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Apatinib for Chemotherapy-Refractory Advanced Metastatic Gastric Cancer: Results From a Randomized, Placebo-Controlled, Parallel-Arm, Phase II Trial

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ABSTRACT

Purpose
Patients with metastatic gastric cancer (mGC) who do not respond to or who experience progression with second-line chemotherapy have no treatment options that clearly confer a survival benefit. This trial investigated the safety and efficacy of apatinib, an inhibitor of vascular endothelial growth factor receptor, as a treatment option for heavily pretreated patients with mGC.

Patients and Methods
Patients who experienced treatment failure with at least two chemotherapeutic regimens were randomly assigned to receive placebo (group A), apatinib 850 mg once daily (group B), or apatinib 425 mg twice daily (group C).

Results
We enrolled 144 patients onto this study. In groups A, B, and C, the median overall survival (OS) times were 2.50 months (95% CI, 1.87 to 3.70 months), 4.83 months (95% CI, 4.03 to 5.97 months), and 4.27 months (95% CI, 3.83 to 4.77 months), respectively, and the median progression-free survival (PFS) times were 1.40 months (95% CI, 1.20 to 1.83 months), 3.67 months (95% CI, 2.17 to 6.80 months), and 3.20 months (95% CI, 2.37 to 4.53 months), respectively. There were statistically significant differences between the apatinib and placebo groups for both PFS ($P < .001$) and OS ($P < .001$ and $P = .0017$). Nine patients had a partial response (three patients in group B and six patients in group C). Toxicities were tolerable or could be clinically managed. The most common grade 3 to 4 adverse events were hand-foot syndrome and hypertension. Hematologic toxicities were moderate, and grade 3 to 4 hematologic toxicities were rare.

Conclusion
Apatinib showed improved PFS and OS in heavily pretreated patients with mGC who had experienced treatment failure with two or more chemotherapy regimens.

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INTRODUCTION

In the last decade, front-line chemotherapy has been considered a standard therapeutic regimen for the extension of survival time in patients with metastatic gastric cancer (mGC). New evidence suggests that salvage chemotherapies, as second-line treatments, may have a survival advantage when compared with best supportive care.[1,2] After failure of second-line chemotherapy, the results of further treatment are poor, yielding response rates of 0% to 5% with no evidence of prolonged survival.[3,4] Novel, more effective treatment options are urgently needed to provide survival benefit for patients with mGC.

Targeting angiogenesis by inhibition of vascular endothelial growth factors (VEGFs) was shown to be effective in lung, breast, renal, hepatic, and colon cancers.[5,6] However, evidence of antitumor activity leading to improved overall survival (OS) or progression-free survival (PFS) in patients with mGC is still limited.

The results of studies with VEGF receptor (VEGFR) inhibitors as a potential second-line treatment for patients with mGC have, thus far, been poor.[6,7,8] Subgroup analysis of data from the phase III Avastin in Gastric Cancer (AVAGAST) trial showed that the VEGF inhibitor bevacizumab tended to improve OS in non-Asian patients with high versus low levels of plasma VEGF-A,[9] indicating that the compound might have some benefit for selected patients. More optimistic results were recently reported from a randomized, placebo-controlled

study. In a phase III study with ramucirumab, patients with mGC treated with ramucirumab had significantly longer PFS and OS times than patients given placebo.[10]

Preclinical experiments indicated that a novel VEGFR inhibitor, apatinib (YN968D1), might have potential as a therapeutic agent for malignancies.[11] Apatinib is a small-molecule VEGFR tyrosine kinase inhibitor, similar to vatalanib (PTK787), but with a binding affinity 10 times that of vatalanib or sorafenib.[11,12]

A phase I clinical trial showed that this agent has antitumor activity in Chinese patients with mGC.[13] On the basis of the preclinical studies and phase I data, we conducted this phase II, randomized, double-blind, placebo-controlled trial. The aims of the present trial were to assess the efficacy and safety of daily administration of apatinib as third-line or later treatment in patients with mGC and to determine whether a once-daily or a twice-daily regimen is better tolerated by these patients (NCT00970138).

PATIENTS AND METHODS

Patients

Patients age between 18 and 70 years with histologically confirmed advanced gastric cancer or mGC (including gastroesophageal junction adenocarcinoma) were eligible for enrollment. Enrollment criteria included prior lack of response or intolerance to at least two chemotherapeutic regimens (including both platinum and fluoropyrimidine). The criteria for progression to second-line chemotherapy were based on computed tomography (CT) and magnetic resonance imaging (MRI) evaluation. The study allowed recruitment of patients who were intolerant to second-line chemotherapy because there are no alternative therapeutic options for these patients. Additional enrollment criteria were as follows: at least one measurable lesion as defined by RECIST; an Eastern Cooperative Oncology Group performance status of 0 or 1; and acceptable hematologic, hepatic, and renal function. Patients with uncontrolled blood pressure on medication (> 140/90 mmHg) or with bleeding tendency or those receiving thrombolytics or anticoagulants were excluded.

Ethical Clearance

The trial was approved by the institutional review board, the Fudan University Shanghai Cancer Center Ethics Committee for Clinical Investigation, and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. All patients signed informed consent before enrollment.

Study Drug Dosing and Treatment

In a phase I trial, apatinib (Jiangsu Hengrui Medicine, Lianyungang, China) showed good oral bioavailability at a dose of 850 mg a day, the maximum-tolerated dose.[10] Considering this, we opted to give patients one of the following regimens: apatinib 850 mg once daily, apatinib 425 mg twice daily, or placebo. We thought that patients might tolerate a dose of 425 mg twice daily better than a dose of 850 mg once daily because of the drug's relatively short half-life. Because the study was blinded, all patients received two tablets every morning and one tablet every afternoon. One treatment cycle was 28 days long. Treatment interruptions, dose reductions to 750 mg or 500 mg of apatinib per day, and supportive care were allowed for the management of adverse events (AEs). We allowed treatment interruptions or dose reductions in the event of grade 3 hematologic or grade 2 nonhematologic toxicities. The maximum allowable period of treatment interruption was 14 days in each 28-day treatment cycle, and treatment interruption was limited to two treatment cycles. In each treatment cycle, dose reductions could be made twice. However, once a dose reduction was made for toxicity, the dose could not be re-escalated. Treatment cycles were repeated until disease progression, intolerable toxicity, or patient request for withdrawal from the study.

Sample Size Considerations

Reported data indicated that the median PFS (mPFS) in patients randomly assigned to the placebo arm would be less than 2 months at the first assessment. We expected the mPFS of patients randomly assigned to receive apatinib to have an improvement of 2.5 months, or an mPFS of 4.5 months. We planned an accrual period of 12 months, with an additional 12 months of follow-up. We expected a drop-out or nonevaluable rate of 20%. An estimated 144 patients needed to be enrolled with 1:1:1 random assignment when significance was set at a two-sided 5% type I error rate and at least 80% power. With Bonferroni adjustment for the two pair-wise comparisons, the overall type I error was 10%.

Random Assignment

The study was conducted at 15 hospitals in China. Random assignment was centrally managed by the Department of Epidemiology and Biostatistics, Nanjing Medical University School of Public Health, Nanjing, China, and random assignment was stratified according to the number of metastatic organs.

Efficacy and Safety Assessments

This was an efficacy-exploring phase II trial designed to further assess the biologic activity of apatinib and to inform the development of a phase III trial. Therefore, we considered PFS as the primary end point. PFS was defined as time from random assignment until disease progression or death, whichever occurred first. The time period before progression or death was thus considered the PFS.

Table 1. Patient Demographics and Clinical Characteristics

Characteristic	Placebo (n = 48)		Apatinib 850 mg QD (n = 47)		Apatinib 425 mg BID (n = 46)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
Sex						
Male	36	75	39	83	34	74
Female	12	25	8	17	12	26
Median age, years	54		55		53	
ECOG PS						
0	1	2	3	6	2	4
1	47	98	44	94	44	96
Time since initial diagnosis, years	1.98		1.96		2.25	
Prior surgery of primary tumor						
Yes	36	75	37	79	35	76
No	12	25	10	21	11	24
Stage						
II	0	0	1	3	1	2
III	0	0	3	6	0	0
IV	48	100	43	91	45	98
No. of metastatic sites						
≤ 2	34	71	36	77	30	67
> 2	14	29	11	23	16	33
Previous chemotherapy lines	32	67	32	68	29	63
2	16	33	15	32	17	37
≥ 3						
Prior radiotherapy	7	15	7	15	4	9
Intolerance to second-line treatment at time of enrollment	3	6.4	0	0	5	10.9
Metastasis site/organ						
Liver	23	48	28	60	20	43
Lung(s)	9	19	5	11	11	24
Posterior peritoneum lymph node	11	23	9	19	11	24

Abbreviations: BID, twice a day; ECOG, Eastern Cooperative Oncology Group; PS, performance status; QD, once a day.

Table 2. Distribution of Peritoneal Metastases Among the Different Treatment Groups

Group	Total No. of Patients	No. of Patients			Objective Response Rate (%)	Disease Control Rate (%)	Median Progression-Free Survival (days)
		Partial Response	Complete Response	Stable Disease			
Placebo	6	0	0	1	0	17	39
Apatinib 850 mg once daily	4	0	0	4	0	100	155
Apatinib 425 mg twice daily	4	0	0	2	0	50	78

Secondary end points included disease control rate (DCR), objective response rate (ORR), OS, and quality of life (QoL). Disease control was defined as complete response (CR), partial response (PR), or stable disease (SD), and objective response was considered a reduction in tumor size. For DCR, we considered whether the patient had CR, PR, or SD at week 8 of the study. Deaths within the first 8 weeks were thus not controlled for DCR.

RECIST version 1.0 was used to assess tumor responses. Five independent radiologists from different hospitals who were blinded to the treatment had to agree on evidence of efficacy.

Pretreatment evaluation included physical examination, CBCs and blood chemistry, and MRI or CT scan of measurable lesions at baseline. Physical examinations, blood counts, and assessment of toxicity were

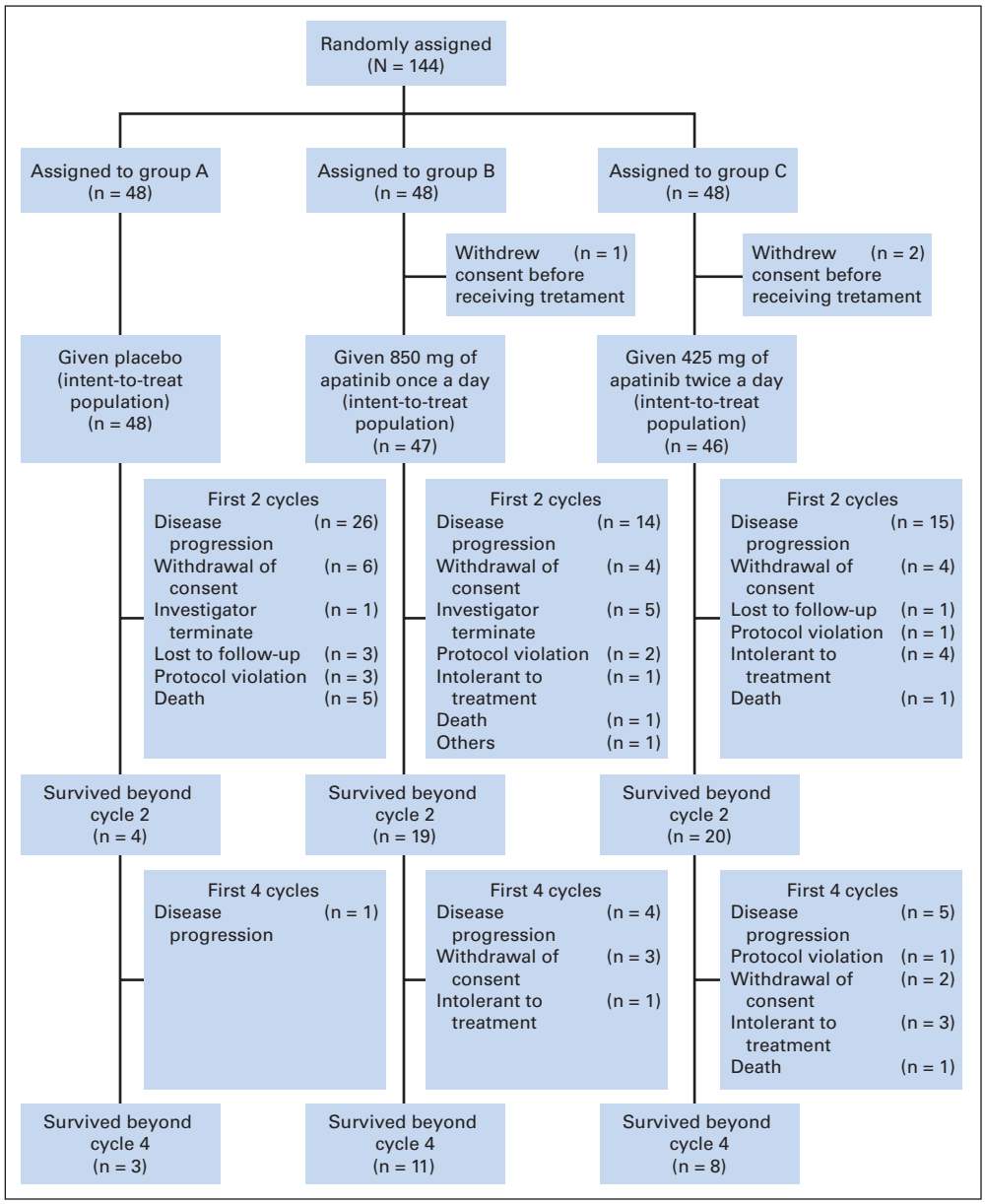

Fig 1. CONSORT diagram, enrollment and outcome.

performed biweekly. Hepatic and renal function tests were performed monthly. MRI or CT scans of measurable lesions were assessed after every two cycles (8 weeks). MRI or CT scans could be scheduled ahead of time if there was evidence of substantial progression.

Patients were observed until death, loss to follow-up, or end of study. QoL was evaluated according to the Chinese version of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30.[14] AEs were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0).

Statistical Analysis

The full analysis set (FAS) consisted of all intent-to-treat (ITT) patients, including those who were randomly assigned to a treatment group but who did not adhere to the full course of treatment, with the last observation taken as the final result. The per-protocol set (PPS) was a subset of the FAS. Patients included in the PPS met all the trial criteria, were compliant and took at least two cycles of the treatment, did not take prohibited medication, and had a completed case report form. Patients who did not complete the trial because of an end point event (PD, death, or intolerable AE) were also included in the PPS. The primary end point and other study objectives were analyzed for both the FAS and PPS.

Quantitative variables were compared among groups using the analysis of variance or Kruskal-Wallis tests. Pearson χ^2 test or Fisher's exact test was used to analyze categorical variables. The Kruskal-Wallis test was used to analyze ordered variables. We compared PFS, OS, ORR, and DCR between the treatment groups using a log-rank (Mantel-Cox) test and used the Cox proportional hazards model to estimate hazard ratios (HRs) and to test for significance. We used the multiple Cox model to evaluate whether there were significant differences in PFS and OS between the groups after adjusting for age ($> v \leq 60$ years), sex (male *v* female), Eastern Cooperative Oncology Group performance status (0 *v* 1), pathologic grading (1 to 2 *v* 3), previous chemotherapy lines ($\geq$ three *v* two chemotherapy lines), and number of metastatic sites ($> v \leq$ two sites). The ORR and DCR analyses were based on frequencies. All statistical analyses were two-sided, and significance was set at $P < .025$ for pair-wise analyses and at $P < .05$ or at the 95% CI for the results of other statistical tests.

RESULTS

Patient Demographics

From June 2009, we enrolled 144 patients with advanced gastric cancer or mGC onto the study and observed them until October 2010, when 75% of OS events were reached. The data were locked on November 8, 2010. Three patients withdrew before random assignment. The remaining 141 patients were randomly assigned to receive 28-day cycles of placebo (n = 48), apatinib 850 mg once daily (n = 47), or apatinib 425 mg twice daily (n = 46). Eight of the enrolled patients (5.7%) did not complete the second-line chemotherapy because of intolerance, and one third of the 141 enrolled patients had previously experienced progression to three or more lines of therapy (16 patients [33%], 14 patients [30%], and 17 patients [37%] in the placebo, apatinib 850 mg once daily, and apatinib 425 mg twice daily groups, respectively). These patients were equally distributed among the three treatment groups.

The baseline characteristics of patients in the different groups were similar with regard to age, sex ratio, surgical history, disease stage, and number of metastatic organs. Patient characteristics are listed in Table 1, and the distribution of peritoneal metastasis in the different treatment groups is provided in Table 2.

Study Treatment Administration

The percentages of patients receiving at least two cycles of treatment were as follows: 47.9% of patients given placebo, 74.5% of patients given apatinib 850 mg once daily, and 69.6% of patients given apatinib 425 mg twice daily. More patients in the placebo group discontinued treatment because of progression or worsening illness. In total, 15.6% of patients had dose reductions. Dose reductions were considerably more common among patients who were given apatinib 425 mg twice daily (32.6% *v* 12.8% of patients given apatinib 850 mg once daily and 2% of patients given placebo; Fig 1).

Efficacy

PFS. The ITT patients given apatinib had significantly improved PFS when compared with patients given placebo. mPFS was 3.67 months (110 days; 95% CI, 2.17 to 6.80 months [65 to 204 days]) and 3.20 months (96 days; 95% CI, 2.37 to 4.53 months [71 to 136 days]) for patients given apatinib 850 mg once daily and 425 mg twice daily, respectively, and 1.40 months (42 days; 95% CI, 1.20 to 1.83 months [36 to 55 days]) for patients given placebo.

Multiple Cox regression model showed that there were significant differences between the groups (ITT patients) who received apatinib 850 mg once daily versus placebo (HR, 0.18; 95% CI, 0.10 to 0.34; $P < .001$), as well as between the groups who received apatinib 425 mg twice daily versus placebo (HR, 0.21; 95% CI, 0.11 to 0.38; $P < .001$). However, there was no significant difference between apatinib 425 mg twice daily versus 850 mg once daily (HR, 1.22; 95% CI, 0.68 to 2.20; $P = .511$; Fig 2). Multiple Cox regression model showed that the results for the PPS were similar to those for the ITT patients (apatinib 850 mg once daily *v* placebo: HR, 0.19; 95% CI, 0.11 to 0.36; $P < .001$; and apatinib 425 mg twice daily *v* placebo: HR, 0.21; 95% CI, 0.11 to 0.38; $P < .001$).

OS. The ITT patients given apatinib had significantly longer median OS (mOS) than those given placebo. Patients in the placebo group had a mOS time of 2.50 months (75 days; 95% CI, 1.87 to 3.70 months [56 to 111 days]). Patients given apatinib 850 mg once daily and 425 mg twice daily had mOS times of 4.83 months (145 days; 95% CI, 4.03 to 5.97 months [121 to 179 days]) and 4.27 months (128 days; 95% CI, 3.83 to 4.77 months [115 to 143 days]), respectively.

Multiple Cox regression model showed significant differences between the groups who received apatinib 850 mg once daily versus placebo (HR, 0.37; 95% CI, 0.22 to 0.62; $P < .001$) and between the groups who received apatinib 425 mg twice daily versus placebo (HR,

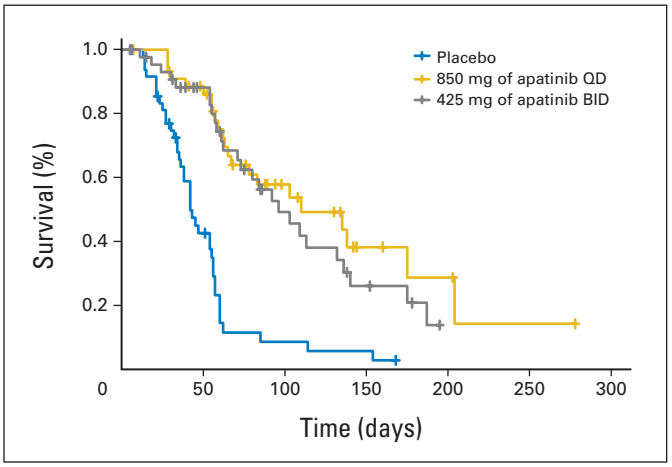

Fig 2. Kaplan-Meier estimates of progression-free survival in the intent-to-treat population for the three treatment groups. BID, twice a day; QD, once a day.

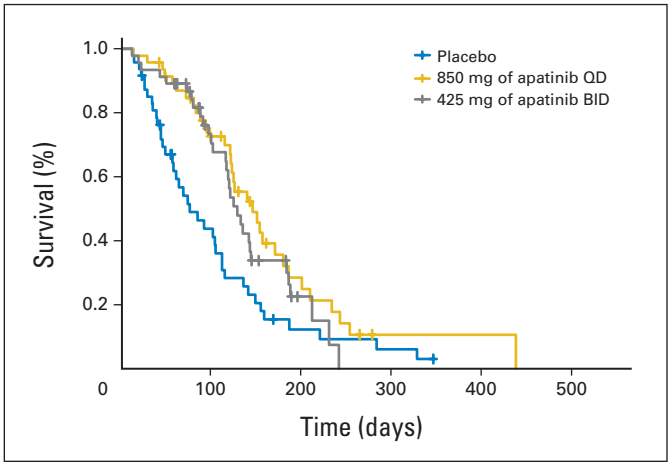

Fig 3. Kaplan-Meier curves with estimated overall survival in the intention-to-treat population. BID, twice a day; QD, once a day.

0.41; 95% CI, 0.24 to 0.72; $P = .0017$). There was no significant difference between the groups who received apatinib 425 mg twice daily and 850 mg once daily (HR, 1.28; 95% CI, 0.75 to 2.17; $P = .119$; Fig 3).

Results for the PPS were similar to the results reported for the ITT patients. Multiple Cox regression model showed that OS was significantly improved compared with patients given placebo (apatinib 850 mg once daily *v* placebo: HR, 0.29; 95% CI, 0.16 to 0.52; $P < .001$; and apatinib 425 mg twice daily *v* placebo: HR, 0.34; 95% CI, 0.18 to 0.64; $P < .001$).

ORR. Nine patients treated with apatinib had a PR (confirmed on CT scan and in accordance with RECIST version 1.0)—three receiving apatinib 850 mg once daily and six receiving apatinib 425 mg twice daily. Table 3 lists the ORRs for the three groups.

DCRs. Significantly more patients in the groups treated with apatinib had CR, PR, or SD than in the placebo group. Patients treated with apatinib had significantly better DCRs ($P < .001$; Table 3) than those given placebo. Among the ITT patients, 10.42% (n = 5), 51.06% (n = 24), and 34.78% (n = 16) in the placebo, apatinib 850 mg once daily, and apatinib 425 mg twice daily groups, respectively, achieved disease control. Among the PPS patients, 11.63% (n = 5), 58.54% (n = 24), and 40% (n = 6) in the placebo, apatinib 850 mg once daily, and apatinib 425 mg twice daily groups, respectively, achieved disease control. Table 3 shows the comparison between groups.

Safety

Toxicities were generally well tolerated. Grade 3 to 4 AEs that occurred in more than 5% of patients were hand-foot syndrome, hypertension, thrombocytopenia, anemia, and liver toxicities, as indicated by elevated aminotransferase and bilirubin levels, as well as diarrhea. Grade 3 to 4 AEs that occurred in more than 10% of patients were hand-foot syndrome and hypertension. Hematologic toxicities were mostly moderate, and grade 3 to 4 hematologic toxicities were rarely noted. Fatigue was a common adverse effect among patients enrolled onto this study. In total, 10.4%, 17.0%, and 15.2% of patients receiving placebo, apatinib 850 mg once daily, or apatinib 425 mg twice daily, respectively, experienced fatigue. However, only approximately 2% of patients experienced grade 3 to 4 fatigue. Table 4 lists the reported AEs.

QoL

There were no significant differences between the three treatment groups with regard to the QoL scores for the different parameters of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30. The only significant change in QoL over the course of treatment was found in the score for insomnia. After two cycles of treatment, insomnia was significantly improved in patients treated with apatinib than in those given placebo ($P = .002$). Cognitive function tended to be scored higher in the apatinib treatment groups than in the placebo group after two cycles of treatment, but significance was not reached ($P = .067$).

DISCUSSION

The number of patients with mGC offered second-line chemotherapy is growing, especially in Asia,[4,14,15] and there is an increasing need for further active treatments beyond second-line chemotherapy. This study investigated the efficacy of apatinib in patients with gastric cancer who experienced treatment failure with two or more lines of chemotherapy.

Table 3. Overall Response and Disease Control Rates Among Patients in the Different Treatment Groups

		Overall Response Rate				Disease Control Rates			
Treatment Group	No. of Patients	No. of Responses	%	95% CI (%)	95% CI of Rate Difference (group *v* group)	No. of Patients With Disease Control	%	95% CI (%)	95% CI of Rate Difference (group *v* group)
Intent-to-treat patients									
Group A*	48	0	0.00	0.0 to 7.4	—	5	10.42	3.5 to 22.7	—
Group B†	47	3	6.38	1.3 to 17.5	−0.61 to 13.37 (B *v* A)	24	51.06	36.1 to 65.9	23.94 to 57.34 (B *v* A)
Group C‡	46	6	13.04	4.9 to 26.3	3.31 to 22.77 (C *v* A)	16	34.78	21.4 to 50.2	8.11 to 40.61 (C *v* A)
Per-protocol patients									
Group A*	43	0	0.00	0.0 to 8.2	—	5	11.63	3.9 to 25.1	—
Group B†	41	3	7.32	1.5 to 19.9	−0.65 to 15.29 (B *v* A)	24	58.54	42.1 to 73.7	29.04 to 64.78 (B *v* A)
Group C‡	40	6	15.00	5.7 to 29.8	3.93 to 26.07 (C *v* A)	16	40.00	24.9 to 56.7	10.42 to 46.32 (C *v* A)

*Placebo.
†Apatinib 850 mg once daily.
‡Apatinib 425 mg twice daily.

Table 4. Adverse Events

Adverse Event	Adverse Event Grade (No. of patients)						Comparison Between Groups	*P*	Incidence (%)	*P*	Incidence of Severe Adverse Events (%)	*P*
	0	1	2	3	4	Total						
Hypertension												
Group A*	46	2	0	0	0	48	20.57	< .001	4.17	< .001	0.00	.0473
Group B†	28	7	8	4	0	47			40.43		8.51	
Group C‡	28	5	8	5	0	46			39.13		10.87	
Proteinuria												
Group A	42	6	0	0	0	48	8.21	.0165	12.50	.0307	0.00	.2128
Group B	34	4	8	1	0	47			27.66		2.13	
Group C	30	5	9	2	0	46			34.78		4.35	
Hand-foot syndrome												
Group A	46	1	0	1	0	48	21.26	< .001	4.17	< .001	2.08	.0877
Group B	35	4	6	2	0	47			25.53		4.26	
Group C	25	7	8	6	0	46			45.65		13.04	
Diarrhea												
Group A	46	1	1	0	0	48	10.27	.0059	4.17	.0045	0.00	.0792
Group B	39	6	1	1	0	47			17.02		2.13	
Group C	33	6	4	3	0	46			28.26		6.52	
Abdominal pain												
Group A	43	2	2	1	0	48	0.47	.7890	10.42	.7461	2.08	.7714
Group B	43	2	2	0	0	47			8.51		0.00	
Group C	40	4	1	1	0	46			13.04		2.17	
Fatigue												
Group A	43	2	2	1	0	48	0.88	.6427	10.42	.6263	2.08	1.000
Group B	39	3	4	1	0	47			17.02		2.13	
Group C	39	3	3	1	0	46			15.22		2.17	
Vomiting												
Group A	43	1	3	1	0	48	0.14	.9347	10.42	1.000	2.08	1.000
Group B	42	3	2	0	0	47			10.64		0.00	
Group C	42	2	2	0	0	46			8.70		0.00	
Nausea												
Group A	43	2	2	1	0	48	0.69	.7071	10.42	.7647	2.08	1.000
Group B	44	2	1	0	0	47			6.38		0.00	
Group C	41	4	1	0	0	46			10.87		0.00	
Fever												
Group A	47	1	0	0	0	48	7.62	.0222	2.08	.0166	0.00	
Group B	47	0	0	0	0	47			0.00		0.00	
Group C	41	2	3	0	0	46			10.87		0.00	
Elevated aminotransferase												
Group A	42	3	2	1	0	48	11.79	.0028	12.50	.0037	2.08	.2604
Group B	38	6	1	2	0	47			19.15		4.26	
Group C	27	9	6	4	0	46			41.30		8.70	
Leukopenia												
Group A	44	2	0	2	0	48	17.90	< .001	8.33	< .001	4.17	.4689
Group B	24	10	13	0	0	47			48.94		0.00	
Group C	28	8	8	2	0	46			39.13		4.35	
Thrombocytopenia												
Group A	42	2	2	2	0	48	8.53	.0141	12.50	.0101	4.17	.5964
Group B	33	9	3	2	0	47			29.79		4.26	
Group C	28	6	8	4	0	46			39.13		8.70	
Neutropenia												
Group A	45	1	0	2	0	48	13.19	.0014	6.25	< .001	4.17	.8702
Group B	29	8	9	1	0	47			38.30		2.13	
Group C	31	5	8	2	0	46			32.61		4.35	
Anemia												
Group A	39	2	4	2	1	48	0.03	.9846	18.75	1.000	6.25	.6312
Group B	38	5	3	1	0	47			19.15		2.13	
Group C	38	2	3	2	1	46			17.39		6.52	

*Placebo.
†Apatinib 850 mg once daily.
‡Apatinib 425 mg twice daily.

Patients given placebo experienced faster tumor progression than we expected. Although the mPFS of patients given apatinib did not reach our anticipated improvement of 2.5 months and, therefore, the study's primary end point, PFS was still significantly longer in patients given apatinib than in those given placebo. The longer PFS of patients given apatinib translated into an improvement of OS. The mOS was significantly longer in patients treated with apatinib versus those given a placebo (4.5 *v* 2.5 months, respectively). On average, 43% of patients given apatinib reached disease control, which is acceptable when compared with the treatment outcomes of antiangiogenic agents in other solid tumors.

The leading grade 3 to 4 AE was hypertension, which occurred in 8.51% and 10.86% of patients treated with apatinib at a dose of 850 mg once daily and 425 twice daily, respectively. Hypertension, hand-food syndrome, and proteinuria are known to be the most common AEs of antiangiogenic agents. The incidence of proteinuria in this study was comparable with the results of other investigations with VEGFR inhibitors.[16] Only 4% of patients developed grade 3 proteinuria, and none of the patients developed glomerulonephritis secondary to apatinib treatment. The incidence of hematologic toxicities was low. Although one death could be related to severe AEs in this study, the adverse effects of apatinib were considered moderate and acceptable when compared with historical reports from other antiangiogenic agents. We propose that apatinib had a favorable safety profile because it is a relatively clean tyrosine kinase inhibitor that selectively inhibits VEGFR2.

Apatinib at the two dose levels of 850 mg once daily and 425 mg twice daily had different safety profiles. Patients given apatinib as a once-daily regimen had fewer grade 3 to 4 AEs than those given apatinib at a dose of 425 mg twice daily. Also, the incidence of hypertension, hand-foot syndrome, thrombocytopenia, and diarrhea was reduced among patients treated with apatinib 850 mg once daily. Therefore, we recommended the dosing regimen of 850 mg once daily for the phase III trial, which is ongoing (NCT01512745).

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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