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Clinical Trial Results

Apatinib in Combination with S-1 as First-Line Treatment in Patients with Advanced Metastatic Gastric Cancer: Results from an Open, Exploratory, Single-Arm, Phase II Trial

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Key Words. Apatinib • S-1 • Gastric cancer • Efficacy • Safety

Trial Information

- **ClinicalTrials.gov Identifier**: NCT02525237
- **Sponsor**: Xiaochun Zhang
- **Principal Investigator**: Xiaochun Zhang
- **IRB Approved**: Yes

Lessons Learned

- Apatinib combined with S-1 was not superior to other chemotherapy regimens as first-line therapy for advanced gastric cancer.
- There was a tendency for patients with lymph node metastasis to have prolonged median progression-free survival and median overall survival, compared with patients with liver metastasis.

Abstract

Background. The best choice of first-line chemotherapy regimen for patients with metastatic gastric cancer is still debated. We combined apatinib and S-1 as a new first-line therapy to treat advanced gastric cancer. The efficacy and safety of the combination were assessed, with the goal of determining the most appropriate subgroup of patients who could benefit from this new regimen.

Methods. This study was an open, exploratory single-arm, phase II trial. Enrolled patients received apatinib plus S-1 treatment (apatinib, 500 mg, once a day [qd], days 1–21; S-1, 40 mg/m^2, bid, days 1–14). The primary endpoints were progression-free survival (PFS) and safety of this new regimen. Next-generation sequencing was used to explore potential biomarkers.

Results. A total of 30 patients were enrolled. The median progression-free survival (mPFS) was 4.21 months (95% confidence interval [CI], 2.29–6.13 months). The median overall survival (mOS) was 7.49 months (95% CI, 4.81–-10.17 months). Patients with lymph node metastasis had prolonged mPFS and mOS when compared with those with liver metastasis (mPFS, 4.21 vs. 1.84 months; mOS, 8.21 vs. 6.31 months, p = .08). The most common grade 3 to 4 adverse events were abdominal pain, dizziness, and diarrhea. Gene mutation profiles between the two subgroups were significantly different.

Conclusion. Apatinib combined with S-1 was not superior to other chemotherapy regimens as first-line therapy for advanced gastric cancer. Toxicity was consistent with known profiles when given as monotherapy. There was a tendency toward prolonged mPFS and mOS in patients with lymph node metastasis compared with patients with liver metastasis, which could support the need to design a future clinical trial with a better defined patient population. ***The Oncologist*** 2021;26:e374–e381

Discussion

There is no consensus about a first-line chemotherapy regimen for patients with metastatic gastric cancer. How to improve the short-term and long-term efficacy of first-line chemotherapy for gastric cancer patients and, at the same

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Table 1. Post hoc subgroup analysis

Efficacy	Lymph nodes metastasis subgroup	Liver metastasis subgroup
No. of patients (%)	19 (63.33)	11 (36.67)
Response assessment (n = 23)[a]		
CR	1 (6.25)	0
PR	4 (25.00)	0
SD	9 (56.25)	4 (57.14)
PD	2 (12.5)	3 (42.86)
Duration assessments, mo		
mPFS	4.21	1.84
mOS	8.21	6.31

[a]23 patients were deemed eligible for evaluation of treatment response; 3 patients were missed in the lymph nodes metastasis subgroup, and 4 patients were missed in the liver metastasis subgroup.
Abbreviations: CR, complete response; mOS, median overall survival; mPFS, median progression-free survival; PD, progressive disease; PR, partial response; SD, stable disease.

time, improve patient tolerance and reduce serious adverse reactions as far as possible are currently urgent problems. We combined two oral medicines, apatinib and S-1, as a new first-line therapy to treat advanced gastric cancer. Our two primary endpoints were the progression-free survival and safety of this new regime.

Of the 30 enrolled patients, the median number of completed cycles was 5.5. Ten patients completed more than six cycles. The mPFS was 4.21 months and the mOS was 7.49 months, which failed to show clinical benefit compared with previous chemotherapy and antiangiogenesis regimens. Adverse events (AEs) observed in this study were consistent with the known safety profiles of S-1 and antiangiogenesis therapy. Because this was an exploratory trial, the small sample size and broad population may be important factors contributing to this outcome. However, we gained more than the negative results. We discovered that patients with abdominal lymph node metastasis had prolonged mPFS and mOS compared with patients with liver metastasis, although this difference did not meet significance (Table 1). Considering this trend, we could design future clinical trials with an expanded sample size to choose the best population for this kind of combination therapy.

We also used next-generation sequencing to explore potential biomarkers. Gene mutation profiles between the two subgroups were significantly different. TP53 is the most commonly mutated gene (18/25); CDH1 and APC are second (5/25). There is also research on the association between gene mutations and cancer pathological characteristics. *PIK3CA* mutation cases were significantly associated with bone metastases. Patients with CDH1 or ARID1A mutation had a greater risk of peritoneal recurrence, and patients with EGFR or CCNE1 amplification had a greater risk of liver recurrence. This is also consistent with our research, which was shown in the genetic profiles distribution.

Trial Information	
Disease	Gastric cancer
Stage of Disease/Treatment	Metastatic/advanced
Prior Therapy	None
Type of Study	Phase II, single arm
Primary Endpoints	Progression-free survival, toxicity
Secondary Endpoints	Overall response rate, overall survival, disease control rate
Investigator's Analysis	Correlative endpoints not met but clinical activity observed

Drug Information	
Drug 1	
Generic/Working Name	Apatinib
Trade Name	Ai-tan
Company Name	Jiangsu Hengrui Pharmaceutical Co., Ltd
Drug Type	Small molecule
Drug Class	Angiogenesis -
Dose	250 mg mg per flat dose
Route	oral (po)
Schedule of Administration	apatinib, 500 mg, qd, days 1–21
Drug 2	
Generic/Working Name	S-1
Trade Name	Ai-Yi
Company Name	Jiangsu Hengrui Pharmaceutical Co., Ltd

Drug Type	Small molecule
Drug Class	Other
Dose	40 mg/m^2
Route	oral (po)
Schedule of Administration	S-1, 40 mg/m^2, b.i.d., days 1–14

Patient Characteristics	
Number of Patients, Male	20
Number of Patients, Female	10
Age	Median (range): 62.97 ± 7.94 (41–76) years
Number of Prior Systemic Therapies	Median: 0
Performance Status: ECOG	0 — 4 1 — 24 2 — 6 3 — 0 Unknown — 0

Other
No. of metastatic sites ≤2: 20 (66.67%)
No. of metastatic sites >2: 10 (33.33%)
Metastasis site, posterior peritoneum lymph node: 19 (63.33%)
Metastasis site, liver: 11 (36.67%)

Cancer Types or Histologic Subtypes	G1 (High) 0 G2 (Middle) 7 G3 (Low) 19 G4 (Undifferentiated) 2 Gx (Unknown) 2

Primary Assessment Method: Overall Assessment	
Number of Patients Screened	31
Number of Patients Enrolled	30
Number of Patients Evaluable for Toxicity	27
Number of Patients Evaluated for Efficacy	23
Evaluation Method	RECIST 1.1
Response Assessment CR	*n* = 1 (4.35%)
Response Assessment PR	*n* = 4 (17.39%)
Response Assessment SD	*n* = 13 (56.52%)
Response Assessment PD	*n* = 5 (21.74%)
(Median) Duration Assessments PFS	4.21 months, CI: 2.29–6.13
(Median) Duration Assessments TTP	6.11 months, CI: 3.71–14.03
(Median) Duration Assessments OS	7.49 months, CI: 4.81–10.17
(Median) Duration Assessments Response Duration	3.24 months
(Median) Duration Assessments Duration Of Treatment	4.04 months

Adverse Events							
All Cycles							
Name	**NC/NA**	**1**	**2**	**3**	**4**	**5**	**All grades**
Fatigue	48%	26%	22%	4%	0%	0%	52%
Abdominal pain	56%	22%	15%	7%	0%	0%	44%
Nausea	62%	19%	19%	0%	0%	0%	38%
Dizziness	71%	11%	11%	7%	0%	0%	29%
Abdominal distension	70%	19%	11%	0%	0%	0%	30%
Hypertension	70%	15%	11%	4%	0%	0%	30%
Diarrhea	75%	11%	7%	7%	0%	0%	25%
Headache	74%	11%	11%	4%	0%	0%	26%
Vomiting	74%	7%	15%	4%	0%	0%	26%
Anorexia	78%	7%	11%	4%	0%	0%	22%
Proteinuria	89%	4%	7%	0%	0%	0%	11%

Adverse events occurring in >10% of patients.
Abbreviation: NC/NA, no change from baseline/no adverse event

Assessment, Analysis, and Discussion	
Completion	Study completed
Investigator's Assessment	Correlative endpoints not met but clinical activity observed

Because there is still no common consensus about a first-line chemotherapy regimen for patients with metastatic gastric cancer, several doublet and triplet chemotherapy combinations or that combined with antiangiogenesis therapy have been tried to improve the clinical efficacy. Patient demographic and clinical characteristics are shown in Table 2. To our knowledge, this is the first phase II study evaluating the efficacy and safety of apatinib combined with S-1 in patients with advanced or metastatic gastric cancer as first-line therapy. In this trial, the combination of apatinib and S-1 failed to show clinical benefit compared with previous chemotherapy and antiangiogenesis regimens including S-1 as a single agent. Table 3 shows best response results. The median progression-free survival (mPFS) was 4.21 months and the median overall survival (mOS) was 7.49 months. The mPFS of cisplatin plus S-1 was 4.8 months, whereas the mPFS of cisplatin plus capecitabine was 5.6 months [1, 2]. The regimen of bevacizumab plus fluoropyrimidine-cisplatin showed an mPFS of 6.7 months, and ramucirumab combined with FOLFOX (oxaliplatin, 135 mg/m^2 (IV) intravenous glucose tolerance test (gtt) (2 hours) day 1; calcium folinate, 200 mg IV gtt (2h) days 1-3; fluorouracil, 2600 mg/m^2 IV 46 hours, pumping in) as front-line therapy showed an mPFS of 6.4 months [3, 4]. The mOS of cisplatin plus S-1 regimen and cisplatin plus capecitabine regimen was 8.6 months and 10.5 months, respectively [1, 2]. For antiangiogenesis combined chemotherapy, the regimen of bevacizumab plus fluoropyrimidine-cisplatin showed an mOS of 12.1 months, and ramucirumab combined with FOLFOX as front-line therapy showed an mOS of 11.7 months [3, 4]. Because this is an explored trial, the small sample size and broad population may be important factors for this outcome. However, we learned more than the negative results. We discovered that patients with abdominal lymph node metastasis had prolonged mPFS and mOS compared with those with liver metastasis, although there was no statistically significant difference but only a tendency (Figs. 1, 2). According to this tendency, we could further design clinical trials with an expanded sample size to choose the best population for this kind of combination therapy.

Adverse events (AEs) observed in this study were consistent with the known safety profiles of S-1 and antiangiogenesis therapy. The most common toxicities of apatinib observed in phase II and phase III trials were proteinuria, hypertension, and hand-foot syndrome (Table 4) [5, 6]. In this trial, proteinuria, hypertension, and hand-foot syndrome were also observed, which were not major AEs of this combination. Common AEs observed with apatinib plus S-1 in this study were fatigue, abdominal pain, and nausea. Although fatigue, abdominal pain, and nausea were reported AEs of apatinib or S-1 used alone, they did not occur with high incidence [7].

Apatinib alone as second-line or followed therapy in treating metastatic adenocarcinoma gastric cancer showed improved progression-free survival (PFS) and overall survival compared with placebo [5, 6]. Massive studies about apatinib combined with chemotherapy are ongoing, and there are few data about the efficacy compared with chemotherapy alone. This exploratory phase II trial was initiated based on the convenience and tolerance in advanced age and poor performance status, combined with previous reports on ramucirumab or bevacizumab combined with chemotherapy [3, 8, 9], which indicated the feasibility of this combination. However, we did not reach the expected endpoint. Although patients with abdominal lymph node metastasis may have prolonged mPFS and mOS compared with those with liver metastasis, mPFS and mOS in this subgroup were even shorter than chemotherapy alone. The efficacy of antiangiogenic therapy combined with chemotherapy in advanced gastric cancer was not up to

expectations. After the current phase II trial was nearly ended, results from a randomized phase II trial (RAINFALL) in previously untreated patients (n = 645) became available. In RAINFALL, although the primary analysis for progression-free survival was statistically significant, this outcome was not confirmed in a sensitivity analysis of progression-free survival by central independent review and did not improve overall survival. Therefore, the addition of ramucirumab to cisplatin plus fluoropyrimidine chemotherapy is not recommended as first-line treatment for this patient population [10]. Also, the addition of ramucirumab to front-line mFOLFOX-6 (oxaliplatin, 135 mg/m^2 (IV) intravenous glucose tolerance test (gtt)(2 hours) day 1; calcium folinate, 200 mg IV gtt (2h) days 1-3; fluorouracil, 2600 mg/m^2 IV 46 hours, pumping in) did not improve PFS of advanced gastric cancer [4].

Recently, the field of gastric cancer genomics has been revolutionized by improvements in next-generation sequencing (NGS) technology. But unlike lung cancer, there are still fewdriver gene mutation data in gastric cancer to guide therapy beyond HER2. Gastric cancer involves a complicated arrangement of protein expression and gene alterations, and it is still difficult to accurately detect prevalent therapeutic targets [11]. Antiangiogenesis therapy including apatinib has different effects in different populations, and there is no effective biomarker guiding the choice of exactly the right patients to improve anticancer activity. NGS in tumor tissues is in progress to identify potential biomarkers of primary resistance and prognosis for ramucirumab plus paclitaxel as switch maintenance versus continuation of first-line chemotherapy in patients with advanced HER2-negative gastric (the ARMANI phase III trial), and there is still no result [12]. To our knowledge, this is the first exploratory study to seek biomarkers for apatinib as first-line therapy in patients ith gastric cancer using NGS. Unfortunately, we did not find an effective gene mutation. However, we did discover a significant difference in gene mutation profiles between the different metastatic groups, which represents differential activity. Mutations in TP53 and CDH1 often were considered classic driver mutations of gastric cancer (Fig. 3), even before the NGS era [13]. In our research, we also found that TP53 is the most frequent mutation (18/25); CDH1 and APC are the second most frequent ones (5/25). There is also research about the association between gene mutations and cancer pathological characteristics. PIK3CA mutation cases were significantly associated with the recurrence of bone metastases. Patients with CDH1 or ARID1A mutation had a greater risk of peritoneal recurrence, and patients with EGFR or CCNE1 amplification had a greater risk of liver recurrence [14]. This is also consistent with our research, which was shown in the genetic profiles distribution.

Apatinib combined with S-1 was not superior to other chemotherapy regimens as first-line therapy for patients with advanced or metastatic gastric cancer. Safety data were consistent with known profiles of these agents when given as monotherapy. There was a tendency that patients with abdominal lymph nodes metastasis had prolonged mPFS and mOS compared with those with liver metastasis, which could be the basis and evidence for us to design clinical trials for a more accurate population.

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Disclosures

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Figures and Tables

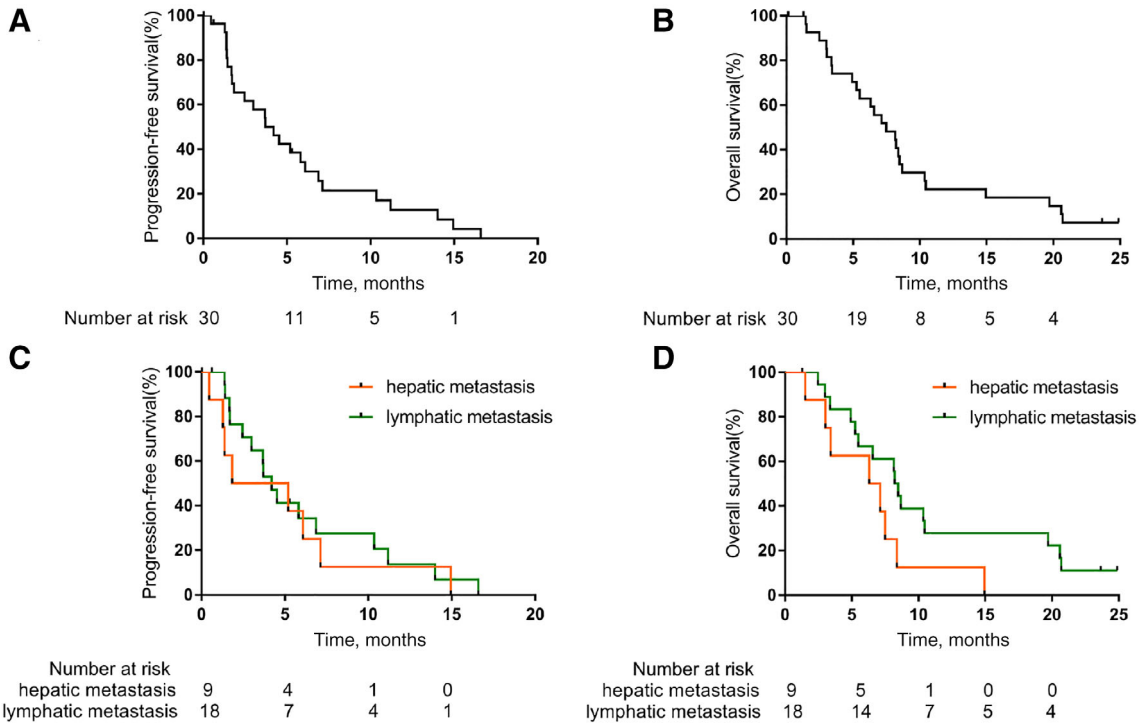

Figure 1. Kaplan-Meier estimates of progression-free survival (PFS) and overall survival (OS). **(A):** The median PFS for the intention-to-treat (ITT) patients was 4.21 months. **(B):** The median OS for the ITT patients was 7.49 months. **(C):** Median PFS was 4.21 months for patients with posterior peritoneum lymph node metastasis compared with 1.84 months for those with liver metastasis. **(D):** Median OS was 8.21 months for patients with posterior peritoneum lymph node metastasis compared with 6.31 months for those with liver metastasis.

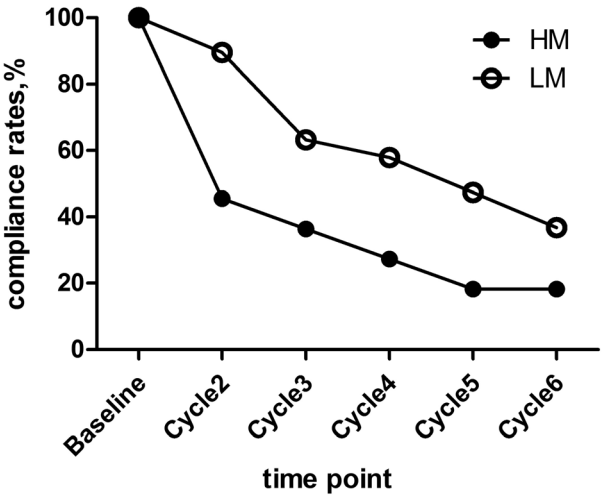

Figure 2. The trend of compliance rates responding to the quality of life questionnaire between the different subgroups.
Abbreviations: HM, hepatic metastasis; LM, lymphatic metastasis.

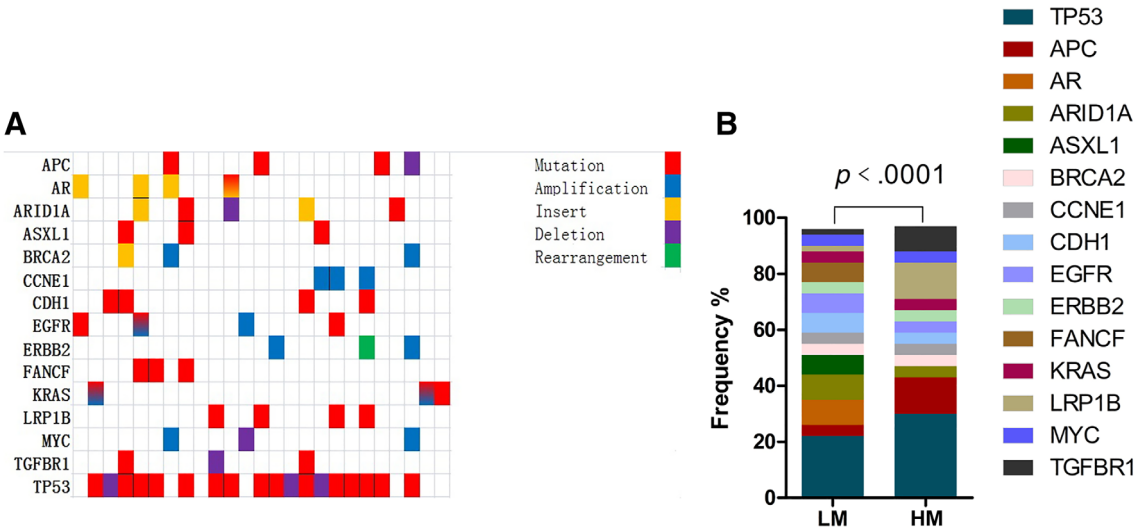

Figure 3. Genetic alterations analysis of enrolled patients. **(A):** Comprehensive annotation of top 15 actionable genetic alterations identified by next-generation sequencing assay in 25 patients. **(B):** The distribution of representative targeted genetic alterations between the lymph node metastasis subgroup and liver metastasis group. Statistical significance was defined as $p < .05$. Abbreviations: HM, hepatic metastasis; LM, lymphatic metastasis.

Table 2. Patient demographics and clinical characteristics

Characteristic	Patients (*n* = 30)
Age	
Mean ± SD	62.97 ± 7.94
Median (Q1, Q3)	64.00 (58.00, 68.00)
Minimum, maximum	41.00, 76.00
Sex	
Male	20 (66.67)
Female	10 (33.33)
Differentiation	
G1 (high)	0 (0.00)
G2 (middle)	7 (23.33)
G3 (low)	19 (63.33)
G4 (undifferentiated)	2 (6.67)
Gx (unknown)	2 (6.67)
ECOG PS	
0	4 (13.33)
1	24 (80.00)
2	2 (6.67)
No. of metastatic sites	
≤ 2	20 (66.67)
>2	10 (33.33)
Metastasis site/organ	
Posterior peritoneum lymph node	19 (63.33)
liver	11 (36.67)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; G, grade; Q, quartile.

Table 3. Best response to apatinib plus S-1 as first-line treatment

Response	No. of patients (%)
n (missing)	23 (7)
CR, *n* (%)	1 (4.35)
PR, *n* (%)	4 (17.39)
SD, *n* (%)	13 (56.52)
PD, *n* (%)	5 (21.74)
ORR, % (95% CI)	21.74 (3.05–36.34)
DCR, % (95% CI)	78.26 (58.09–94.55)

Abbreviations: CI, confidence interval; CR, complete response; DCR, disease control rate; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Table 4. Summary of adverse event

Adverse events	No. of any grade (%)	No. of grade 3 or 4 (%)
Fatigue	14 (46.67)	1 (3.33)
Abdominal pain	12 (40.00)	2 (6.67)
Nausea	10 (33.33)	0
Dizziness	8 (26.67)	2 (6.67)
Abdominal distension	8 (26.67)	0
Hypertension	8 (26.67)	1 (3.33)
Diarrhea	7 (23.33)	2 (6.67)
Headache	7 (23.33)	1 (3.33)
Vomiting	7 (23.33)	1 (3.33)
Anorexia	6 (20.00)	1 (3.33)
Hoarseness	4 (13.33)	0
Proteinuria	3 (10.00)	0
Occult blood	3 (10.00)	0
Hand-foot syndrome	2 (6.67)	0
Hyperbilirubinemia	3 (10.00)	2 (6.67)
Elevated aminotransferase	2 (6.67)	0
Elevated LDH	2 (6.67)	0
Neutropenia	2 (6.67)	0
Thrombocytopenia	2 (6.67)	0

Abbreviation: LDH, lactate dehydrogenase.