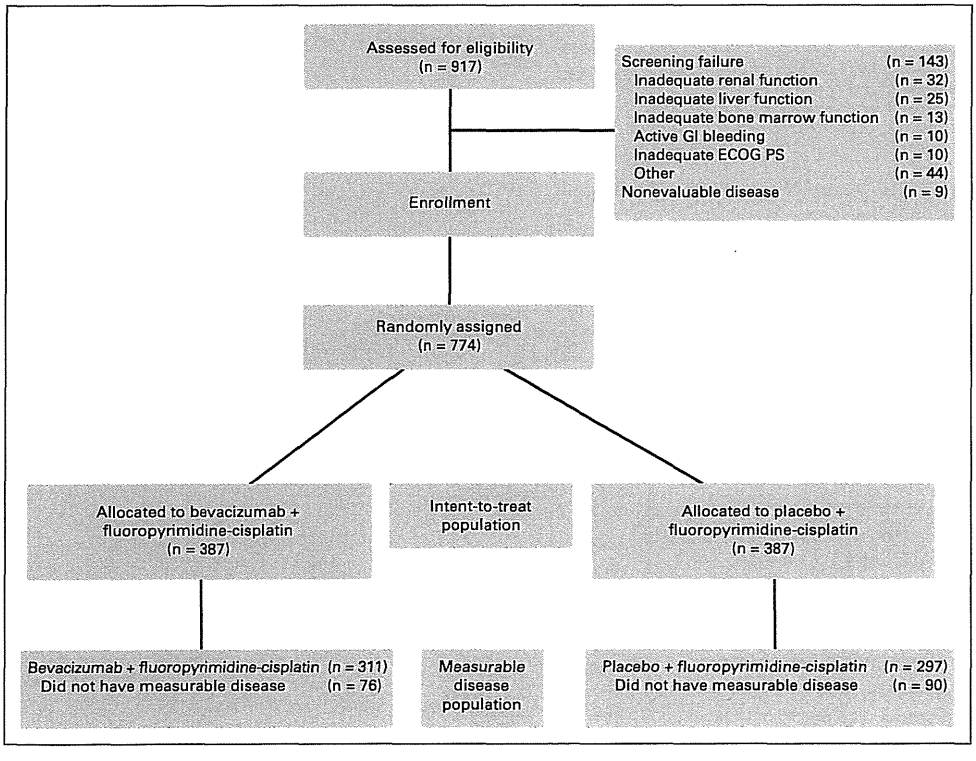

Fig 1. CONSORT diagram. ECOG, Eastern Cooperative Oncology Group; PS, performance status.

Treatment

Bevacizumab or placebo (bevacizumab vehicle) 7.5 mg/kg was administered on day 1 as a 30-minute infusion (infusion rate, 0.25 mg/kg/min) every 3 weeks. In the absence of infusion-related reactions, subsequent infusions were delivered over 15 minutes (infusion rate, 0.5 mg/kg/min). Following bevacizumab or placebo, cisplatin 80 mg/m^2 was given on day 1 as a 2-hour intravenous infusion with standard premedication and hydration, followed by oral capecitabine 1,000 mg/m^2 twice daily for 14 days every 3 weeks. Cisplatin was given for six cycles; capecitabine and bevacizumab were administered until disease progression or unacceptable toxicity. If any study drugs were discontinued, patients could continue with the remaining drugs. For patients unable to take oral medications, FU 800 mg/m^2/d was administered as a continuous intravenous infusion on days 1 to 5 every 3 weeks instead of capecitabine. Switching from capecitabine to FU during the study was not permitted. In the presence of toxicity, the bevacizumab dose was not modified or reduced, whereas dose modifications for fluoropyrimidines and cisplatin were performed per the study protocol.

Assessments

Medical history, chest x-ray, and ECG were performed within 21 days before random assignment. Assessments of vital signs, ECOG performance status, creatinine clearance, and a routine blood analysis were performed within 7 days of random assignment. Baseline samples from the primary or recurrent tumor were collected for biomarker analysis. During treatment, physical examination, hematology, biochemistry, and urinalysis were repeated at the beginning of each cycle.

Tumor assessments (computed tomography scan of chest, abdomen, and pelvis or computed tomography scan of chest and magnetic resonance imaging scan of abdomen and pelvis) were performed within 21 days before random assignment and were repeated every 6 weeks for the first year after random assignment and every 12 weeks thereafter until disease progression. The same radiologic method used to document disease at baseline was used at subsequent assessments. RECIST guidelines were used to define all responses.[23] No independent radiologic review was performed. Survival status was assessed every 3 months after completion of study treatment.

Safety assessments were performed until 28 days after the last exposure to study treatment, followed by an additional 6-month safety follow-up period. Intensity of adverse events was graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. An independent data safety monitoring board regularly reviewed study safety and efficacy data.

Statistical Analysis

The intention-to-treat patient population, the primary population for efficacy analysis, included all randomly assigned patients. The safety population included all randomly assigned patients who received at least one dose of study medication. The measurable disease population was used to evaluate response rate only. In the safety analysis, patients were analyzed as treated. The primary study end point was OS, defined as time between random assignment and death irrespective of cause. Secondary end points were progression-free survival (PFS; defined as time between random assignment and first documented disease progression or death), overall response rate, and safety.

AVAGAST was designed as a group sequential study with up to two data looks, with the final analysis planned after approximately 517 deaths had occurred. Per protocol, the preplanned interim analysis (after two thirds of the expected events [ie, 345]) was dropped because, at the time the analysis was due, it was estimated that the final analysis would follow in ≤ 6 months. On the basis of a systematic literature review, it was assumed that median OS in the placebo group would be 10 months. The study was powered to test the hypothesis that the addition of bevacizumab would improve median OS to 12.8 months, equivalent to a hazard ratio (HR) of 0.78 between study groups, assuming an exponential distribution for the time-to-death variable. Because no interim analysis was performed, the study became a fixed-sample study. To detect an HR of 0.78, 509 deaths were necessary to ensure 80% power for a two-sided log-rank test at a significance level of 0.05.

Survival functions of time-to-event end points were estimated by using the Kaplan-Meier method, and differences between treatment groups were tested by using an unstratified two-sided log-rank test. OS was also tested by using a stratified log-rank test as a preplanned supporting analysis. Preplanned analyses of OS that used Cox's proportional hazards models were conducted with the stratification variables and other relevant covariates (ECOG performance status, prior neoadjuvant chemotherapy, sex, age, presence of baseline bone metastases, number of baseline metastatic sites, prior gastrectomy, liver metastases, and gastric cancer type). Exploratory subgroup analyses of OS and analyses by region were also performed.

RESULTS

Patients

From September 2007 to December 2008, 774 patients (387 in each group) were enrolled and underwent random assignment at 93 centers in 17 countries (intention-to-treat population; Fig 1, CONSORT diagram). Almost half (49%; n = 376) the patients were enrolled from the Asia-Pacific region (90% from Japan and Korea); the remainder were enrolled in Europe (32%; n = 249) and Pan-America (19%; n = 149), mainly Eastern Europe and Latin America, respectively. Both study groups were well balanced in terms of baseline characteristics (Table 1).

Table 1. Baseline Characteristics (intention-to-treat population)

Variable	Fluoropyrimidine-Cisplatin + Bevacizumab (n = 387) No.	%	Fluoropyrimidine-Cisplatin + Placebo (n = 387) No.	%
Sex				
Male	257	66	258	67
Female	130	34	129	33
Age, years				
Median	58		59	
Range	22-81		22-82	
ECOG performance status				
0-1	365	94	367	95
≥ 2	22	6	20	5
Geographic region				
Asia-Pacific	188	49	188	49
Europe	125	32	124	32
Pan-America	74	19	75	19
Fluoropyrimidine treatment				
Capecitabine	364	94	365	94
Fluorouracil	23	6	22	6
Primary tumor site				
Stomach	333	86	338	87
Gastroesophageal junction	54	14	49	13
Measurable disease	311	80	297	77
Extent of disease				
Metastatic	367	95	378	98
Locally advanced	20	5	9	2
Liver metastases	130	34	126	33
Previous treatment				
Neoadjuvant therapy	30	8	30	8
Gastrectomy	110	28	107	28

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

Table 2. Unadjusted Analysis of Efficacy (intention-to-treat population)

Variable	Fluoropyrimidine-Cisplatin + Bevacizumab (n = 387) No.	%	95% CI	Fluoropyrimidine-Cisplatin + Placebo (n = 387) No.	%	95% CI	HR for Difference*	95% CI	P†
Overall survival									
Deaths	252	65.1		265	68.5		0.87	0.73 to 1.03	.1002
Median overall survival, months	12.1		11.1 to 13.8	10.1		9.0 to 11.3			
1-year survival		50.2	45.1 to 55.3		42.3	37.2 to 47.3	7.9	0.8 to 15.1	.0301
Progression-free survival									
Progression events	324	83.7		339	87.6		0.80	0.68 to 0.93	.0037
Median progression-free survival, months	6.7		5.9 to 7.1	5.3		4.4 to 5.6			
Response	311			297					
Overall response rate	143	46.0	40.3 to 51.7	111	37.4	31.9 to 43.1	8.61	0.6 to 16.6	.0315
Complete response	5	1.6		3	1.0				
Partial response	138	44.4		108	36.4				
Stable disease	93	29.9		90	30.3				

Abbreviation: HR, hazard ratio.
*The ratios listed are hazard ratios, except for 1-year survival and overall response rates for which the differences are shown.
†*P* values were calculated by using the log-rank test, except for overall response rate (χ^2 test) and 1-year survival (approximate Z-test).

Treatment

Mean treatment duration was 6.8 (± 5.1) months in the bevacizumab plus fluoropyrimidine-cisplatin group and 5.8 (± 4.9) months in the placebo plus fluoropyrimidine-cisplatin group (Appendix Table A1, online only). Median dose intensities (ie, actual dose administered divided by planned dose) were more than 80% for bevacizumab and capecitabine-FU or placebo and capecitabine-FU, and 79% and 71% for cisplatin in the bevacizumab and placebo groups, respectively. The use of second-line therapy was balanced between study groups (41%, bevacizumab group; 45%, placebo group) but not between regions (66%, Asia-Pacific; 31%, Europe; 21%, Pan-America). The most commonly used agents included irinotecan (19%), paclitaxel (16%), FU (16%), and docetaxel (12%), which were equally distributed between study groups (Appendix Table A2, online only). Second-line bevacizumab was given to one patient (< 1%) in each treatment group.

Efficacy

The cutoff date for this analysis was November 30, 2009, after 517 deaths had occurred. Median follow-up was 11.4 months in the bevacizumab group and 9.4 months in the placebo group. Median OS, the primary study end point, was 12.1 months (95% CI, 11.1 to 13.8 months) in the bevacizumab group and 10.1 months (95% CI, 9.0 to 11.3 months) in the placebo group (Table 2). The estimated HR was 0.87 (95% CI, 0.73 to 1.03), indicating a 13% reduction in the risk of death (P = .1002; Figure 2A. A similar outcome was observed when the analysis was adjusted for stratification variables (ie, region, disease status, and fluoropyrimidine; HR, 0.87; 95% CI, 0.73 to 1.04; P = .1300) or all preplanned covariates (HR, 0.84; 95% CI, 0.70 to 1.00; P = .0563). The estimated 1-year OS rate was improved significantly with bevacizumab (50.2% *v* 42.3% in the placebo group; P = .0301).

PFS was prolonged significantly in the bevacizumab group compared with the placebo group (HR, 0.80; 95% CI, 0.68 to 0.93; P = .0037; Figure 2B). Median PFS was 6.7 months (95% CI, 5.9 to 7.1 months) in the bevacizumab group and 5.3 months (95% CI, 4.4 to 5.6 months) in the placebo group. Overall response rate was improved significantly with the addition of bevacizumab (46.0% *v* 37.4% in the placebo group; P = .0315).

Safety

The safety population comprised 767 patients (n = 386, bevacizumab group; n = 381, placebo group). The overall incidence of grade 3 to 5 adverse events was 76% in the bevacizumab group and 77% in the placebo group (Table 3); 66% and 64%, respectively, were judged to be treatment-related. The most common adverse events were neutropenia, anemia, decreased appetite, and nausea. The addition of bevacizumab appeared to cause no clinically relevant increase in chemotherapy-related toxicity, with the possible exceptions of diarrhea (8% *v* 4% in the placebo group) and hand-foot syndrome (6% *v* 3%). The overall incidence of predefined grade 3 to 5 events potentially related to bevacizumab was 20% in the bevacizumab group versus 15% in the placebo group (Table 3); the difference between groups was mainly attributable to a higher incidence of hypertension in the bevacizumab group (6% *v* < 1% in the placebo group). Grade 3 to 5 venous thromboembolic events were more common in the placebo group (9% *v* 6% in the bevacizumab group). Grade 3 to 4 bleeding was documented in 4% of patients in both groups. GI perforation occurred in nine (2.3%) and two (0.5%) patients in the bevacizumab and placebo groups, respectively, which is similar to the incidence found in colorectal cancer. All other events of special interest to bevacizumab were rare. No new bevacizumab-related safety signals were identified. Infusion-related adverse reactions were documented in five patients (1%); all events occurred in the bevacizumab group and were grade 1 to 2 (hypersensitivity, n = 2; headache, dysphonia, hypotension, n = 1 each).

Adverse events or laboratory abnormalities led to withdrawal from a component of study treatment in 81 patients (21%) in the bevacizumab group versus 71 patients (19%) in the placebo group.

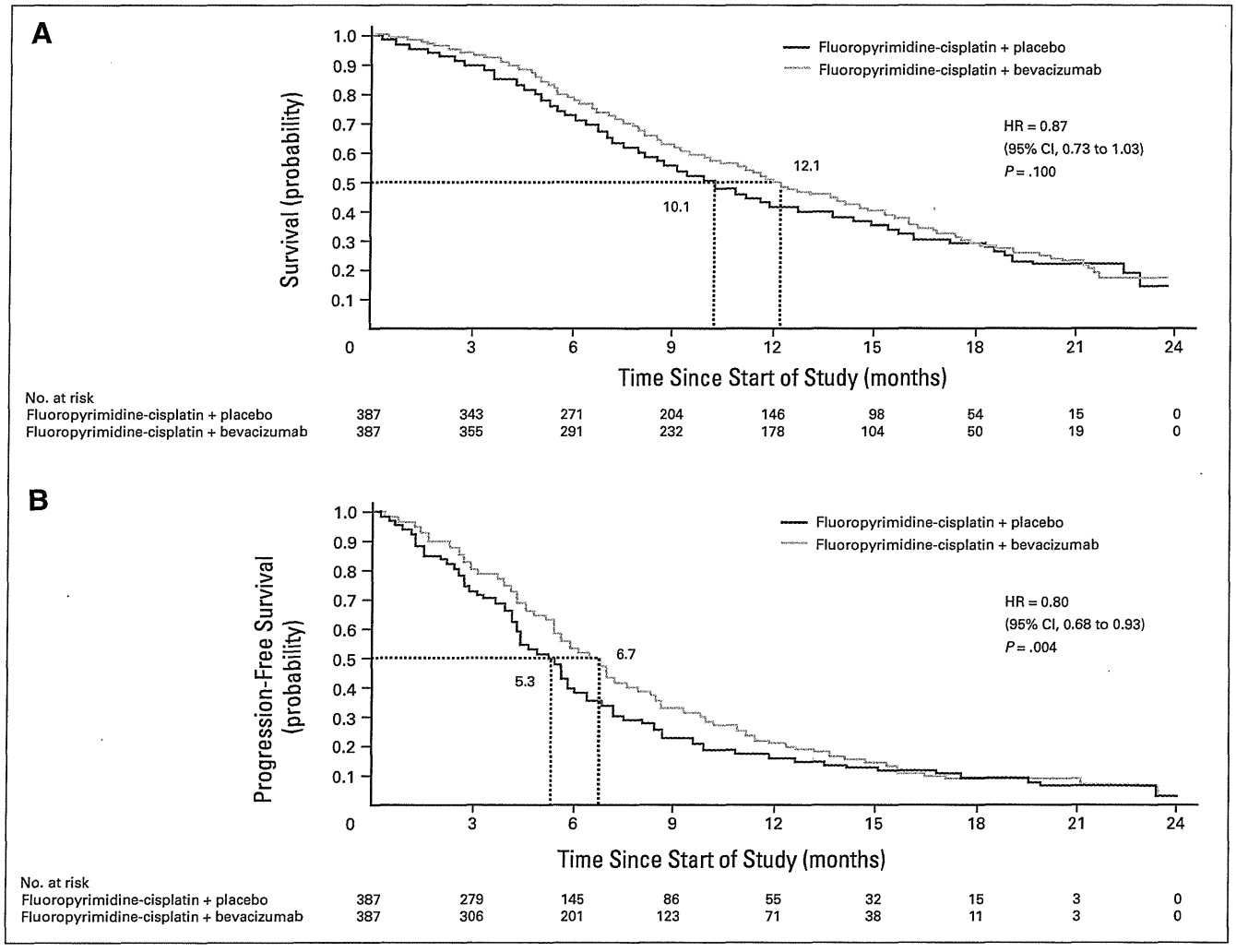

Fig 2. Kaplan-Meier estimates of overall survival (A) and progression-free survival (B) in the intention-to-treat population. HR, hazard ratio.

Seven (2%) and 12 (3%) deaths (all considered related to treatment) occurred in the bevacizumab and placebo groups, respectively. Sixty-day mortality rates were 3% and 6% in the bevacizumab and placebo groups, respectively.

Subgroup Analysis

Preplanned subgroup analyses of OS were consistent with the overall estimate in most patient subgroups (ie, point estimates < 1 and CI included 1; Figure 3). Subgroups in which the 95% CI upper limits were less than 1 were patients recruited at Pan-American centers, patients with locally advanced disease, and patients with nonmeasurable disease.

On the basis of differences in patient outcome according to region, an exploratory analysis of baseline patient characteristics according to region was performed (Table 4). Differences of more than 10% were observed between regions in the proportions of patients with gastroesophageal junction tumors, measurable lesions, liver metastases, and tumor histology. (For details on quality of life, see Appendix).

DISCUSSION

To the best of our knowledge, AVAGAST is the first phase III evaluation of an antiangiogenic agent with chemotherapy in advanced gastric cancer. The primary objective was to improve median OS from an estimated 10.0 months with chemotherapy alone to 12.8 months with the addition of bevacizumab to chemotherapy, for an estimated reduction in the risk of death by 22% (HR, 0.78). We observed that adding bevacizumab to fluoropyrimidine-cisplatin in the first-line treatment of advanced gastric cancer was associated with a risk reduction of death by 13% (HR, 0.87; $P = .1002$) in the overall study population, improving OS from 10.1 months in the placebo group to 12.1 months. However, other efficacy measures showed clear activity with bevacizumab and chemotherapy versus chemotherapy alone, including PFS (6.7 *v* 5.3 months; HR, 0.80; $P = .0037$), response rate (46.0% *v* 37.4%; $P = .0315$), and 1-year survival (50% *v* 42%; $P = .0301$).

Although there are several standard three-drug regimens for the first-line treatment of advanced gastric cancer,[24,25] toxicity and convenience limit the routine use of these combinations for most patients with advanced disease.[7] The capecitabine-cisplatin doublet was reported to be noninferior to cisplatin and infusional FU[21] and is an acceptable standard first-line doublet regimen, as demonstrated in recent and ongoing phase III registration studies.[9,26] Patients randomly assigned to the control arm of the AVAGAST study