Neoadjuvant apatinib plus tegafur/gimeracil/oteracil potassium (S-1)/oxaliplatin chemotherapy vs. chemotherapy alone in patients with locally advanced gastric carcinoma

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Received March 23, 2022; Accepted May 20, 2022

DOI: 10.3892/etm.2022.11562

Abstract. The current study aimed to evaluate the efficacy and safety of neoadjuvant apatinib plus tegafur/gimeracil/oteracil potassium (S-1) plus oxaliplatin (SOX) chemotherapy in patients with locally advanced gastric carcinoma (LAGC). Therefore, patients with LAGC treated with neoadjuvant apatinib plus SOX chemotherapy (apatinib + SOX group; n=25) or SOX chemotherapy (SOX group; n=35) were enrolled in the present study. Subsequently, the objective response (ORR) and disease control rates (DCR), pathological response, disease-free survival (DFS), overall survival (OS) and adverse events were recorded. The results showed that patients in the apatinib + SOX group exhibited a higher ORR (64.0 vs. 37.1%; P=0.040), but a similar DCR (96.0 vs. 88.6%; P=0.580), compared with those in the SOX group. The pathological response rates in patients with grade 0, 1, 2 and 3 LAGC were 0.0, 20.8, 62.5 and 16.7%, respectively, in the apatinib + SOX group, while in those treated with SOX alone they were 9.1, 39.4, 42.4 and 9.1%, respectively. By contrast, the pathological response was elevated in the apatinib + SOX group compared with the SOX group (P=0.030). During a median follow-up period of 21.0 months (range, 6.4-38.1 months), median DFS and OS were not reached. More specifically, the 1-, 2- and 3-year DFS rates were 91.7, 75.2 and 75.2% in the apatinib + SOX group and 71.8, 59.6 and 44.7% in the SOX group, respectively. In addition, the 1-, 2- and 3-year OS rates were 100.0, 89.6 and 78.4% in the apatinib + SOX group, while those in the SOX group were 90.3, 69.2 and 55.4%, respectively. However, no differences in DFS (P=0.094) or OS (P=0.155) were observed between the two groups. Additionally, the most common adverse events in the SOX group were mild leukopenia (42.9%) and fatigue (34.3%), while those in the apatinib + SOX group were tolerable leukopenia (44.0%) and hypertension (44.0%). In conclusion, the present study suggested that neoadjuvant apatinib plus SOX chemotherapy could be more effective and tolerable compared with SOX chemotherapy alone in patients with LAGC.

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Key words: neoadjuvant apatinib plus S-1 plus oxaliplatin chemotherapy, locally advanced gastric carcinoma, treatment response, survival, safety profile

Introduction

Gastric carcinoma is one of the most common types of cancer and the 3rd leading cause of cancer-associated mortality worldwide (1). It has been reported that China accounted for 45% of all global gastric carcinoma cases in 2019 (2-4). Currently, the treatment approaches for early-stage gastric carcinoma include surgery, chemotherapy and targeted treatments, which provide favorable survival rates (5). However, patients with locally advanced gastric carcinoma (LAGC) exhibit limited treatment options and poor prognoses (2,4,6). Currently, neoadjuvant chemotherapy is recommended for patients with LAGC in China to decrease tumor volume and stage, as well as improve R0 resection rate, thus increasing survival (3,7,8). However, there remains a group of patients who do not benefit from neoadjuvant chemotherapy, partially due to the heterogeneity of tumors and chemotherapy resistance (9-11). Therefore, identifying more effective neoadjuvant therapies for patients with LAGC is of clinical value.

Recently, molecular targeted therapy has attracted increasing attention for patients with advanced gastric carcinoma owing to favorable efficacy and satisfactory safety (12-14). In this field, apatinib is the first oral VEGFR tyrosine kinase inhibitor developed in China, which provides obvious survival benefits and tolerable toxicity in patients with advanced gastric carcinoma (3,6,15). Notably, two previous trials demonstrated that apatinib combined with S-1 plus oxaliplatin (SOX) chemotherapy as neoadjuvant therapy exhibited favorable clinical and pathological response rates, as

well as mild and manageable adverse events in patients with LAGC (12,13). However, the survival profile and data under real clinical settings were not evaluated in the aforementioned two single-armed trials (12,13). Therefore, studies on the survival profile of patients in real-world settings are needed.

Overall, the current study aimed to evaluate the efficacy and safety of neoadjuvant apatinib plus SOX chemotherapy in patients with LAGC by comparing treatment response, survival, and adverse events between neoadjuvant apatinib plus SOX and SOX chemotherapy alone.

Materials and methods

Subjects. In the present prospective, cohort study, a total of 25 patients with LAGC, who were about to receive apatinib combined with tegafur/gimeracil/oteracil potassium SOX chemotherapy as neoadjuvant therapy, were consecutively enrolled between March 2018 and May 2020. The patients were treated in the Second People's Hospital of Liaocheng (Liaocheng, Shandong, China) and the People's Hospital of Xiajin Affiliated to Shandong First Medical University (Xiajin, Shandong, China). The enrollment criteria were as follows: i) Patients with confirmed gastric adenocarcinoma both pathologically and histologically; ii) aged >18 years; iii) with clinical tumor-node-metastasis (cTNM) stage III (cT3-cT4a, cN1-cN3 and cM0) according to the 8th edition of TNM classification; iv) Eastern Cooperative Oncology Group (ECOG) score of 0-1 (16); v) with a resectable tumor as determined via tumor resectability assessment; and vi) patients who were about to receive apatinib combined with SOX chemotherapy as neoadjuvant therapy. The exclusion criteria were the followings: i) Patients with a history of other types of cancer or malignancies; ii) with an allergy to the drugs used in the present study; iii) who were unwilling to be followed up regularly; and iv) pregnant or lactating women. All 25 patients were included in the apatinib + SOX group. The current study was approved by the Institutional Review Board of The Second People's Hospital of Liaocheng [approval no. (2018)0203; Linqing, China] and all patients provided written informed consent.

Treatment procedures. Patients with gastric carcinoma in the apatinib + SOX group were treated with apatinib combined with SOX chemotherapy as neoadjuvant therapy. At 3-5 weeks following neoadjuvant therapy, the tumor resectability was assessed by three independent surgeons with >10 years of experience in operating gastric cancer, in accordance with the Japanese classification of gastric carcinoma (17), then the surgical resections were operated on the patients whose tumor was deemed resectable (n=24). At 4-8 weeks after surgery, the patients continued to be treated by SOX chemotherapy as adjuvant therapy for 3-5 cycles (18). The detailed regimen of neoadjuvant therapy was as follows: Apatinib was orally administered at a dose of 500 mg/day for two consecutive cycles (21 days per cycle), followed by one cycle of withdrawal (18). Subsequently, patients were treated with SOX chemotherapy for three cycles (21 days per cycle). The detailed regimen of SOX chemotherapy was as follows: Oxaliplatin was intravenously administered at a dose of 130 mg/m^2 on day 1 for three cycles. S-1 was orally administered for two continuous cycles, followed by one cycle of withdrawal. The dose of S-1 dependent on body surface area (BSA): BSA <1.25 m^2, 80 mg/day; BSA 1.25-1.50 m^2, 100 mg/day; BSA >1.50 m^2, 120 mg/day, as previously described (12). Dose adjustment was allowed depending on the response and tolerance of patients.

Outcome assessment. At 4 weeks after the end of the last neoadjuvant therapy cycle, clinical response was evaluated in all patients using computed tomography (CT), according to the Response Evaluation Criteria in Solid Tumors (RECIST) (19). During surgery, the pathological response was assessed in patients undergoing surgical resection based on intraoperative pathological examinations, according to the Japanese classification of gastric carcinoma (17). Based on the aforementioned classification system, gastric carcinoma was classified into the following four grades: Grade 0, no evidence of effect; grade 1, viable tumor cells in >1/3 of the tumor area; grade 2, viable tumor cells in <1/3 of the tumor area; and grade 3, no viable tumor cells in the tumor area. Viable tumor cells were considered as the cells judged to be capable of proliferating. After surgery, R0 resection was evaluated in patients undergoing surgical resection using formalin-fixed paraffin-embedded tumor specimens. R0 resection was defined as the resection without remaining macroscopic or microscopic residual lesions. Furthermore, the adverse events were recorded and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0; https://ctep.cancer.gov).

All patients were followed up regularly until March 31, 2022. The median follow-up duration was 24.4 months, and the range was from 9.5 to 38.1 months. Based on follow-up information, and disease-free survival (DFS) and overall survival (OS) were calculated. DFS was defined as the time between the date of surgery to disease relapse or death. In addition, OS was defined as the time between the date of surgery and to patient's death.

Control cohort. During the same period, a total of 35 patients with LAGC, who were treated with SOX neoadjuvant chemotherapy, were also reviewed. The screening criteria were as follows: i) Patients diagnosed with gastric adenocarcinoma; ii) >18 years old; iii) with cTNM stage III; iv) ECOG score 0-1; v) with a resectable tumor as determined by tumor resectability assessment, and vi) treated with SOX chemotherapy as a neoadjuvant therapy. The patients who met any of the exclusion criteria set for patients in the apatinib + SOX group were also not eligible for the study. All 35 patients were included in the SOX group. The recommended regimen for patients in the SOX group was as follows: Patients were treated with SOX neoadjuvant chemotherapy for three cycles. After tumor resectability reassessment, surgical resection was performed in patients with resectable tumors (n=33). At 4-8 weeks after surgery, patients were treated with SOX adjuvant chemotherapy for three to five cycles (29 patients received three cycles, one patient received four cycles and three patients received five cycles). The dose of SOX administration was the same as previously described for patients in the apatinib + SOX group. To evaluate clinical outcomes, the clinical response rate was measured in all patients. In addition, pathological response rate, R0 resection rate, DFS and OS were determined in all patients who had undergone surgical resection. The median

Table I. Clinical characteristics of patients with locally advanced gastric carcinoma.

Characteristic	SOX (n=35)	Apatinib + SOX (n=25)	P-value
Age (years), mean ± SD	58.2±9.9	55.2±10.0	0.250
Sex, n (%)			0.880
Female	9 (25.7)	6 (24.0)	
Male	26 (74.3)	19 (76.0)	
Current smoker, n (%)	10 (28.6)	4 (16.0)	0.256
Current drinker, n (%)	14 (40.0)	9 (36.0)	0.753
Hypertension, n (%)	9 (25.7)	7 (28.0)	0.844
Hyperlipidemia, n (%)	12 (34.3)	5 (20.0)	0.226
Diabetes, n (%)	4 (11.4)	2 (8.0)	1.000
Helicobacter pylori infection, n (%)			0.526
Negative	21 (60.0)	17 (68.0)	
Positive	14 (40.0)	8 (32.0)	
Tumor location, n (%)			0.756
Cardia	15 (42.9)	12 (48.0)	
Gastric body	13 (37.1)	7 (28.0)	
Gastric antrum	7 (20.0)	6 (24.0)	
Tumor differentiation, n (%)			0.514
Well	1 (2.9)	2 (8.0)	
Moderate	12 (34.3)	9 (36.0)	
Poor	22 (62.8)	14 (56.0)	
Clinical T stage, n (%)			0.609
T3	12 (34.3)	7 (28.0)	
T4a	23 (65.7)	18 (72.0)	
Clinical N stage, n (%)			0.303
N1	14 (40.0)	7 (28.0)	
N2	13 (37.1)	10 (40.0)	
N3	8 (22.9)	8 (32.0)	
Clinical TNM stage, n (%)			-
Stage III	35 (100.0)	25 (100.0)	

SOX, S-1 plus oxaliplatin; SD, standard deviation; TNM, tumor-node metastasis.

follow-up duration was 20.1 months, and the range was from 6.4 to 36.8 months. Additionally, adverse events were also recorded.

Statistical analysis. All statistical analyses and figure plotting were performed using SPSS 26.0 (IBM Corp.) and GraphPad Prism version 7.02 (GraphPad Software Inc.), respectively. Count data are expressed as percentages, while measurement data are expressed as the mean ± SD. The differences between two groups were compared using a unpaired Student's t-test, a χ^2 test or a Wilcoxon rank sum test. DFS and OS were analyzed using Kaplan-Meier curves and compared using log-rank test. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Clinical characteristics. A total of 35 and 25 patients were included in the SOX and apatinib + SOX groups, respectively. The mean age of patients in the SOX group, including nine females (25.7%) and 26 males (74.3%), was 58.2±9.9 years. Accordingly, six females (24.0%) and 19 males (76.0%) patients were enrolled in the apatinib + SOX group, with a mean age of 55.2±10.0 years. No differences in the demographic characteristics, chronic diseases, *helicobacter pylori* infection, tumor location, tumor differentiation and clinical T, N or TNM stage were observed between the two groups (all $P>0.05$; Table I).

Clinical response. In the SOX group, none of the patients achieved complete response (CR), while 13 (37.1%) patients achieved partial response (PR), 18 (51.4%) stable disease (SD) and four (11.4%) had progressive disease (PD). In addition, the objective response (ORR) and disease control rates (DCR) were 37.1 and 88.6%, respectively. In the apatinib + SOX group, one (4.0%), 15 (60.0%), eight (32.0%) and one (4.0%) patients achieved CR, PR, SD and PD, respectively, while the ORR and DCR were 64.0 and 96.0%, accordingly. Furthermore, comparative analyses revealed that the general response

Table II. Clinical response by RECIST.

Parameter	SOX (n=35)	Apatinib + SOX (n=25)	P-value
Clinical response, n (%)			0.030
CR	0 (0.0)	1 (4.0)	
PR	13 (37.1)	15 (60.0)	
SD	18 (51.4)	8 (32.0)	
PD	4 (11.4)	1 (4.0)	
ORR, n (%)			0.040
No	22 (62.9)	9 (36.0)	
Yes	13 (37.1)	16 (64.0)	
DCR, n (%)			0.580
No	4 (11.4)	1 (4.0)	
Yes	31 (88.6)	24 (96.0)	

RECIST, Response Evaluation Criteria in Solid Tumors; SOX, S-1 plus oxaliplatin; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate.

Table III. R0 resection and pathological response rates.

Parameter	SOX (n=33)	Apatinib + SOX (n=24)	P-value
R0 resection, n (%)			0.847
No	3 (9.1)	1 (4.2)	
Yes	30 (90.9)	23 (95.8)	
Pathological response, n (%)			0.030
Grade 0	3 (9.1)	0 (0.0)	
Grade 1	13 (39.4)	5 (20.8)	
Grade 2	14 (42.4)	15 (62.5)	
Grade 3	3 (9.1)	4 (16.7)	

SOX, S-1 plus oxaliplatin.

rate (P=0.030) and ORR (64.0% vs. 37.1%; P=0.040) were increased in the apatinib + SOX group compared with the SOX group. However, no differences in DCR (96.0 vs. 88.6%) were revealed between the apatinib + SOX and SOX groups (P=0.580; Table II).

R0 resection and pathological response. Tumor resectability reassessment was conducted at 4 weeks after the end of the last neoadjuvant therapy cycle. The results showed that 2/4 patients with PD in the SOX group and 1 patient with PD in the apatinib + SOX group could not be treated by surgery. Therefore, R0 resection rate, pathological response rate, DFS and OS were not determined in these patients. Finally, the data form 33 patients in the SOX group and 24 patients in the apatinib + SOX group were analyzed. In the SOX group, the R0 resection rate was 90.9%. In terms of pathological response, three (9.1%) patients were of grade 0, 13 (39.4%) of grade 1, 14 (42.4%) of grade 2 and three (9.1%) of grade 3. In the apatinib + SOX group, R0 resection rate was 95.8%, while 0 (0.0%), 5 (20.8%), 15 (62.5%) and 4 (16.7%) patients were of pathological response grade of 0, 1, 2 and 3, respectively. Overall, the pathological response rate was higher in the apatinib + SOX group compared with the SOX group (P=0.030), while no differences in the R0 resection rate (95.8 vs. 90.9%) were observed between the two groups (P=0.847; Table III).

Survival. During a median follow-up period of 21.0 months (range, 6.4-38.1 months), median DFS and OS were not reached in both groups (Fig. 1A and B). More specifically, the 1-, 2- and 3-year DFS rates in the SOX group were 71.8, 59.6 and 44.7%, respectively. Additionally, in the apatinib + SOX group, the 1-, 2- and 3-year DFS rates were 91.7, 75.2 and 75.2%, respectively. However, no statistical differences were observed in DFS between the two groups (P=0.094; Fig. 1A). In the SOX group, the 1-, 2- and 3-year OS rates were 90.3, 69.2 and 55.4%, respectively, while those in the apatinib + SOX group were 100.0, 89.6 and 78.4%, accordingly. Consistently, no differences in OS were obtained between both groups (P=0.155; Fig. 1B).

Adverse events. The main adverse events of SOX chemotherapy included leukopenia (42.9%), fatigue (34.3%), anemia (31.4%), hand-foot syndrome (28.6%), elevated transaminase (28.6%)

Table IV. Adverse events.

Adverse event	SOX (n=35)			Apatinib + SOX (n=25)		
	Total	Grade 1-2	Grade 3-4	Total	Grade 1-2	Grade 3-4
Leukopenia, n (%)	15 (42.9)	14 (40.0)	1 (2.9)	11 (44.0)	11 (44.0)	0 (0.0)
Hypertension, n (%)	10 (28.6)	10 (28.6)	0 (0.0)	11 (44.0)	9 (36.0)	2 (8.0)
Thrombocytopenia, n (%)	8 (22.9)	8 (22.9)	0 (0.0)	9 (36.0)	8 (32.0)	1 (4.0)
Hand-foot syndrome, n (%)	10 (28.6)	10 (28.6)	0 (0.0)	8 (32.0)	7 (28.0)	1 (4.0)
Elevated transaminase, n (%)	10 (28.6)	9 (25.7)	1 (2.9)	8 (32.0)	7 (28.0)	1 (4.0)
Pruritus, n (%)	10 (28.6)	10 (28.6)	0 (0.0)	7 (28.0)	7 (28.0)	0 (0.0)
Neutropenia, n (%)	9 (25.7)	8 (22.9)	1 (2.9)	7 (28.0)	5 (20.0)	2 (8.0)
Proteinuria, n (%)	2 (5.7)	2 (5.7)	0 (0.0)	6 (24.0)	6 (24.0)	0 (0.0)
Nausea and vomiting, n (%)	7 (20.0)	6 (17.1)	1 (2.9)	6 (24.0)	5 (20.0)	1 (4.0)
Fatigue, n (%)	12 (34.3)	11 (31.4)	1 (2.9)	5 (20.0)	5 (20.0)	0 (0.0)
Anemia, n (%)	11 (31.4)	10 (28.6)	1 (2.9)	5 (20.0)	4 (16.0)	1 (4.0)
Diarrhea, n (%)	5 (14.3)	5 (14.3)	0 (0.0)	4 (16.0)	4 (16.0)	0 (0.0)
Anorexia, n (%)	4 (11.4)	4 (11.4)	0 (0.0)	4 (16.0)	4 (16.0)	0 (0.0)
Increased bilirubin, n (%)	4 (11.4)	4 (11.4)	0 (0.0)	3 (12.0)	3 (12.0)	0 (0.0)
Fever, n (%)	3 (8.6)	3 (8.6)	0 (0.0)	2 (8.0)	2 (8.0)	0 (0.0)

SOX, S-1 plus oxaliplatin.

and pruritus (28.6%). The grade 3-4 adverse events included leukopenia (2.9%), elevated transaminase (2.9%), neutropenia (2.9%), nausea and vomiting (2.9%), fatigue (2.9%) and anemia (2.9%). The rest of the adverse events were of grade 1-2. Accordingly, the most common adverse events recorded in patients treated with neoadjuvant apatinib plus SOX chemotherapy were leukopenia (44.0%), hypertension (44.0%), thrombocytopenia (36.0%) and hand-foot syndrome (32.0%), and elevated transaminase (32.0%). The grade 3-4 adverse events were hypertension (8.0%), thrombocytopenia (4.0%), hand-foot syndrome (4.0%), elevated transaminase (4.0%), neutropenia (8.0%), nausea and vomiting (4.0%) and anemia (4.0%). Finally, the rest of the adverse events were of grade 1-2 (Table IV).

Discussion

A previous study revealed that ORR, DCR and R0 resection rates are 60.0, 84.4 and 64.4%, respectively, in patients with LAGC treated with neoadjuvant SOX chemotherapy (20). Additionally, another study showed that the R0 resection and pathological response rates are 87.2 and 59.5%, respectively, in SOX chemotherapy-treated patients (21). However, several patients with LAGC fail to show obvious survival benefits from neoadjuvant SOX chemotherapy mainly due to chemoresistance (9,12,22). Therefore, several clinical trials have investigated the effect of antiangiogenic drugs combined with chemotherapy as neoadjuvant therapies to improve treatment responses in patients with LAGC (12,13,23). Notably, two single-arm trials suggest that neoadjuvant apatinib plus SOX chemotherapy exhibits promising efficacy in patients with LAGC (12,13).

More specifically, regarding treatment response, ORR and DCR in patients treated with apatinib combined with SOX chemotherapy are 79.3 and 96.6%, respectively. Furthermore, the grade 3 pathological response rate is 13.8% in the aforementioned patients (12). Another study has demonstrated that CR, PR, SD and PD are 5, 70, 20 and 5%, respectively, in patients

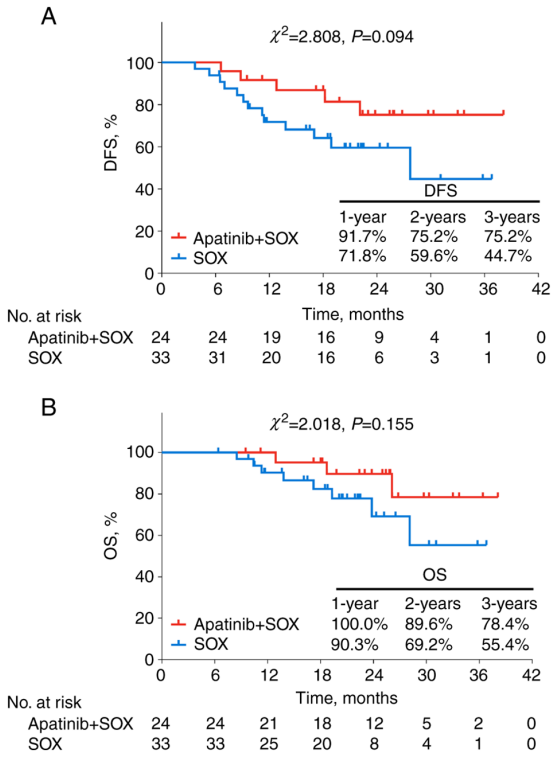

Figure 1. Survival of patients after treatment. (A) Comparison of disease-free survival between apatinib + SOX and SOX groups. (B) Comparison of overall survival between apatinib + SOX and SOX groups. SOX, S-1 plus oxaliplatin; DFS, disease-free survival; OS, overall survival.

with LAGC treated with apatinib plus chemotherapy (13). In the current study, the results indicated that ORR was 64%. In addition, grade 0, 1, 2, and 3 pathological responses were 0.0, 20.8, 62.5 and 16.7%, respectively, in patients treated with neoadjuvant apatinib combined with SOX chemotherapy, which was superior compared with SOX chemotherapy alone. The possible reasons could be the following: i) Apatinib could suppress VEGFR2 activation and subsequently inhibit the VEGFR2 downstream pathways involved in angiogenesis, such as the PI3K/AKT/mTOR and MAPK pathways, consequently inhibiting tumor activity in LAGC (13,15,24); and ii) the synergistic effect of anti-angiogenetic drugs with chemotherapy could display improved efficacy (25).

At present, the survival rate of patients with LAGC remains unsatisfactory (7,20,21,26). For instance, a study revealed that the 3-year RFS and OS rates in patients with LAGC treated with neoadjuvant SOX chemotherapy are 53.2 and 62.9%, respectively (21). Additionally, another study showed that the 3- and 5-year OS rates are 55.1 and 25.8%, respectively, in patients treated with neoadjuvant SOX chemotherapy alone (20). However, the data regarding the survival of patients treated with neoadjuvant apatinib combined with SOX chemotherapy are obscure. Therefore, the current study aimed to explore the survival rate of the above patients.

The results showed that during a median follow-up period of 21.0 months (range, 6.4-38.1 months), the 1-, 2- and 3-year DFS rates were 91.7, 75.2 and 75.2%, respectively, while the 1-, 2- and 3-year OS rates were 100.0, 89.6, and 78.4%, respectively, in patients receiving neoadjuvant apatinib plus SOX chemotherapy. DFS and OS were increased in patients treated with neoadjuvant apatinib combined with SOX chemotherapy compared with those treated with SOX chemotherapy alone. However, the trend did not reach statistical significance. The above finding could be due to the following reasons: i) The favorable treatment response of apatinib combined with SOX chemotherapy could result in satisfactory survival; ii) apatinib could synergize with the chemotherapeutic drug, eventually leading to improved efficacy of the neoadjuvant therapy (25); iii) the short-term follow-up period and the limited sample size could lead to reduced events of disease recurrence and death. Therefore, it could be difficult to observe statistically significant differences in survival between the two cohorts; and iv) surgery and adjuvant chemotherapy could affect survival, which in turn could affect the differences in survival between the two groups.

Emerging evidence has suggested that the most common adverse events associated with apatinib are mild hand-foot syndrome, hypertension, proteinuria and neutropenia (27,28). Furthermore, it has been also reported that the main neoadjuvant SOX chemotherapy-related toxic effects in patients with LAGC are grade 1-2 leukopenia, neutropenia, thrombocytopenia, and amenia (29). Herein, the main adverse events of SOX chemotherapy included leukopenia, fatigue and anemia, while those of neoadjuvant apatinib combined with SOX chemotherapy were leukopenia, hypertension, thrombocytopenia, hand-food syndrome and neutropenia. The majority of the adverse events belonged to grades 1-2. Interestingly, the adverse events of neoadjuvant apatinib combined with SOX chemotherapy were not more severe than those reported for SOX chemotherapy in a previous study (29). Therefore, the results of the current study further supported the safety profile of neoadjuvant apatinib combined with SOX chemotherapy in patients with LAGC.

However, the present study has several limitations. Firstly, the sample size was relatively small; thus, in order to clarify the influence of the small sample size, the confidence level and margin of error of group difference in ORR, DCR, R0 resection and the pathological response were calculated and presented in Table SI. Additionally, in the present study, the quality of life in patients with LAGC after apatinib combined with SOX chemotherapy and SOX chemotherapy alone was not assessed. Therefore, further studies are needed.

In conclusion, the present study demonstrated that neoadjuvant apatinib plus SOX chemotherapy was more effective and well-tolerated compared with SOX chemotherapy alone in patients with LAGC.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

DY and ZW made substantial contributions to the conception and design of the current study. TH and XQ performed the experiments and collected data. AG and HY interpreted the data, and drafted and revised the manuscript. DY and ZW confirm the authenticity of the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Institutional Review Board of The Second People's Hospital of Liaocheng [approval no. (2018)0203; Linqing, China]. Written informed consent was collected from all patients.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Mukkamalla SKR, Recio-Boiles A and Babiker HM: Gastric Cancer. In: StatPearls [Internet]. Treasure Island (FL); StatPearls Publishing, 2022.

2. Goetze OT, Al-Batran SE, Chevallay M and Monig SP: Multimodal treatment in locally advanced gastric cancer. Updates Surg 70: 173-179, 2018.
3. Wang FH, Shen L, Li J, Zhou ZW, Liang H, Zhang XT, Tang L, Xin Y, Jin J, Zhang YJ, *et al*: The Chinese Society of Clinical Oncology (CSCO): Clinical guidelines for the diagnosis and treatment of gastric cancer. Cancer Commun (Lond) 39: 10, 2019.
4. Sada YH, Smaglo BG, Tran Cao HS, Mok H, Musher BL and Massarweh NN: National trends in multimodality therapy for locally advanced gastric cancer. J Surg Res 237: 41-49, 2019.
5. Johnston FM and Beckman M: Updates on management of gastric cancer. Curr Oncol Rep 21: 67, 2019.
6. Patel TH and Cecchini M: Targeted therapies in advanced gastric cancer. Curr Treat Options Oncol 21: 70, 2020.
7. Sah BK, Zhang B, Zhang H, Li J, Yuan F, Ma T, Shi M, Xu W, Zhu Z, Liu W, *et al*: Neoadjuvant FLOT versus SOX phase II randomized clinical trial for patients with locally advanced gastric cancer. Nat Commun 11: 6093, 2020.
8. Reddavid R, Sofia S, Chiaro P, Colli F, Trapani R, Esposito L, Solej M and Degiuli M: Neoadjuvant chemotherapy for gastric cancer. Is it a must or a fake? World J Gastroenterol 24: 274-289, 2018.
9. Marin JJ, Al-Abdulla R, Lozano E, Briz O, Bujanda L, Banales JM and Macias RI: Mechanisms of resistance to chemotherapy in gastric cancer. Anticancer Agents Med Chem 16: 318-334, 2016.
10. Luo H, Wu L, Huang M, Jin Q, Qin Y and Chen J: Postoperative morbidity and mortality in patients receiving neoadjuvant chemotherapy for locally advanced gastric cancers: A systematic review and meta-analysis. Medicine (Baltimore) 97: e12932, 2018.
11. Mohamed Abd Elaziz L, Salah T and Gharib F: The role of neoadjuvant FLOT chemotherapy with and without omega 3 in locally advanced gastric carcinoma. J BUON 25: 2672-2677, 2020.
12. Zheng Y, Yang X, Yan C, Feng R, Sah BK, Yang Z, Zhu Z, Liu W, Xu W, Ni Z, *et al*: Effect of apatinib plus neoadjuvant chemotherapy followed by resection on pathologic response in patients with locally advanced gastric adenocarcinoma: A single-arm, open-label, phase II trial. Eur J Cancer 130: 12-19, 2020.
13. Lin JX, Xu YC, Lin W, Xue FQ, Ye JX, Zang WD, Cai LS, You J, Xu JH, Cai JC, *et al*: Effectiveness and safety of apatinib plus chemotherapy as neoadjuvant treatment for locally advanced gastric cancer: A nonrandomized controlled trial. JAMA Netw Open 4: e2116240, 2021.
14. Shitara K, Honma Y, Omuro Y, Yamaguchi K, Chin K, Muro K, Nakagawa S, Kawakami S, Hironaka S and Nishina T: Efficacy of trastuzumab emtansine in Japanese patients with previously treated HER2-positive locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma: A subgroup analysis of the GATSBY study. Asia Pac J Clin Oncol 16: 5-13, 2020.
15. Scott LJ: Correction to: Apatinib: A review in advanced gastric cancer and other advanced cancers. Drugs 78: 759, 2018.
16. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET and Carbone PP: Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 5: 649-655, 1982.
17. Japanese Gastric Cancer Association: Japanese classification of gastric carcinoma: 3rd English edition. Gastric Cancer 14: 101-112, 2011.
18. Zhang X, Liang H, Li Z, Xue Y, Wang Y, Zhou Z, Yu J, Bu Z, Chen L, Du Y, *et al*: Perioperative or postoperative adjuvant oxaliplatin with S-1 versus adjuvant oxaliplatin with capecitabine in patients with locally advanced gastric or gastro-oesophageal junction adenocarcinoma undergoing D2 gastrectomy (RESOLVE): An open-label, superiority and non-inferiority, phase 3 randomised controlled trial. Lancet Oncol 22: 1081-1092, 2021.
19. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, *et al*: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 45: 228-247, 2009.
20. Zhang X, Huang H, Wei Z, Zhu Z, Yang D, Fu H, Xu J, Hu Z, Zhang Y, You Q, *et al*: Comparison of Docetaxel + Oxaliplatin + S-1 vs Oxalipatin + S-1 as neoadjuvant chemotherapy for locally advanced gastric cancer: A propensity score matched analysis. Cancer Manag Res 12: 6641-6653, 2020.
21. Iwatsuki M, Orita H, Kobayashi K, Hidaka S, Arigami T, Kusumoto T, Satake H, Oki E, Tsutsumi S, Tobimatsu K, *et al*: Phase II study of S-1 and oxaliplatin as neoadjuvant chemotherapy for locally advanced adenocarcinoma of the gastric or esophagogastric junction: KSCC1601. Gastric Cancer 25: 180-187, 2022.
22. Teng R, Hu Y, Zhou J, Seifer B, Chen Y, Shen J and Wang L: Overexpression of Lin28 decreases the chemosensitivity of gastric cancer cells to oxaliplatin, paclitaxel, doxorubicin, and fluorouracil in part via microRNA-107. PLoS One 10: e0143716, 2015.
23. Ma J, Yao S, Li XS, Kang HR, Yao FF and Du N: Neoadjuvant therapy of DOF regimen plus bevacizumab can increase surgical resection ratein locally advanced gastric cancer: A randomized, controlled study. Medicine (Baltimore) 94: e1489, 2015.
24. Liu K, Ren T, Huang Y, Sun K, Bao X, Wang S, Zheng B and Guo W: Apatinib promotes autophagy and apoptosis through VEGFR2/STAT3/BCL-2 signaling in osteosarcoma. Cell Death Dis 8: e3015, 2017.
25. Feng J and Qin S: The synergistic effects of Apatinib combined with cytotoxic chemotherapeutic agents on gastric cancer cells and in a fluorescence imaging gastric cancer xenograft model. Onco Targets Ther 11: 3047-3057, 2018.
26. Li Z, Shan F, Ying X, Zhang Y, E JY, Wang Y, Ren H, Su X and Ji J: Assessment of laparoscopic distal gastrectomy after neoadjuvant chemotherapy for locally advanced gastric cancer: A randomized clinical trial. JAMA Surg 154: 1093-1101, 2019.
27. Li J, Qin S, Xu J, Xiong J, Wu C, Bai Y, Liu W, Tong J, Liu Y, Xu R, *et al*: Randomized, double-blind, placebo-controlled phase III trial of apatinib in patients with chemotherapy-refractory advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction. J Clin Oncol 34: 1448-1454, 2016.
28. Geng R, Song L, Li J and Zhao L: The safety of apatinib for the treatment of gastric cancer. Expert Opin Drug Saf 17: 1145-1150, 2018.
29. Zhao Q, Li Y, Huang J, Fan L, Tan B, Tian Y, Yang P, Jiao Z, Zhao X, Zhang Z, *et al*: Short-term curative effect of S-1 plus oxaliplatin as perioperative chemotherapy for locally advanced gastric cancer: A prospective comparison study. Pharmazie 72: 236-240, 2017.