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Original Article

Adjuvant chemotherapy for chemotherapy-naive advanced gastric cancer patients with oxaliplatin plus tegafur versus oxaliplatin plus S-1

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Abstract: Background: Advanced gastric cancer (AGC) causes a huge economic burden to the society. This open-label study was conducted to compare the efficacy and acceptability of oxaliplatin plus tegafur (OXT) vs. oxaliplatin plus S-1 (OXS) for chemotherapy-naive advanced gastric cancer patients. Material and methods: In this study, patients were randomly assigned to receive OXT or OXS. In a 3-week treatment cycle, the S-1 was given 80-120 mg/day for 2 weeks, tegafur was given 1 g/day for the first five days and oxaliplatin was given 130 mg/m^2 on day 1. The following indexes were assessed: progression-free survival (PFS), overall survival (OS), overall response rate (ORR), disease control rate (DRR) and adverse events. Results: Totally, 332 AGC patients were recruited to receive OXT (164 patients) or OXS (168 patients). The recruited patients had at least one metastatic site, and most of them were curatively unresectable. The median PFS for OXT and OXS were 6.1 and 5.5 months, respectively. The median PFS for OXT and OXS were 14.2 and 13.4 months, respectively. No significant difference was found in the PFS and OS. The OXT and OXS had comparable ORR (44.5% vs. 48.8%) and DRR (71.9% vs. 72.6%). The hyponatremia, diarrhea, nausea, vomiting, anorexia and constipation were more frequently observed in OXT than in OXS. Conclusions: These results showed that OXS was as effective as OXT for AGC patients with favorable safety profile; therefore, OXS could be a potential replacement method for OXT.

Keywords: Advanced gastric cancer, AGC, S-1, oxaliplatin, tegafur

Introduction

Gastric cancer is one of the common gastrointestinal cancers in clinical practice with high mortality. This cancer accounts for 8% of new cancer cases and 10% of cancer-related deaths in the worldwide. Siegel et al. reported that the number of new gastric cancer cases and its related deaths would be 24,590 and 10,720, respectively, in 2015 in the USA [1]. In China, the incidence of this cancer is very high. Previous study reported that about 46.8% of new cases and 47.8% deaths in the worldwide were reported from China [2]. Nowadays, surgical resection is the mainstay of treatment for this cancer. But, most patients miss the chance of curative treatment and have to receive palliative chemotherapy [3].

Currently, the combination therapies based on platinum drugs have been widely viewed as the first-line treatments for advanced gastric cancer (AGC) [4-6]. However, there is still no standard regimen for chemotherapy of AGC [7]. Cisplatin, as a platinum drug, has an important role in the treatment of AGC. Oxalipatin, as a new promising anticancer drug, is also effective in treating AGC [8]. A trial found that the combination of 5-fluorouracil (5-FU) and oxaliplatin was as effective as the combination of 5-fluorouracil (5-FU) and cisplatin in treating metastatic gastroesophageal adenocarcinoma [9]. Another study reported that oxaliplatin plus S-1 (OXS) was equivalent to cisplatin plus S-1 (CS) in treating AGC [10]. In Japan, CS is viewed as the standard first-line treatment for AGC, and some studies suggested that cisplatin plus 5-FU could be replaced by CS [11, 12]. Meanwhile, a phase II trial reported that the OXS could yield a promising outcome with good tolerability for AGC treatment [13]. But, few studies investigated whether the OXS could be a

substitute for oxaliplatin plus tegafur (OXT) in treating AGC. Therefore, we conducted this study to compare the efficacy and acceptability of OXT *vs.* OXS for chemotherapy-naive advanced gastric cancer patients.

Materials and methods

Recruited patients

AGC patients were recruited from the Department of Gastrointestinal Colorectal and Anal Surgery, China-Japan Union Hospital, Jilin University. Our work was approved by the Ethical Committee of Jilin University, and the procedure was strictly conducted according to the approved guidelines. The main inclusion criteria included: 1) age >18 years; 2) the histologically proven, curatively unresectable, advanced or recurrent gastric cancer; 3) tumor-node-metastasis (TNM) stage IIIb-IV; 4) the confirmed measureable lesions by computed tomography; 5) oral intake capability; 6) previously received no radiotherapy or chemotherapy. Additionally, patients were not recruited if they: 1) had active infection, markedly impaired cardiac function, serious concurrent disease, gastrointestinal bleeding, interstitial pneumonia, serious diarrhea, and pleural effusion; 2) had a history of blood transfusion 3 weeks before enrollment; 3) previously received platinum as an adjuvant chemotherapy. The written informed consent was provided by patients or their families before treatment.

Study design

This study was a prospective, single-center, open-label randomized clinical trial conducted at China. AGC patients meeting the inclusion/exclusion criteria were randomly (about 1:1 ratio) assigned to receive OXT or OXS, considering the demographics and clinical characteristics data as the adjustment factors using the minimization method. The randomization was performed using a computer-generated random number sequence. The treatment methods in this study were not masked from the investigators or the patients.

Treatment methods

In OXS group, S-1 was given orally twice daily after the breakfast and dinner for the first two weeks of a 3-week cycle. The dose was 40 mg/time for body surface area (BSA)<1.25 m^2, 50 mg/time for 1.25 m^2≤BSA<1.5 m^2 and 60 mg/time for BSA≥1.5 m^2. In OXT group, tegafur was given 1 g/day with a slow intravenous injection in the first five days of a 3-week cycle. In both treatment groups, oxaliplatin at 130 mg/m^2 with 500 ml 5% glucose injection was intravenous infused for 2 hours at the first day of each cycle [13]. Each patient received computed tomography scan to assess the efficacy at the end of the second week of a 3-week cycle. The treatments were continued for eight cycles until one of the criteria (consent withdrawal; indications for surgery; serious adverse events and other reasons) for withdrawal of the study treatment was encountered.

Outcomes assessment

Progression-free survival (PFS) was defined as the time from the initiation of treatment to the documented progressive disease. Overall survival (OS) was defined as the interval from the randomization to the death from any cause or the last follow-up date. The primary endpoint was to evaluate the efficacy in PFS in the two groups, and the other primary endpoint was to assess the efficacy in OS in the two groups. The clinical efficacy was assessed by the response evaluation criteria in solid tumors (RECIST). The complete remission (CR), partial remission (PR), stable disease (SD) and disease progression (PD) was defined as no tumor, tumor shrinkage of more than 30%, tumor shrinkage of 20%-30% and tumor increased more than 20% or new tumor, respectively. The overall response rate (ORR) was defined as the sum of CR and PR divided by the total number of evaluable patients, and the disease control rate (DRR) was defined as the sum of CR, PR and SD divided by the total number of evaluable patients. Adverse events were assessed according to the Common Terminology Criteria for Adverse Events, version 3.0 (CTCAE version 3.0).

Statistical analyses

Continuous and dichotomous data were showed as the mean ± standard deviation (SD) and number with percentage, respectively. The student's T test was used to assess whether the demographics and clinical characteristics data were matched between two groups. The chi-square test was used to assess the ORR and DRR. The Kaplan-Meier test was used to do

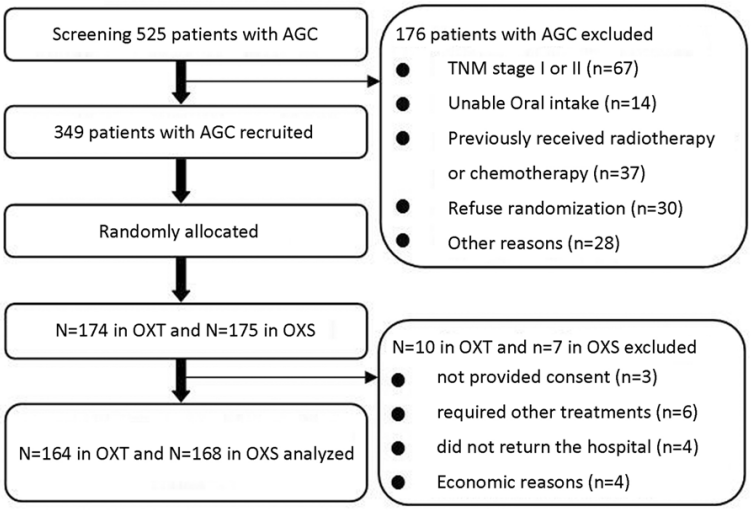

Figure 1. The flow diagram of this study.

Table 1. Baseline characteristics of the included patients

Variables	OXT	OXS	*P*-value
Gender			
Female	71	80	0.429
Male	93	88	
Age			
>60	48	53	0.652
≤60	116	115	
Primary tumor site			
Cardia	37	34	0.739
Gastric body	79	88	
Pylorus	48	46	
TNM stage			
IIIb	92	101	0.458
IV	72	67	
Unresectable	127	131	0.906
Recurrent	37	37	
Adjuvant chemotherapy (+)	20	18	
Adjuvant chemotherapy (-)	17	19	
Locally advanced incurable	54	62	
Distant metastatic disease	110	106	
No. of metastatic sites			
1	37	36	0.868
2	103	110	
≥3	24	22	

survival analysis using the time-to-events data. The stratified Cox proportional hazards model was used to calculate the hazard ratios (HR). The multivariate analyses were performed on demographic and stratification factors in the model. Statistical analyses were conducted using SPSS 19.0.

Results

Patient's characteristics

At first, 525 patients with AGC were strictly screened according to the aforementioned inclusion/exclusion criteria, and 176 patients were excluded. Then, the 349 patients were enrolled to randomly assign into the OXT group (174 patients) and OXS group (175 patients). Before the treatment, 10 patients in OXT group and 7 patients in OXS group were excluded. The reasons of exclusion included: 1) not provided consent; 2) required other treatments; 3) did not return the hospital; 4) abandoned the treatments due to the economic reasons. Finally, there were 164 patients receiving OXT and 168 patients receiving OXS (**Figure 1**). The demographic characteristics of patients in the two groups were well balanced (**Table 1**).

ORR and DRR

At the end of study, there were 73 patients in OXT group and 82 patients in OXS group responding to the treatment (**Table 2**). Compared to the OXT group, the OXS group had more patients that met the criteria of CR and PR, but there was no significantly different about the ORR between the two groups (P=0.702). There were 45 SD patients in OXT group and 40 SD patients in OXS group. The number of PD patients in OXT and OXS group was 46 and 46, respectively. The difference of DRR between the two groups were also not significant (P= 0.892).

PFS and OS

The median follow-up for PFS was 7.1 months (inter-quartile range (IQR)=3.0-9.8 months). The median PFS in OXS and OXT groups was 6.1 months (95% CI=5.6-6.4 months, 130 events) and 5.5 months (95% CI=4.6-6.2 months, 134 events), respectively (**Figure 2**). The HR

Table 2. Clinical efficacy of OXT and OXS at the end of treatment

Group	CR	PR	ORR	SD	PD	DRR
OXT	10 (6.1%)	63 (38.4%)	73 (44.5%)	45 (27.4%)	46 (28.1%)	118 (71.9%)
OXS	12 (7.1%)	70 (41.7%)	82 (48.8%)	40 (23.8%)	46 (27.4%)	122 (72.6%)
χ^2	-	-	0.147	-	-	0.018
p-value	-	-	0.702	-	-	0.892

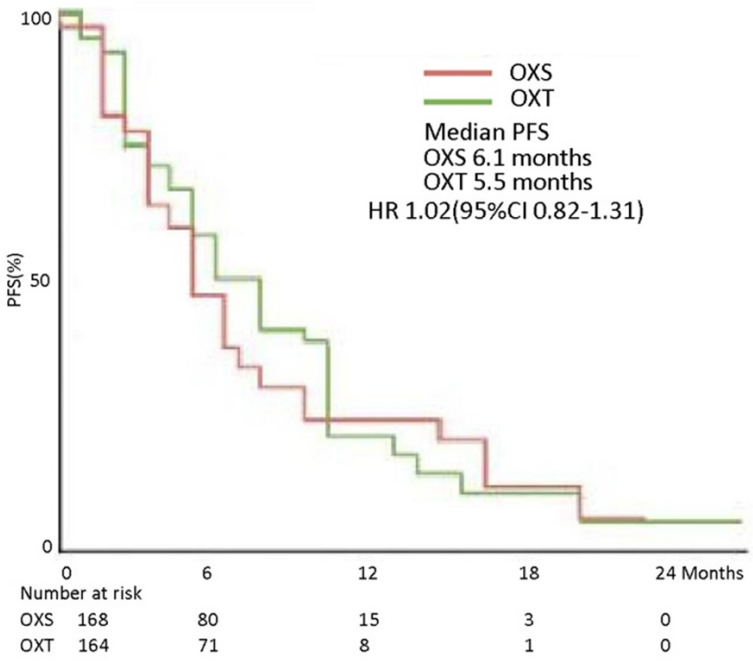

Figure 2. Kaplan-Meier curves for PFS.

was 1.02 (95% CI=0.82-1.31). The median follow-up for OS was 25.2 months (IQR=21.8-28.7 months). The media OS in OXS and OXT groups was 14.2 months (95% CI=13.1-16.0 months, 134 events) and 13.4 months (95% CI=12.2-15.1 months, 140 events), respectively (**Figure 3**). The HR was 0.96 (95% CI=0.80-1.39). Multivariate analyses showed that the poor prognosis in OS was related with TNM stage (IV), unresectable disease and distant metastatic disease. The adjusted HR in the treatment efficacy for OS was 0.95 (95% CI= 0.81-1.37).

Adverse events

The main treatment-related adverse events in the two groups were displayed in the **Table 3**. The Hyponatremia, diarrhea, nausea, vomiting, anorexia and constipation were more frequently observed in OXT group than in OXS group. No remarkable differences were observed in the incidence of thrombocytopenia, stomatitis, fatigue, sensory neuropathy, renal dysfunction and Liver dysfunction between the two groups. Grade 3 or worse nausea, vomiting and constipation were more frequently observed in OXT group than in OXS group.

Discussion

Gastric cancer accounts for a high portion of cancer-related death globally. In china, this cancer is a highly prevalent gastrointestinal malignancy, and the five-year survival rate of patient with AGC was reported by only about 20%-36% [14]. Currently, surgical resection is still the potentially curative for early gastric cancer patients. But for many patients, the surgery alone could not reach to the biologically significant radical cure. Therefore, developing alternative treatment methods is an important objective for patients with AGC. Neoadjuvant chemotherapy was first used to treat gastric cancer in 1989 [15]. Nowadays, many studies showed that this method, such as cisplatin and docetaxel, could be very useful during AGC management [16, 17]. But, the standard neoadjuvant chemotherapy is still not established.

In this study, we recruited 332 patients with AGC to compare the efficacy and acceptability of OXT and OXS. We found that these two methods had comparable median PFS (6.1 months in OXS *vs.* 5.5 months in OXT) and median OS (14.2 months in OXS *vs.* 13.4 months in OXT). Moreover, the OXS and OXT had the similar ORR (48.8% vs. 44.5%) and DRR (72.6% *vs.* 71.9%). These results indicated that these two methods had the comparable efficacy in

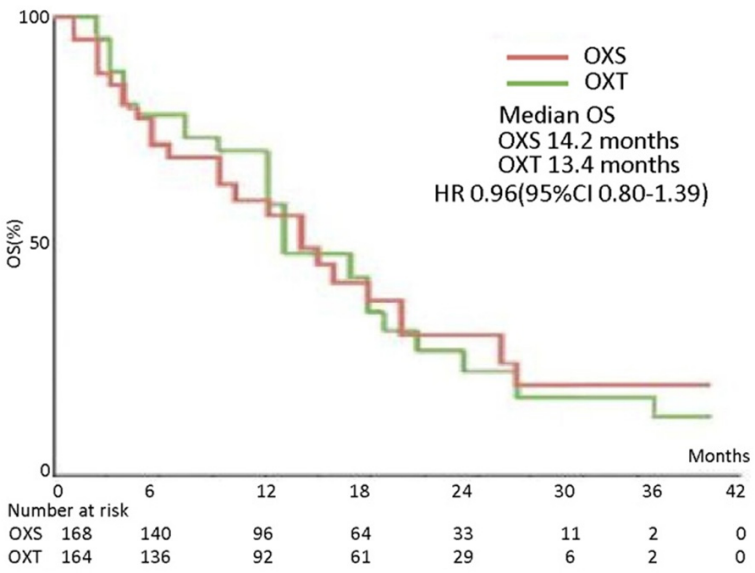

Figure 3. Kaplan-Meier curves for OS.

Table 3. Treatment-related adverse events in the OXT and OXS groups

Adverse events	OXT		OXS		*P*-value	
	Any	Grade ≥3	Any	Grade ≥3	Any	Grade ≥3
Leukopenia	92	6	101	8	0.458	0.617
Anemia	85	25	98	30	0.234	0.552
Thrombocytopenia	80	10	70	8	0.193	0.591
Hyponatremia	61	8	35	6	0.001	0.554
Diarrhea	83	6	61	6	0.009	0.966
Nausea & Vomiting	134	36	108	15	0.0003	0.001
Stomatitis	67	5	53	1	0.078	0.093
Anorexia	125	22	108	18	0.017	0.450
Constipation	105	27	74	11	0.0002	0.005
Fatigue	86	12	91	10	0.926	0.617
Sensory neuropathy	130	6	139	8	0.420	0.618
Renal dysfunction	22	5	18	2	0.450	0.279
Liver dysfunction	45	0	50	1	0.640	0.985

the treatment of AGC patients. The results of OXS was similar to those observed in a phase III study (median PFS 5.5 months and OS 14.1 months in OXS) [10], which suggested the robustness of our findings.

The adverse events observed for OXS in this study were similar to the previously reported results [10]. Takechi *et al*. reported that S-1 could protect the gastrointestinal tract from 5-FU-induced toxicity, but not decreased the antitumor activity [18]. Here, we found that the OXS had considerable advantages in safety over OXT: grade 3 or worse nausea, vomiting and constipation were more frequently observed in OXT, and all grade of hyponatremia, diarrhea, nausea, vomiting, anorexia and constipation developed were more commonly in OXT. Additionally, in **Table 3**, we found that the incidence of peripheral sensory neuropathy in both groups was very high. This was because this adverse event was mainly induced by oxaliplatin. However, previous study reported that this adverse event could not hinder the use of subsequent chemotherapy [10].

As a new oral antitumor agent, S-1 was composed of tegafur, potassium oxonate (OXO) and 5-chloro-2,4-dihydroxypyridine (CDHP) (a molar ratio of 1:1:0.4). The tegafur was a pro-drug of-FU and acted as an effector, and the latter two drugs acted as modulators [18, 19]. In human body, under the mediation of cytochrome P-450, tegafur was bio-activated to 5-FU to produce anti-tumor effects [20]. But the 5-FU could be deactivated by the dihydropyrimidine dehydrogenase (DPD) in liver. CDHP, as a DPD inhibitor, could decrease the catabolism of 5-FU, and then significantly increased the plasma concentrations of 5-FU [21, 22]. Meanwhile, OXO could decrease the gastrointestinal toxicity of 5-FU by inhibiting the 5-FU phosphorylation in gastrointestinal tract [23]. These factors might explain the higher acceptability of OXS than OXT in this study.

Although there was no standard regimen for chemotherapy of AGC, and the neoadjuvant therapy was not standard in Asia [7], the multimodality therapy including neoadjuvent the-

rapy was regarded as the standard therapy for patients with stage 2B and above [24]. Meanwhile, in many western series, stage 3B was still regarded as be suitable for attempted curative treatment using multimodality therapy including neoadjuvent therapy, but in Asia, it was usually treated as be not amenable to curative treatment [25]. These phenomena might be caused by the geographical difference. Previous studies showed that this difference could limit the applicability of the similar findings [26, 27]. Additionally, due to the different pharmacokinetics and toxicities of S-1 among the Asia patients and others, this drug was not widely used outside of Asia [28, 29].

Limitations of this study included: i) although there were about 160 patients in each group, the sample size was referred to the similar studies [30, 31], not based on primary endpoints; ii) the HER2 expression in tumors was not tested here, then its exact influence on the findings was unclear and needed future studies to find out; iii) S-1 was not widely used outside of Asia, then clinicians should be cautious in using OXS for AGC patients outside of Asia.

This study found that the OXS was non-inferior to OXT in terms of PFS and OS for in treating patients with AGC. Also, the ORR and DRR of the two treatment methods were similar. However, the OXS had less treatment-related adverse events than OXT, and then was more acceptability. The acceptability was an important factor for AGC patients, especially for the elder patients. Therefore, the clinical applicability of OXS showed greater promise, and OXS should be treated as a potential replacement method for OXT to further explore.

Disclosure of conflict of interest

None.

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