Original Article

# Apatinib plus S-1 for previously treated, advanced gastric or gastro-oesophageal junction adenocarcinoma: a phase 2, single-arm, prospective study

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**Background:** The current management of advanced gastric or gastro-oesophageal junction adenocarcinoma remains unsatisfactory. We investigated the efficacy and safety of the combination therapy of apatinib and S-1, considering the potential advantage of home-based treatment without hospital admission, in patients with platinum-refractory gastric or gastro-oesophageal junction adenocarcinoma.

**Methods:** In this open-label, single-arm, phase 2 trial, in each 21-day cycle, eligible patients received apatinib at an initial dose of 500 mg once daily continuously and S-1 at a dose of 40–60 mg twice daily on days 1–14 until the trail was discontinued disease progression, development of intolerable toxicity, or withdrawal of consent. The primary endpoints were progression-free survival. The secondary endpoints were objective response rates, disease control rates, and safety, and overall survival. This study was registered at ClinicalTrials.gov, NCT04338438.

**Results:** Between April 2015 and May 2019, we included 37 patients with advanced gastric or gastro-oesophageal junction adenocarcinoma refractory to first-line platinum-containing therapy. At the data cutoff, the 6-month progression-free survival was 31.5%, the median progression-free survival and overall survival were 4.2 (95% CI: 3.50–4.90) months and 8.2 (95% CI: 4.69–11.71) months, respectively. Of 37 eligible patients, 8 (21.6%) patients reached objective responses, 31 (83.8%) patients reached disease control. Grade 3 or 4 adverse events occurred in 8 (21.6%) patients, including hand-foot syndrome, hypertension, and diarrhea, etc.

**Conclusions:** The combination of Apatinib and S-1 showed promising efficacy and manageable toxicity as a home-based, second-line therapy in patients with advanced gastric or gastro-oesophageal junction adenocarcinoma, especially for the elder patients with poor performance status.

**Trial Registration:** NCT04338438.

**Keywords:** Molecular targeted therapy; apatinib; S-1; stomach neoplasms

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## Introduction

Based on the Global Cancer Statistics (1), gastric cancer is the fifth most commonly diagnosed cancer and is the third leading cause of cancer deaths. In 2018, there were more than 1 million new cases and approximate 783,000 deaths because of gastric cancer. With the increased use of gastroscopy and the development of other screening methods, East Asian countries such as Japan and Korea currently show much lower mortality rates (2). However, because of the limitation of skills of endoscopic physicians and the low availability of gastroscopy (3,4), many regions lag in comprehensive gastric cancer screening, and 80% of gastric cancer patients in China are already in late-stages when diagnosed (5). According to the National Comprehensive Cancer Network (NCCN) (6) and Chinese Society of Clinical Oncology (CSCO) (7) guidelines, there are only limited choices of second-line treatment for advanced gastric cancer.

With intensive research on tumor angiogenesis, it was discovered that anti-angiogenesis therapy could effectively inhibit gastric cancer growth and significantly enhance the efficacy of chemotherapy (8). Apatinib, an oral small molecule vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFR-TKI), inhibited the tyrosine kinase activity of VEGFR-2 with high selectivity, thereby strongly inhibiting tumor angiogenesis (9). Several clinical studies have shown apatinib's efficacy and safety in third-line treatment of advanced gastric cancer and it has been approved by the National Medical Products Administration (NMPA, China) as a monotherapy for patients with advanced gastric or gastric-esophageal junction adenocarcinoma (10,11). S-1 is a fluorouracil-derived combination anticancer agent consisting of tegafur (FT), gimeracil (CDHP) and oteracil (OXO) (12). Numerous studies (13,14) demonstrated that S-1 was suitable for adjuvant, first-line, and second-line chemotherapy for gastric cancer. Both apatinib and S-1 are the most widely used oral drugs for gastric cancer in clinical practice in China. In addition, the clinical and laboratory studies of ramucirumab or bevacizumab combined with chemotherapy have shown that anti-angiogenesis therapy combined with chemotherapy has synergistic effects and anti-tumor activity (15-17). Based on the above research, we designed this study to explore a convenient, effective and manageable second-line therapy for gastric cancer patients after the failure of platinum-containing treatments, especially for the elderly patients or with poor performance status (7).

We present the following article in accordance with the TREND reporting checklist (available at https://dx.doi.org/10.21037/jgo-21-186).

## Methods

### *Patient characteristics*

We conducted this phase 2, single-arm, prospective study at the Beijing Friendship Hospital affiliated to Capital Medical University between April 2015 and May 2019. Eligible patients were aged 18 years or older; had unresectable advanced or recurrent gastric or gastro-oesophageal junction cancer histologically confirmed to be adenocarcinoma; had a measurable tumor which progressed during the first-line platinum-containing (XELOX or FOLFOX regimen, which includes oxaliplatin plus capecitabine or fluorouracil plus oxaliplatin respectively) treatment, or within 6 months after last platinum-containing adjuvant chemotherapy; with Her-2 negative status; had Eastern Cooperative Oncology Group (ECOG) performance status score of 0–2 and a life expectancy of at least 3 months; had adequate organ function. Exclusion criteria were: previous application of apatinib or other TKIs or S-1; uncontrollable hypertension; various factors affecting oral drug absorption (such as severe dysphagia, severe vomiting, chronic diarrhea, and obstruction of digestive tract etc.); serious heart and lung dysfunction; neurological and mental illness. The full inclusion and exclusion criteria are shown in the appendix. The time of data cut-off was set at Jan 31, 2020.

### *Ethical statement*

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Research Ethics Committee of the Beijing Friendship Hospital affiliated to Capital Medical University (2015-P2-105-01) and informed consent was taken from all the patients. This trial was registered with ClinicalTrials.gov, number NCT04338438.

### *Procedures*

Eligible patients received apatinib at an initial dose of 500 mg once daily continuously, plus S-1 at a dose of 40–60 mg twice daily depending on the patient's body surface area (40 mg if <1.25 $m^2$; 50 mg if 1.25–1.5 $m^2$; and 60 mg if >1.5 $m^2$) on days 1–14 of a 21-day cycle.

The trial was discontinued for the following reasons:

 

when tumor progressed, or serious adverse events occurred, or the patients requested withdrawal, or the investigator determined that there was a need to discontinue the trial.

Before treatment initiation, we used abdominal enhanced CT/MRI to measure and document the measurable lesions. During the treatment period, he investigators evaluated the treatment response every 6 weeks with enhanced CT/MRI of abdomen and pelvis and metastatic sites, according to the Response Evaluation Criteria In Solid Tumors (RECIST, version 1.1) (18), until the experiment was discontinued. In addition, patients were assessed in outpatient every three weeks, including: vital signs, blood routine examination, blood biochemical examination, urine routine test, 12-lead ECG, etc. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE, version 4.03) and monitored continuously during the course of treatment.

Management of adverse events was based on the type and severity of the adverse events, including supportive cure, dose adjustment and interruption of dosage. For apatinib, if patients had grade 4 hematologic adverse events, treatment was suspended until recovery to grade 1 or below, and, then restarted with the reduced dose. If the patients had grade 3 hematologic adverse events or grade 3–4 non-hematologic adverse events, at the first instance, apatinib was suspended until recovery to grade 1 or below, and, then restarted with the non-reduced dose. At the second instance of the grade 3 hematologic adverse events or grade 3–4 non-hematologic adverse events, the subsequent treatment with apatinib was administered using the reduced dose. For S-1, if patients had grade 3–4 adverse events, it was suspended until recovery to grade 1 or below, and, then the single dose was reduced from 60 to 50 mg, or from 50 to 40 mg twice daily, as applicable, and no further dose re-escalation was allowed (11).

### *Outcomes*

The primary endpoints were 6-month progression-free survival (6-month PFS). Six-month PFS referred to the proportion of patients kept PFS when the treatment reached 6 months. The secondary endpoints were the objective response rates (ORR), and PFS and overall survival (OS), and disease control rates (DCR) (according to RECIST 1.1), and safety. The ORR was defined as the proportion of patients with measurable disease who achieved complete or partial response. PFS refers to the duration from the beginning of the treatment to the disease progression, or death from any cause, or last PFS assessment for patients alive without progression. OS was defined as the interval from the enrollment to death from any cause. The DCR was defined as the proportion of patients achieving stable disease or complete response or partial response.

### *Statistical analysis*

Using the Exact single-stage phase-2 design, with a power of 90% and a type I error of 5% the study, detected an improvement in the 6-month PFS from previous controls of about 18–36% (16,19). We initially set a threshold for 6-month PFS of 18% and an expectation of 40%, and under these assumptions, 36 or more patients should be enrolled. Eventually, if the 6-month PFS reached 30.5%, the treatment regimen would be considered success. We used Stata (version 15.0) software to estimate the sample size, with the SAMPSI_FLEMING module (https://ideas.repec.org/c/boc/bocode/s457055.html).

All patients who received at least 2 cycles of treatment, with good compliance and adherence to the protocol, and baseline and post-treatment evaluation would be assessed for efficacy and safety. We assessed the median PFS and OS and their 95% CI using the Kaplan-Meier Model. We calculated the proportions of patients with different treatment responses and prognoses, and we assessed 95% CI using Wilson procedure. In addition, we also used multiple Kaplan-Meier Model to assess whether there were significant differences in median PFS or median OS between different subgroups, such as patients with recurrent tumors, or with unresectable tumors. All statistical analyses were two-sided and significance was set at $P<0.05$. The software used for all statistical analyses was SPSS Statistics (version 25.0) and Stata (version 15.0).

## Results

### *Patient characteristics*

Between April 2015 and May 2019, 39 patients were screened, 37 of whom were enrolled in this study. One patient was excluded due to previous treatment with S-1, and another patient was due to pre-existing severe vomiting that might affect oral drug intake. All patients enrolled were Her-2 negative. The patients' baseline information is displayed in *Table 1*.

At the time of data collection (Jan 31, 2020), 2 patients were still on treatment, while treatment was discontinued

 

**Table 1** Baseline demographic and clinical characteristics of full analysis set (n=37)

| Characteristics | Values |
|---|---|
| Age (years), median [range (IQR)] | 59 [28–84 (IQR 50–66)] |
| Sex | |
| Male | 29 (78.4) |
| Female | 8 (21.6) |
| ECOG PS | |
| 0 | 7 (18.9) |
| 1 | 25 (67.8) |
| 2 | 5 (13.5) |
| Primary lesion | |
| Gastroesophageal junction | 9 (24.3) |
| Gastric | 28 (75.7) |
| Tumor status | |
| Recurrent | 14 (37.8) |
| Unresectable* | 22 (59.5) |
| No. of metastatic sites | |
| >2 | 9 (24.3) |
| ≤2 | 28 (75.7) |
| First-line treatment | |
| XELOX | 29 (78.4) |
| FOLFOX | 8 (21.6) |
| Platinum-containing treatment duration | |
| >4 months | 16 (43.2) |
| ≤4 months | 21 (56.8) |
| Presence of ascites under CT assessment | |
| Positive | 21 (56.8) |
| Negative | 16 (43.2) |

Data are presented as median (IQR range) or n (%). *, the unresectable tumor: peritoneal cancer index >6, bilobar hepatic metastases, nodal involvement outside D1-3 stations, technically unresectable metastases. All patients enrolled were Her-2 negative. XELOX, Oxaliplatin + Xeloda; FOLFOX, oxaliplatin + 5-fluorouracil (5-FU)/leucovorin. ECOG, Eastern Cooperative Oncology Group.

in 35 patients. Among them, 29 patients eventually discontinued the trial because of disease progression, 4 patients discontinued the trial because of intolerable adverse events, while 2 patients discontinued due to consent withdrawal (*Figure 1*). The median follow-up duration for the cohort (n=37) was 8.4 months.

### *Efficacy*

At the end of the follow-up, 26 (70.3%) patients had died, and 11 (29.7%) patients were still alive. With the 6-month PFS reaching 31.5% (95% CI: 16–48), we met the primary endpoint. As the secondary endpoints, median PFS was 4.2 months (IQR 2.7–7.0; 95% CI: 3.50–4.90) and the median OS was 8.2 months (IQR 4.95–12.6; 95% CI: 4.69–11.71); 9-month PFS was 17.5% (95% CI: 6–33); 6-month OS was 62% (95% CI: 45–76); 12-month OS was 36% (95% CI: 20–51); 2-year OS was 21.7% (95% CI: 8–39) (*Figure 2*). Among all patients with efficacy evaluation, 0 (0%) of 37 patients achieved complete response, 8 (21.6%) of 37 patients achieved partial response, 23 (62.1%) of 37 patients reached stable disease, and 6 (16.2%) patients achieved progressive disease after first post-baseline imaging evaluation (*Figure 3*). As for the secondary endpoints, objective response was achieved in 8 of 37 patients (ORR: 21.6%; 95% CI: 10.4–38.7%); disease control was achieved in 31 of 37 patients (DCR: 83.8%; 95% CI: 67.3–93.2%).

In the post-hoc analysis of this study, we also observed that the patients with recurrent gastric or gastro-oesophageal junction adenocarcinoma had a significantly longer median OS than patients with radically unresectable disease (18.0 *vs.* 6.0 months; HR: 3.318; 95% CI: 1.362–8.085; P=0.005) (*Figure 4*). In addition, we analyzed the relationship between efficacy and ascites status, and patients without ascites showed a better ORR (31.3%, 95% CI: 14.1–55.6), as well as better OS and PFS (*Figure 4*).

### *Safety*

All 37 patients were included in the safety analysis. The overall incidence of any-grade adverse events was 100%. Most events were graded 1 or 2. The most common AEs were hypertension in 11 patients (29.7%), hand-foot syndrome in 12 patients (32.4%), diarrhea in 12 patients (32.4%), elevated transaminase in 14 patients (37.8%), leukopenia in 12 patients (32.4%). Eight patients (21.6%) had grade 3–4 adverse events, including hand-foot syndrome, acute intestinal obstruction, upper gastrointestinal bleeding and severe anemia, hypertension, fatigue, diarrhea, leukopenia. Among the 8 patients, 4 patients discontinued this trial for AEs: one for serious

 

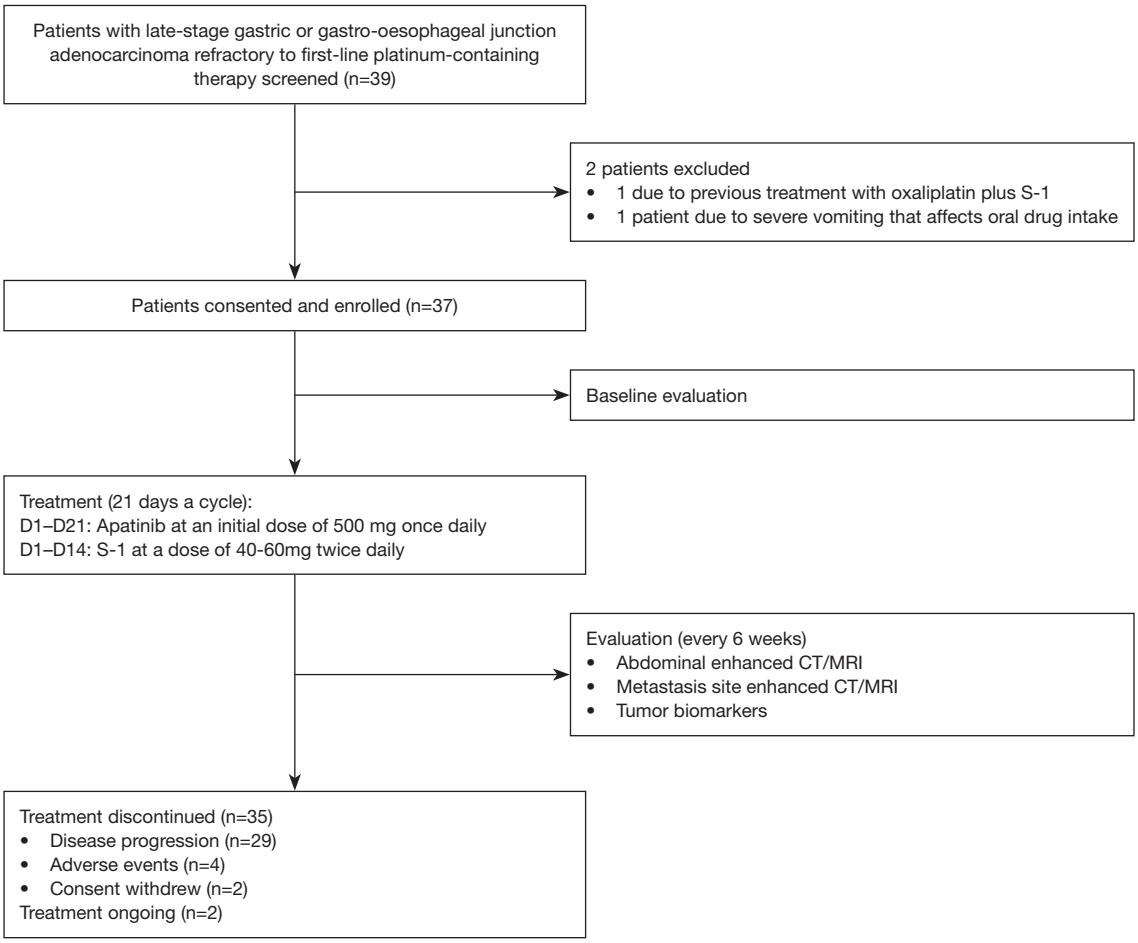


**Figure 1** Trial profile.

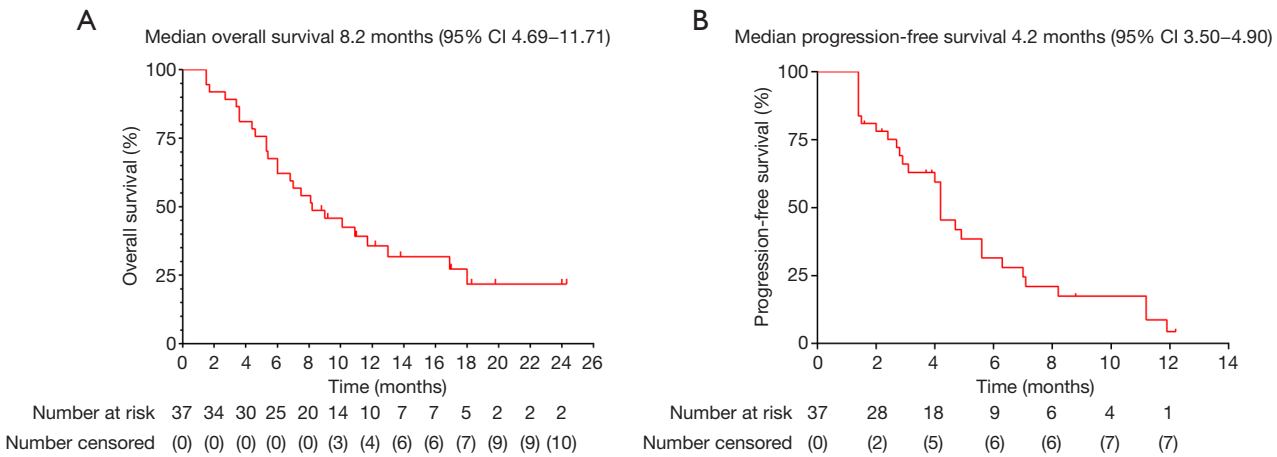


**Figure 2** Kaplan-Meier curve for (A) OS and (B) PFS in patients with at least one post-baseline efficacy assessment (n=37).

 

fatigue, one for acute intestinal obstruction, one for upper gastrointestinal bleeding and severe anemia, and one for grade 4 hand-foot syndrome. No treatment-related deaths occurred. Details of adverse events are shown in the *Table 2*.

Eventually, there were 9 patients (24.3%) who required dose reduction for apatinib, of whom 6 patients experienced only one dose reduction and 3 patients had two dose reductions. And there were 6 patients (16.2%) for S-1, among whom 4 patients required one dose reduction and 2 patients had 2 dose reductions.

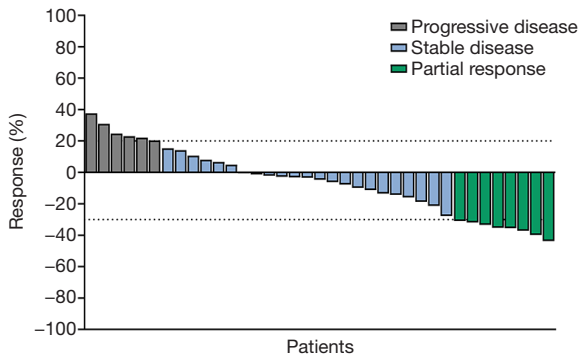


**Figure 3** Waterfall plot for the best percentage change in target lesions size. This plot shows the best percentage change in sum of the longest target lesion diameters of 37 patients who had at least one post-baseline efficacy assessment.

In the analysis of adverse events and efficacy, it was observed that patients with any grade hand-foot syndrome had a longer median PFS (8.2 *vs.* 4.2 months; HR 0.451; 95% CI: 0.197–1.031; P=0.059; log-rank P=0.043) and median OS (13.0 *vs.* 6.0 months; HR 0.445; 95% CI: 0.186–1.067; P=0.70; log-rank P=0.061). Furthermore, the median PFS of patients who had any grade proteinuria was longer than those who did not (5.6 *vs.* 4.2 months; HR 1.421; 95% CI: 0.632–3.194; P=0.395; log-rank P=0.369).

## Discussion

In this single-arm trial, we assessed the efficacy and safety of the oral combination of apatinib and S-1 in second-line setting for patients with unresectable or recurrent gastric or gastro-oesophageal junction adenocarcinoma. In our study, with the 6-month PFS reach 31.6%, the primary endpoint was met. In addition, 8 (21.6%) patients reached

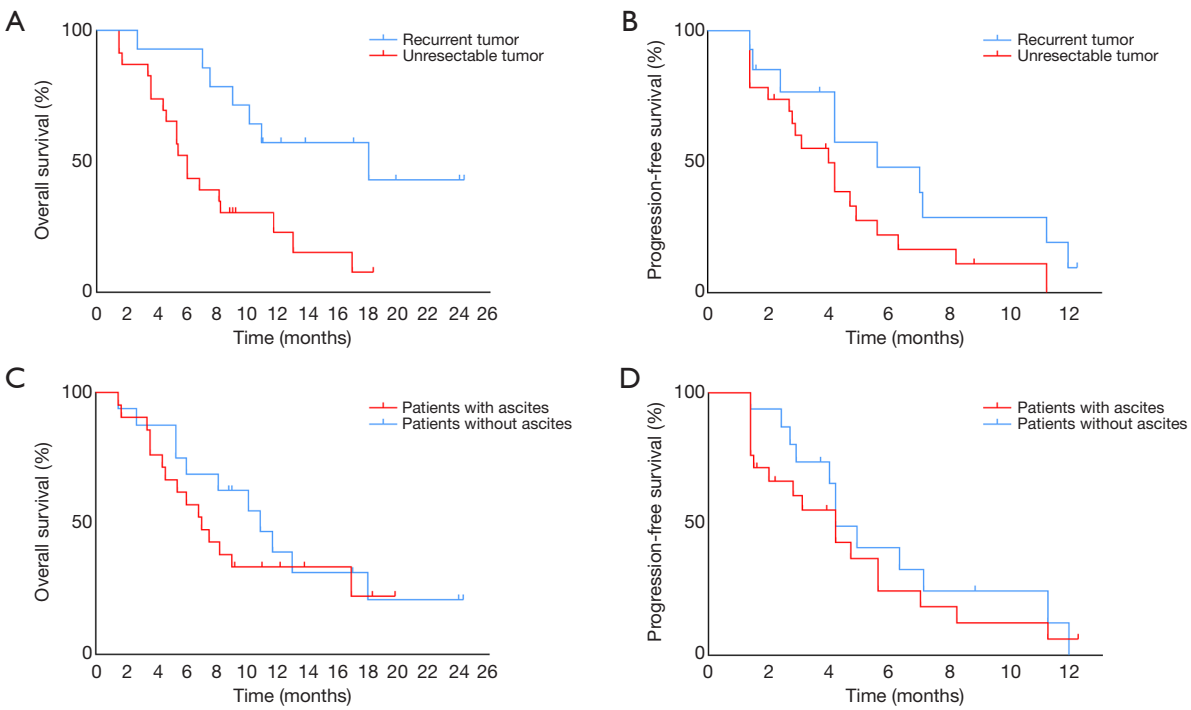


**Figure 4** Kaplan-Meier curve for subgroup analysis. (A) The overall survival of patients with (n=14) and without radical gastrectomy (n=23). (B) The progression-free survival the overall survival of patients with and without radical gastrectomy. (C) The overall survival of patients with (n=21) and without ascites (n=16). (D) The progression-free survival of patients with and without ascites.

 

**Table 2** The incidence of adverse events in the safety population (n=37)

| Adverse events | Any grade, n (%) | Grade 3–4, n (%) |
|---|---|---|
| Non-hematological | | |
| Hypertension | 11 (29.7) | 1 (2.7) |
| Proteinuria | 10 (27.0) | – |
| Hand-foot syndrome | 12 (32.4) | 2 (5.4) |
| Fatigue | 7 (18.9) | 1 (2.7) |
| Anorexia | 11 (29.7) | – |
| Abdominal pain | 10 (27.0) | – |
| Diarrhea | 12 (32.4) | 1 (2.7) |
| Dizziness | 6 (16.2) | – |
| Elevated transaminase | 14 (37.8) | – |
| Elevated bilirubin | 6 (16.2) | – |
| Mucositis | 4 (10.8) | – |
| Acute intestinal obstruction | – | 1 (2.7) |
| Upper gastrointestinal bleeding | – | 1 (2.7) |
| Hematological | | |
| Anemia | 15 (40.5) | 1 (2.7) |
| Leukopenia | 12 (32.4) | 1 (2.7) |
| Thrombocytopenia | 7 (18.9) | – |

objective response and 31 (83.8%) patients reached disease control, the median PFS was 4.2 months and the median OS was 8.2 months, 4 patients had graded 3 treatment related adverse events.

Apatinib has been shown to effectively improve OS and PFS in second-line or third-line treatment of advanced gastric cancer and was approval by NMFA for 3-line treatment of gastric cancer. 5-Fluorouracil is an indispensable part of chemotherapy for advanced gastric cancer, and S-1 is suitable for all stages of the treatment of advanced gastric cancer. As previous studies reported, the outcomes of bevacizumab or ramucirumab in combination with chemotherapy suggest the feasibility of apatinib plus S-1. On this basis, we conducted this exploratory study of apatinib and S-1 in second line setting in patients with advanced gastric cancer.

To our knowledge, the effects of current second-line treatment schemes for advanced gastric cancer remain unsatisfactory. The WJOG 4007 Trial (20), a phase-3 study in Japan, enrolled 233 patients with advanced gastric cancer refractory to treatment with fluoropyrimidine plus platinum. The median PFS and the median OS of the paclitaxel group was 3.6 and 9.5 months, respectively, whereas, the median PFS and the median OS in the irinotecan group was 2.3 and 8.4 months, respectively. In RAINBOW study (16), a phase 3 trial, ramucirumab plus paclitaxel showed a significant improvement in patients with previously treated advanced gastric or gastro-esophageal junction adenocarcinoma; the ORR was 28%, the median PFS reached 4.4 months, and in Asian patients the median OS reached 12.1 months. Compared with the current studies, apatinib combined with S1 in this study is not inferior to other regimens in improving patient survival, and at the same time provides a more convenient and manageable treatment choice. At present, a study (21) has reported that apatinib combined with S-1 as a first-line treatment was not superior to current regimens in efficacy, but it still demonstrated a survival benefit for patients with advanced gastric cancer. The profiles of efficacy and safety in the first-line setting in that study are similar to our findings with second-line therapy, which indicates that apatinib plus S-1 is more suitable for elderly patients with pre-treatment and poor performance status. In the ANGEL study, different from the outcomes of study in China, apatinib failed to demonstrate its therapeutic advantages internationally. However, taking into account the differences in population and other influencing factors, I still believe that apatinib would benefit for gastric cancer patients. Furthermore, with the development of immune checkpoint inhibitor therapy, the combination of ICIs with chemotherapy and targeted therapy is promising (22).

With platinum-based and fluorine-containing treatment as the first-line treatment, apatinib and S-1 are selected as the second-line treatment in this study because of two reasons. Firstly, Fluorouracil, Xeloda and S-1 are different dosage forms of fluorine drugs, and their absorption and metabolism mechanisms in the body are different and secondly, gimeracil (CDHP) contained in S-1 effectively inhibits the dihydropyrimidine dehydrogenase (DPD), by which it inhibits fluorine drug resistance. Therefore, we combined apatinib and S-1 in our study.

In addition, in this study, 12 patients (32.4%) were over 65 years of age at the time of enrolment. In this subgroup, mPFS reached 2.9 months, mOS reached 8.2 months, and DCR reached 75%. In those patients, common adverse events included neutropenia (41.7%), abdominal pain (41.7%), and 1 patient had grade 3 neutropenia. An 84-year-old patient achieved partial response after 3 months treatment and was still receiving treatment at the data cutoff, with a PFS of 8.8 months. Therefore, apatinib

 

combined with S-1 showed a survival benefit in patients older than 65 years, with mild and manageable adverse reactions.

In subgroup pos-hoc analysis, a better prognosis was observed among patients with recurrent tumors. Similar to the analysis of many prognostic factors for gastric cancer (23,24), recurrent gastric cancer patients with lower tumor burden and potential tumor-free period showed better prognosis. In additions, compared with unresectable gastric cancer, recurrent tumors may have a low intratumoral heterogeneity (ITH) (25,26) and are therefore more sensitive to treatment. And different subsequent treatments might influence patients' survival. In this study, 32 patients were administered subsequent therapies. These were as follows: 12 patients received anthracycline, 10 paclitaxel, 7 irinotecan, 2 anti-PD-1 and 1 patient received radiotherapy. It was observed that patients who received anthracycline and paclitaxel had better survival prognosis (mOS reached 9.1 and 7.5months, respectively).

The recommended dose of apatinib is 500–850 mg once daily According to the phase I dose-escalation study and the phase 3 clinical trial (10,11,27). However, in the preliminary trial, we observed that 850 mg of apatinib combined with S-1 is more likely to cause intolerable gastrointestinal adverse reactions such as diarrhea and abdominal pain, while 500 mg of apatinib is effective and safer and easier to tolerate. Therefore, in our study apatinib was given at 500 mg once daily and S-1 at the standard dose.

In term of treatment related adverse events, comparing with paclitaxel and irinotecan and docetaxel In the WJOG study or JACCRO GC-07 study, the hematological adverse events (especially leukopenia and anemia) of apatinib plus S-1 is obviously lower. In the ACTS-GC study, S-1 was recommended as adjuvant therapy for 1 year after radical gastrectomy. Compared with our study, the incidence of accumulated toxicity and accidental adverse events should and do be more. In the REGARD study, the most common adverse event of ramucizumab were fatigue (36%) and abdominal pain (29%), which were similar to ours. In our study, with the appropriate dosage and reasonable and timely administration of adverse events, the incidence of serious adverse events and grade 3–4 adverse events was lower. Therefore, apatinib plus S-1 were more manageable and safer than intravenous chemotherapy drugs especially for the hematological adverse events. In terms of the cost, apatinib and S-1 have been approved by National Medical Products Administration (NMPA) for gastric cancer, by which patients are able to afford those treatment. In the meanwhile, manageable adverse events reduce the cost of symptomatic supportive treatment for side effect. Therefore, there was a well balance between the treatment effectiveness and the cost.

In the analysis of toxicity and efficacy, similar to previous studies (28,29), the occurrence of hand-foot syndrome and proteinuria may indicate a better treatment outcome of anti-angiogenesis therapy, however, it might be attributed to the small sample size, we did not observe the statistical significance in the assessment of toxicity and efficacy.

Recently with the emergence of novel coronavirus (COVID-19) pneumonia, there is a serious scarcity of medical resources worldwide, and limited outdoor activities are being recommended for cancer patients by various cancer societies including European Society for Medical Oncology (ESMO) (30). Considering the global outbreak of the novel coronavirus and the possibility of its long-term existence, oral administration of apatinib combined with S-1 might be a preferred option for patients because it can potentially minimize visits and hospitalization, limiting the spread of COVID-19.

This study has several limitations. In the absence of randomization, the selection bias could not be trimmed, therefore, the strength of the medical evidence was not sufficient. Because of the small number of patients enrolled, our findings might be affected by the sampling error. In addition, because of a large number of new drugs appearing in recent years, considering individual patients' requirements, the wide treatment choices made enrollment difficult, resulting in a longer time span for enrollment in this study. However, encouragingly, the enrolled patients maintained a good compliance to this trial.

In conclusion, the efficacy of apatinib plus S-1 was comparable to the existing research, and the safety profile seemed to be more favorable than that of intravenous treatment regimens. Furthermore, our study provides a new option for the second-line treatment for advanced gastric or gastro-oesophageal junction adenocarcinoma, and explores a low-toxic and more convenient medication regimen, especially for elderly patients with poor condition. In addition, apatinib plus S-1 may be an appropriate choice of second-line treatment for advanced gastric cancer during the COVID-19 pandemic.

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## Footnote

*Reporting Checklist:* The authors have completed the TREND reporting checklist. Available at https://dx.doi.org/10.21037/jgo-21-186

*Data Sharing Statement:* Available at https://dx.doi.org/10.21037/jgo-21-186

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/jgo-21-186). All authors report that the study was supported by National Key Technologies R&D Program (No. 2015BAI13B09) and China Anti-Cancer Association-Hengrui Pharmaceutical Innovative Drugs Clinical Research Fund. The authors have no other conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Research Ethics Committee of the Beijing Friendship Hospital affiliated to Capital Medical University (2015-P2-105-01) and informed consent was taken from all the patients. This trial was registered with ClinicalTrials.gov, number NCT04338438.



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