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ORIGINAL ARTICLE

Retrospective Study

Adjuvant chemotherapy with S-1 plus oxaliplatin improves survival of patients with gastric cancer after D2 gastrectomy: A multicenter propensity score-matched study

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Abstract

AIM

To investigate the safety and efficacy of S-1 plus oxaliplatin (SOX) as an adjuvant chemotherapy regimen in gastric cancer (GC) after D2 dissection.

METHODS

GC Patients who underwent D2 gastrectomy from September 2009 to December 2011 in four Chinese institutions were enrolled. Patients with stage ⅠB-ⅢC GC, who received adjuvant SOX treatment were matched by propensity scores with those who underwent surgery alone and those who conducted capecitabine plus oxaliplatin (XELOX) regimen. Disease-free survival (DFS) and overall survival (OS) were compared among the groups. In addition, adverse events in SOX patients were analyzed.

RESULTS

Of 1944 GC patients who underwent D2 dissection, 867 were included for analysis. One hundred and seventeen patients treated with SOX were matched to 234 patients who conducted surgery alone. Fifty-seven patients treated with SOX were matched to 57 patients who received XELOX. The estimated five-year DFS was 57.5% in the adjuvant SOX group which was higher than that (44.6%) in the surgery alone group (P = 0.001); and the estimated five-year OS was 68.3% which was higher than that (45.8%) of surgery alone group (P < 0.001). Survival benefit was also revealed in stage III and > 60 years old subgroups (P < 0.001 and P = 0.015, respectively). Compared with XELOX regimen, SOX showed no significant difference in DFS (P = 0.340) and OS (P = 0.361). The most common ⩾ 3 grade adverse events of SOX regimen were neutropenia (22.6%), leukopenia (8.9%) and thrombocytopenia (5.6%).

CONCLUSION

Compared with surgery alone, SOX regimen significantly improves the long-term survival and has acceptable toxicity in patients with stage ⅠB-ⅢC GC after D2 dissection. It may be a novel adjuvant chemotherapy regimen in GC patients.

Key words: Gastric cancer; D2 gastrectomy; Adjuvant chemotherapy; S-1; Oxaliplatin; Capecitabine

Core tip: Based on the therapeutic efficacy of both S-1 mono-therapy and oxaliplatin plus capecitabine regimen in ACTS-gastric cancer (GC) and CLASSIC study, we conducted the multi-institutional research using propensity score-matched analysis to evaluate whether patients after D2 resection benefit from adjuvant chemotherapy with S-1 plus oxaliplatin (SOX). Here, we firstly report that SOX adjuvant chemotherapy, compared with surgery alone, significantly improves disease-free survival and overall survival in stage ⅠB-ⅢC GC patients undergoing D2 resection with accepted side effects.

Ren DF, Zheng FC, Zhao JH, Shen GS, Ahmad R, Zhang SS, Zhang Y, Kan J, Dong L, Wang ZY, Zhao FX, Zhao JD. Adjuvant chemotherapy with S-1 plus oxaliplatin improves survival of patients with gastric cancer after D2 gastrectomy: A multicenter propensity score-matched study. *World J Clin Cases* 2018; 6(10): 373-383 Available from: URL: http://www.wjgnet.com/2307-8960/full/v6/i10/373.htm DOI: http://dx.doi.org/10.12998/wjcc.v6.i10.373

INTRODUCTION

Gastric cancer (GC) is one of the most common malignancies with high morbidity and mortality worldwide[1]. Adequate surgical resection is the only curative therapeutic option for GC. In East Asia, gastrectomy with D2 lymphadenectomy is the standard surgical treatment[2,3]. In fact, based on the results of the Dutch D1D2 trial[4], the European and United States guidelines have likewise recommended the procedure[5,6]. However, even with a potentially curative resection, approximately 50% of patients develop recurrence within 5 years after surgery[7,8], and 50%-90% of patients die of tumor relapses[9].

To decrease the risk of postoperative recurrence, various regimens for adjuvant chemotherapy have been implemented over the past 40 years. Results of two large randomized phase 3 trials, which are the ACTS-GC and CLASSIC trials, have shown survival benefit from adjuvant chemotherapy in patients who underwent D2 radical resection for stage Ⅱ-Ⅲ disease[7,8]. In the ACTS-GC study, intake of S-1 treatment for one year after D2 gastrectomy increased the five-year relapse-free survival (RFS) and overall survival (OS) by 12.3% and 10.6%, respectively[7]. In CLASSIC trial, 6 mo of capecitabine plus oxaliplatin (XELOX) therapy improved the estimated five-year disease-free survival (DFS) and OS by 15% and 9%, respectively[8].

To date, only the two adjuvant chemotherapy regimens mentioned above have been proven to be significantly efficient in stage Ⅱ-Ⅲ GC patients who underwent D2 dissection. However, some aspects in the previous two studies on adjuvant chemotherapy

need to be improved. In the ACTS-GC trial, patients had a low compliance (65.8%) in taking S-1 for one year and a subgroup analysis showed that the effect was insufficient in the elderly or stage Ⅲ patients[7]. In the CLASSIC study, patients also had a low treatment completion rate (67%)[8]. Therefore, new adjuvant chemotherapy regimens need to be explored.

Considering that both S-1 mono-therapy and combination therapy with oxaliplatin plus capecitabine have become the standard treatment for GC patients after D2 gastrectomy, a phase 2, single-arm study that investigated the safety of adjuvant chemotherapy regimen with S-1 plus oxaliplatin (SOX) in Japanese patients showed better toxicity profiles and relatively high completion rate (74.2%)[10]. Therefore, adjuvant chemotherapy with SOX for GC is most likely reasonable and efficacious. Based on the aforementioned, we conducted this multicenter retrospective study to evaluate the safety and efficacy of SOX as adjuvant chemotherapy in stage ⅠB-ⅢC GC after D2 gastrectomy.

MATERIALS AND METHODS

Study population

The study included GC patients who underwent D2 gastrectomy at the Affiliated Hospital of Qinghai University, People's Hospital of Qinghai Province, Qinghai Red Cross Hospital, and Cancer Institute and Hospital, Chinese Academy of Medical Sciences from September 2009 to December 2011. Patients were selected if they met the following eligibility criteria: (1) histologically confirmed adenocarcinoma of the stomach; and (2) stage ⅠB (pT1N1M0) or ⅠB (pT2N0M0) with high-risk features including poorly differentiated or higher grade cancer, lymphovascular invasion, neural invasion, or < 50 years of age, stage Ⅱ, or Ⅲ disease according to the Seventh Edition of the American Joint Committee on Cancer (AJCC) classification. The following patients were excluded: (1) stage ⅠA or ⅠB (pT2N0M0) disease without aforementioned high-risk features; (2) those who received radiotherapy before or after surgery; (3) those who received neo-adjuvant chemotherapy; and (4) those who received adjuvant chemotherapy except for SOX or XELOX regimens.

We analyzed the clinicopathologic characteristics of the enrolled patients, including age, sex, tumor location, tumor grade, p-TNM stage (based on the Seventh AJCC classification), lymphatic and venous invasion, and perineural invasion. All eligible patients were divided into three parts, patients who treated with surgery alone, patients who received postoperative SOX adjuvant chemotherapy, and those who received XELOX adjuvant chemotherapy.

The study was approved by the institutional review boards of the Affiliated Hospital of Qinghai University, People's Hospital of Qinghai Province, Qinghai Red Cross Hospital, and Cancer Institute and Hospital, Chinese Academy of Medical Sciences.

Adjuvant chemotherapy regimens

SOX adjuvant chemotherapy was started within 3-6 wk after D2 gastrectomy. In all 3-wk cycles, S-1 was given orally twice daily for 2 wk at a dose of 80 mg/d for patients with a body surface area (BSA) < 1.25 m^2, 100 mg/d for patients with a BSA of 1.25 m^2 to < 1.5 m^2, and 120 mg/d for patients with a BSA of ⩾ 1.5 m^2. On day 1 of each chemotherapy cycle, oxaliplatin was infused intravenously for 2-4 h at a dose of 130 mg/m^2. The Common Toxicity Criteria of the National Cancer Institute (version 4.0) was used to assess the adverse effects of chemotherapy. XELOX adjuvant chemotherapy was also started within 3-6 wk after D2 dissection. Capecitabine was given orally at a dose of 1000 mg/m^2 twice daily on days 1 to 14 of each 3-wk cycle. Oxaliplatin at 130 mg/m^2 was infused intravenously for 2-4 h on day 1 of each chemotherapy cycle.

Postoperative follow-up

Patients in the surgery alone group did not receive any antineoplastic agent until there was a confirmed recurrence. All the enrolled patients underwent hematologic tests, physical examination, and computed tomography every three months for the first two years after surgery, every six months from the third year to the fifth year, and annually thereafter.

Data, including tumor relapse, death from any cause and the last follow-up date were collected. DFS was defined as the time from surgery to tumor recurrence or the last follow-up date. OS was defined as the time from surgery to death or the last follow-up date.

Statistical analysis

To compare the baseline clinicopathologic characteristics between the adjuvant SOX and the surgery alone groups, the adjuvant SOX and the adjuvant XELOX groups, the χ^2 test or Fisher's exact test was used for categorical variables, whereas the Mann-Whitney *U* test was used for continuous variables. Survival outcomes were estimated using the Kaplan-Meier method, and the differences in survival between the treatment groups were compared using the log-rank test. An unadjusted Cox proportional hazards model was used to calculate the hazard ratio (HR) with the 95% confidence interval (CI) for the survival outcomes in all groups. To determine the independent prognostic factors for OS, a multiple regression analysis using a Cox proportional hazards model was performed. All tests were two-sided, and $P < 0.05$ was considered statistically significant.

We used propensity score matching to reduce to the greatest extent the effects of selection bias and the possible confounding factors. Propensity scores were estimated by a logistic regression model of the following covariates: age, sex, tumor location, tumor grade, p-TNM stage, lymphatic and venous invasion, and perineural invasion. Patients in the adjuvant SOX group were matched in a 1:2 ration with those in the

Table 1 Clinicopathologic features of the study population undergoing surgery alone and receiving adjuvant S-1 plus oxaliplatin chemotherapy before and after propensity score-matching *n* (%)

Variable	Before PSM (*n* = 807)			After PSM (*n* = 351)		
	Surgery alone (*n* = 683)	Adjuvant SOX (*n* = 124)	*P* value	Surgery alone (*n* = 234)	Adjuvant SOX (*n* = 117)	*P* value
Age at diagnosis (yr)			0.099			0.443
< 35	9 (1.32)	3 (2.42)		3 (1.28)	0 (0.00)	
35-60	303 (44.36)	66 (53.23)		118 (50.43)	62 (52.99)	
> 60	371 (54.32)	55 (44.35)		113 (48.29)	55 (47.01)	
Gender			0.83			1
Female	177 (25.92)	31 (25.00)		60 (25.64)	30 (25.64)	
Male	506 (74.08)	93 (75.00)		174 (74.36)	87 (74.36)	
Tumor location			0.063			0.424
None-Cardia cancer	425 (62.23)	88 (70.97)		152 (64.96)	81 (69.23)	
Cardia cancer	258 (37.77)	36 (29.03)		82 (35.04)	36 (30.77)	
Tumor grade			0.006			0.725
Moderate to well	50 (7.32)	4 (3.23)		14 (5.98)	4 (3.42)	
Moderate	171 (25.04)	21 (16.94)		36 (15.38)	21 (17.95)	
Poor to moderate	427 (62.52)	97 (78.23)		180 (76.92)	90 (76.92)	
Early cancer or not reported	35 (5.12)	2 (1.61)		4 (1.71)	2 (1.71)	
Pathological stage			< 0.001			0.604
ⅠB[1]	302 (44.22)	8 (6.45)		20 (8.55)	8 (6.84)	
Ⅱ	127 (18.59)	29 (23.39)		48 (20.51)	29 (24.79)	
Ⅲ	254 (37.19)	87 (70.16)		166 (70.94)	80 (68.38)	
Lymphatic and venous invasion			< 0.001			0.574
No	573 (83.89)	86 (69.35)		155 (66.24)	81 (69.23)	
Yes	110 (16.11)	38 (30.65)		79 (33.76)	36 (30.77)	
Perineural invasion			0.437			0.754
No	606 (88.73)	107 (86.29)		197 (84.19)	100 (85.47)	
Yes	77 (11.27)	17 (13.71)		37 (15.81)	17 (14.53)	

[1]Patients of stage ⅠB (pT2N0M0) without high-risk features including poorly differentiated or higher grade cancer, lymphovascular invasion, neural invasion, or < 50 years of age were not included. SOX: S-1 plus oxaliplatin; PSM: Propensity score-matching.

surgery alone group and 1:1 ration with those in the adjuvant XELOX group using calculated propensity scores with a 0.05 caliper width. And only the patients matched with propensity scores were included in the time-to-event analyses. We performed the propensity score matching using the Matching package in R, version 3.3.1 (R Foundation)[11].

Sensitivity analysis was conducted by adding co-morbidity to our propensity score model before repeating the DFS and OS analyses between the adjuvant SOX group and the surgery alone group. Except for the propensity score matching, all statistical analyses were performed using SPSS software version 21.0 (SPSS Inc., Chicago, IL, United States).

RESULTS

Study population

From September 2009 to December 2011, there were 1944 GC patients who were treated by curative gastrectomy with D2 lymphadenectomy. Among them, 1077 patients were excluded for being in stage ⅠA or ⅠB (pT2N0M0) without high-risk features (*n* = 249), having received radiotherapy before or after surgery (*n* = 105), neo-adjuvant chemotherapy (*n* = 60), other adjuvant chemotherapy except for SOX or XELOX regimens after surgery (*n* = 663). A total of 867 patients were analyzed in this study; 124 patients received SOX adjuvant chemotherapy, 60 patients received XELOX adjuvant therapy and 683 patients underwent surgery alone. After propensity score matching, 117 pairs of 1:2 matched patients (*i.e.*, 351patients) and 57 pairs of 1:1 matched patients (*i.e.*, 114 patients) were generated (Figure 1).

The clinicopathologic characteristics of patients in adjuvant SOX group and surgery alone group before and after matching are shown in Table 1. Overall, compared with the surgery alone group, the adjuvant SOX group had more poor to moderate grade tumor (78.23% *vs* 62.52%), more pathologic stage Ⅲ cancer (70.16% *vs* 37.19%), and more lymphatic and venous invasion (30.65% *vs* 16.11%). After matching, all the baseline clinicopathologic characteristics including age, sex, tumor location, tumor grade, p-TNM stage, lymphatic and venous invasion, and perineural invasion, were similar between the two groups. The clinicopathologic characteristics of patients in adjuvant SOX group and adjuvant XELOX group before and after matching are shown in Table 2.

Survival benefit of adjuvant SOX chemotherapy

In adjuvant SOX group, a median cycle of 4 (1-12 cycles) were received. After a median follow-up of 42 mo after gastrectomy, the number of patients who developed relapse and died was 42 (35.9%) and 36 (30.8%), respectively, in the adjuvant SOX group and

Table 2 Clinicopathologic features of the study population in adjuvant S-1 plus oxaliplatin group and adjuvant capecitabine plus oxaliplatin group before and after propensity score-matching *n* (%)

Variable	Before PSM (*n* = 184)			After PSM (*n* = 114)		
	Adjuvant SOX (*n* = 124)	Adjuvant XELOX (*n* = 60)	*P* value	Adjuvant SOX (*n* = 57)	Adjuvant XELOX (*n* = 57)	*P* value
Age at diagnosis (yr)			0.322			0.848
≤ 60	69 (55.65)	38 (63.33)		34 (59.65)	35 (61.40)	
> 60	55 (44.35)	22 (36.67)		23 (40.35)	22 (38.60)	
Gender			1			0.404
Female	31 (25.00)	15 (25.00)		18 (31.58)	14 (24.56)	
Male	93 (75.00)	45 (75.00)		39 (68.42)	43 (75.44)	
Tumor location			0.567			1
None-Cardia cancer	88 (70.97)	45 (75.00)		42 (73.68)	42 (73.68)	
Cardia cancer	36 (29.03)	15 (25.00)		15 (26.32)	15 (26.32)	
Tumor grade			0.521			0.233
Moderate to well	4 (3.23)	1 (1.67)		4 (7.02)	1 (1.75)	
Moderate	21 (16.94)	14 (23.33)		13 (22.81)	12 (21.05)	
Poor to moderate	97 (78.23)	45 (75.00)		38 (66.67)	44 (77.19)	
Early cancer or not reported	2 (1.61)	0 (0.00)		2 (3.51)	0 (0.00)	
Pathological stage			0.038			0.708
ⅠB[1]	8 (6.45)	11 (18.33)		7 (12.28)	9 (15.79)	
Ⅱ	29 (23.39)	10 (16.67)		12 (21.05)	9 (15.79)	
Ⅲ	87 (70.16)	39 (65.00)		38 (66.67)	39 (68.42)	
Lymphatic and venous invasion			0.929			0.839
No	86 (69.35)	42 (70.00)		39 (68.42)	40 (70.18)	
Yes	38 (30.65)	18 (30.00)		18 (31.58)	17 (29.82)	
Perineural invasion			0.102			1
No	107 (86.29)	46 (76.67)		46 (80.70)	46 (80.70)	
Yes	17 (13.71)	14 (23.33)		11 (19.30)	11 (19.30)	

[1]Patients of stage ⅠB (pT2N0M0) without high-risk features including poorly differentiated or higher grade cancer, lymphovascular invasion, neural invasion, or < 50 years of age were not included. SOX: S-1 plus oxaliplatin; XELOX: Capecitabine plus oxaliplatin; PSM: Propensity score-matching.

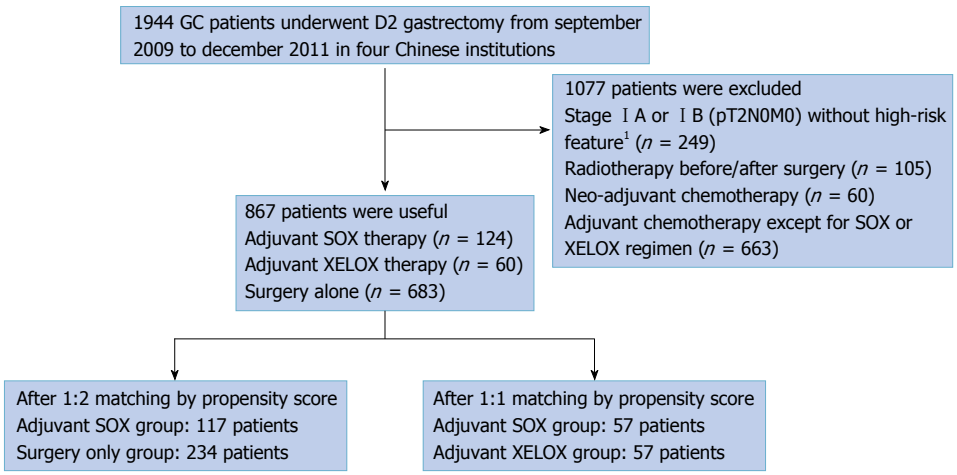

Figure 1 Flowchart of the study population. GC: Gastric cancer; SOX: S-1 plus oxaliplatin.[1]High-risk features include poorly differentiated or higher grade cancer,lymphovascular invasion, neural invasion, or ＜50 years of age.

122 (52.1%) and 117 (50.0%), respectively, in the surgery alone group. The estimated five-year DFS was 57.5% in the adjuvant SOX group and 44.6% in the surgery alone group (HR = 0.559; 95%CI: 0.393-0.794; *P* = 0.001; Figure 2A). The estimated five-year OS was 68.3% in the adjuvant SOX group and 45.8% in the surgery alone group (HR = 0.505; 95%CI: 0.348-0.734; *P* < 0.001; Figure 2B).

After addition of co-morbidity to the propensity score model in the sensitivity analysis, 116 pairs of 1:2 matched patients (*i.e.*, 348 patients) were generated. Repeat analyses showed that compared with the surgery alone group, the adjuvant SOX group had significantly better DFS (HR = 0.542; 95%CI: 0.377-0.779; *P* = 0.001) and OS (HR = 0.496; 95%CI: 0.338-0.728; *P* < 0.001).

Subgroup analysis

To further investigate whether stage Ⅲ or elderly patients can benefit from SOX adjuvant chemotherapy,

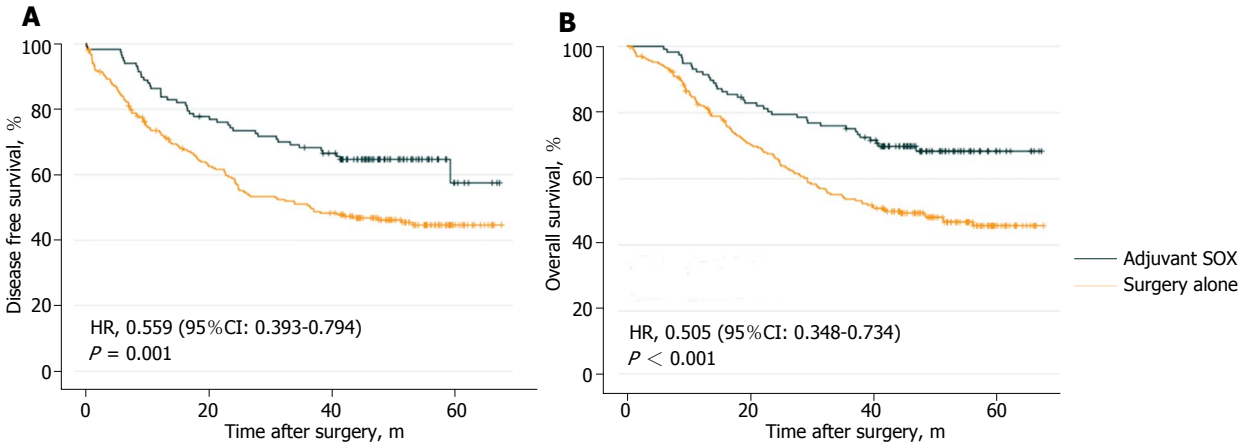

Figure 2 Kaplan-Meier curves for disease-free survival (A) and overall survival (B) between matched patients in the surgery alone group and adjuvant S-1 plus oxaliplatin group. SOX: S-1 plus oxaliplatin; HR: Hazard ratio.

exploratory subgroup analyses were performed among the 351 matched patients. In the stage Ⅲ patients, the estimated five-year DFS rates were 33.4% in the surgery alone group and 49.1% in the adjuvant SOX group, with an HR of 0.530 (95%CI: 0.361-0.779; *P* = 0.001; Figure 3A). The estimated five-year OS rates were 34.1% in the surgery alone group and 62.5% in the adjuvant SOX group, with an HR of 0.458 (95%CI: 0.302-0.692; *P* < 0.001; Figure 3B).

In patients aged ⩽ 60 years, the estimated five-year DFS rates were 54.5% in the surgery alone group and 61.6% in the adjuvant SOX group, with an HR of 0.553 (95%CI: 0.319-0.959; *P* = 0.032; Figure 3C). The estimated five-year OS rates were 55.2% in the surgery alone group and 77.2% in the adjuvant SOX group, with an HR of 0.435 (95%CI: 0.236–0.802; *P* = 0.006; Figure 3D).

For patients > 60 years old, the estimated five-year DFS rates were 34.2% in the surgery alone group and 54.4% in the adjuvant SOX group, with an HR of 0.557 (95%CI: 0.353-0.879; *P* = 0.011; Figure 3E). The estimated five-year OS rates were 36.0% in the surgery alone group and 58.0% in the adjuvant SOX group, with an HR of 0.559 (95%CI: 0.348-0.897; *P* = 0.015; Figure 3F).

Evaluation of prognostic factors

The multivariate Cox proportional hazards model showed that age (HR, 1.629; 95%CI: 1.155-2.297; *P* = 0.005), p-TNM stage Ⅲ (HR = 10.258; 95%CI: 2.202-47.783; *P* = 0.003), perineural invasion (HR = 1.637; 95%CI: 1.056-2.538; *P* = 0.028), and SOX adjuvant chemotherapy (HR = 0.481; 95%CI: 0.329-0.702; *P* < 0.001) were the independent prognostic factors for OS of GC patients after D2 gastrectomy (Table 3).

Safety of adjuvant SOX chemotherapy

Out of 124 patients who received SOX adjuvant chemotherapy, 122 patients (98.4%) developed different grades of adverse events. Table 4 shows all the grades of adverse events reported by ⩾ 10% of patients. Grade 3 or 4 adverse events were reported by 47 (37.9%) patients, and the most common adverse events were neutropenia (22.6%), leukopenia (8.9%) and thrombocytopenia (5.6%). Among all grades of adverse events, neutropenia (75.0%), leukopenia (60.5%) and peripheral sensory neuropathy (52.4%) had the highest event rate. In addition, one patient developed febrile neutropenia during the chemotherapy period. Fifty-six patients (45.2%) experienced reduction of S-1 or/and oxaliplatin dose mainly because of the adverse events of neutropenia, leukopenia and peripheral sensory neuropathy. Seventy-eight patients (62.9%) had a delay in the subsequent treatment and the most common reason is the adverse event of neutropenia.

Efficacy between SOX regimen and XELOX regimen

In adjuvant SOX group (57 patients), patients received 250 cycles chemotherapy in total with median cycles of 4. In adjuvant XELOX group (57 patients), patients received 258 cycles chemotherapy in total with median cycles of 5. After a median follow-up of 42 mo after gastrectomy, 47 patients developed relapse (21 in the SOX group and 26 in the XELOX group), 42 patients died (18 in the SOX group and 24 in the XELOX group). The estimated five-year DFS was 63.1% in the adjuvant SOX group and 54.0% in the adjuvant XELOX group (HR = 0.658; 95%CI: 0.360-1.203; *P* = 0.340; Figure 4A). The estimated five-year OS was 67.0% in the adjuvant SOX group and 56.5% in the adjuvant XELOX group (HR = 0.714; 95%CI: 0.382-1.334; *P* = 0.361; Figure 4B).

DISCUSSION

To the best of our knowledge, this was the first study to report that adjuvant chemotherapy with SOX can significantly improve the long-term survival of patients with GC after D2 radical gastrectomy, compared with surgery alone. After adjustment for confounders in

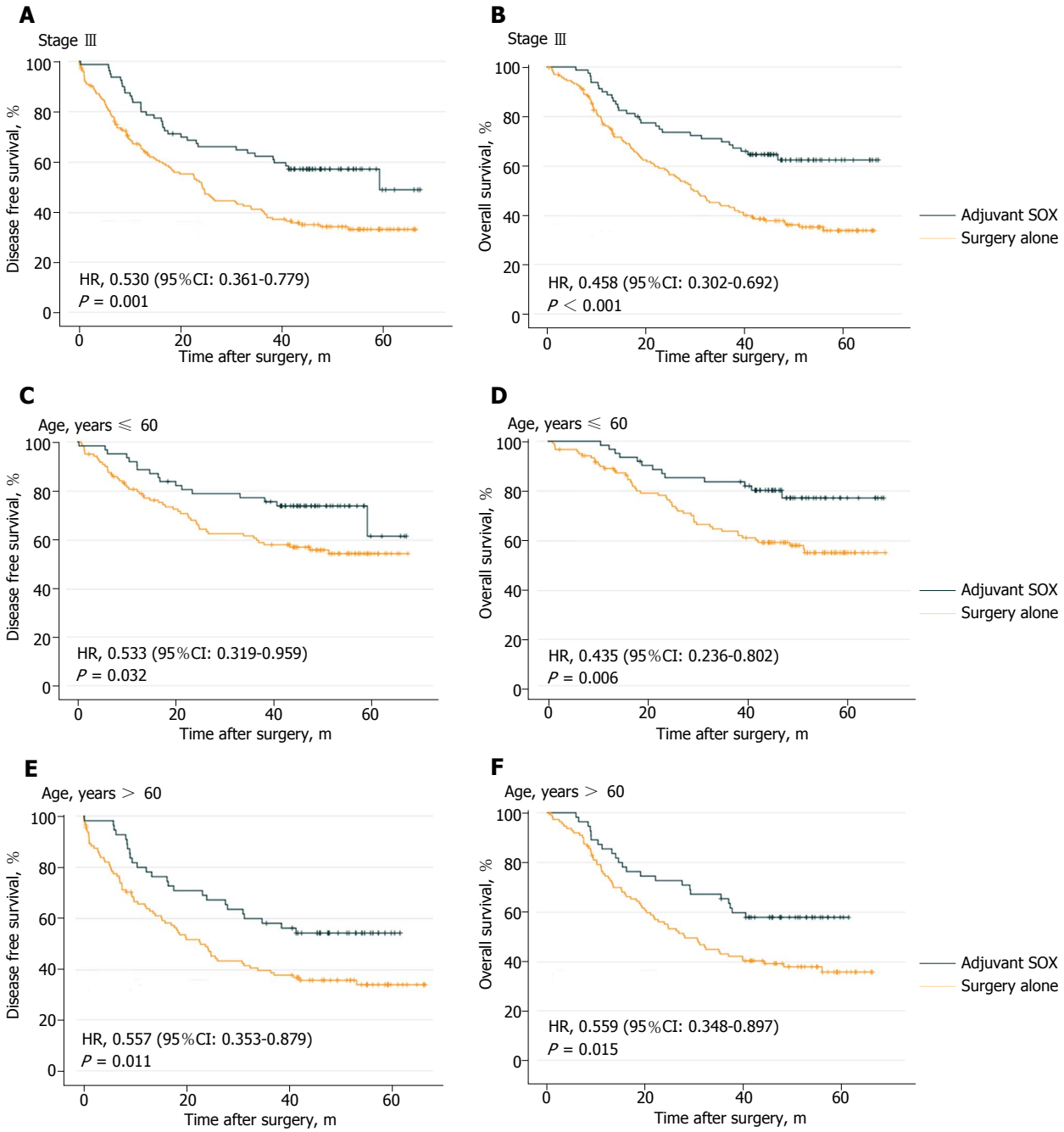

Figure 3 Kaplan-Meier curves for disease-free survival and overall survival of subgroups between matched patients in the surgery alone group and adjuvant S-1 plus oxaliplatin group. A: Disease-free survival (DFS) in matched patients with stage Ⅲ; B: Overall survival (OS) in matched patients with stage Ⅲ; C: DFS in matched patients who ⩽ 60 years old; D: OS in matched patients who ⩽ 60 years old; E: DFS in matched patients who > 60 years old; F: OS in matched patients who > 60 years old. SOX: S-1 plus oxaliplatin; HR: Hazard ratio.

the propensity score-matched analysis, adjuvant chemotherapy with SOX, compared with surgery alone, improved the estimated five-year DFS and OS by approximately 12.9% (P = 0.001) and 22.5% (P < 0.001), respectively, with mild and well-tolerated toxicities. The results were similar in the sensitivity analysis after addition of co-morbidity to the propensity score model; the estimated five-year DFS and OS improved by 13.9% (P = 0.001) and 22.2% (P < 0.001), respectively. Moreover, our research showed that SOX regimen was as effective as XELOX for stage ⅠB-ⅢC GC patients after D2 dissection. These results strongly suggest that SOX is very likely to become a novel adjuvant chemotherapy regimen in patients with GC after D2 radical resection.

D2 gastrectomy is the standard of surgical procedure in patients with GC in East Asia[12,13]. Moreover, the European and United States treatment guidelines have suggested such procedure in resectable patients, based on the Dutch D1D2 clinical study, which showed that D2 gastrectomy reduced the number of cancer-related deaths compared with D1[4-6,14,15]. Two recent,

Table 3 Prognostic factors of overall survival in 351 matched patients with gastric cancer after D2 dissection

Variable	Hazard ratio	95%CI	*P* value
Age at diagnosis (yr)			
≤ 60	1		
> 60	1.629	(1.155-2.297)	0.005
Gender			
Female	1		
Male	1.073	(0.731-1.576)	0.718
Tumor location			
None-Cardia cancer	1		
Cardia cancer	0.862	(0.605-1.227)	0.409
Tumor grade			0.888
Moderate to well	1		
Moderate	1.37	(0.558-3.363)	0.492
Poor to moderate	1.283	(0.551-2.983)	0.563
Early cancer or not reported	1.972	(0.205-18.948)	0.557
Pathological stage			< 0.001
ⅠB[1]	1		
Ⅱ	4.691	(0.994-22.128)	0.051
Ⅲ	9.857	(2.174-44.686)	0.003
Lymphatic and venous invasion			
No	1		
Yes	0.963	(0.670-1.384)	0.837
Perineural invasion			
No	1		
Yes	1.679	(1.091-2.585)	0.019
Adjuvant chemotherapy			
Surgery alone	1		
SOX	0.475	(0.326-0.693)	< 0.001

[1]Patients of stage ⅠB (pT2N0M0) without high-risk features including poorly differentiated or higher grade cancer, lymphovascular invasion, neural invasion, or < 50 years of age were not included. SOX: S-1 plus oxaliplatin.

excellent, and large-scale randomized trials have shown that adjuvant chemotherapy can improve both DFS and OS in patients with resectable GC after D2 gastrectomy[7,8].

The ACTS-GC trial revealed that one year of adjuvant chemotherapy with S-1 for stage Ⅱ/Ⅲ GC patients after D2 dissection increased the five-year RFS and OS rates from 53.1% to 65.4% and 61.1% to 71.7%, respectively[7]. The phase 3 CLASSIC study reported that six months of adjuvant chemotherapy with capecitabine and oxaliplatin after curative D2 gastrectomy in stage Ⅱ to ⅢB GC patients improved the estimated five-year DFS and OS rates from 53% to 68% and 69% to 78%, respectively[8]. However, it should be noted that in the ACTS-GC study, the effect of adjuvant chemotherapy with S-1 in GC was stage-dependent. In particular, a superior treatment effect was observed in stage Ⅱ cases (HR = 0.509), but it was rather ineffective for stage ⅢA (HR = 0.708) and stage ⅢB (HR = 0.791) disease[7]. These results suggested that S-1 treatment was insufficient in eliminating micrometastatic cancer cells in cases with high p-TNM stage. Furthermore, in their subgroup analysis, S-1 treatment was shown to be not beneficial in elderly patients (≥ 60 years) and could not be sustained up to one year, with a 12-mo completion rate of only 65.8%[16]. In the CLASSIC study, only 67% received the planned eight cycles of adjuvant capecitabine and oxaliplatin chemotherapy; 56% experienced grade 3 or 4 adverse events; and 90% needed dose modifications because of adverse events[17]. Therefore, novel adjuvant chemotherapy regimen with high efficiency and mild side effect needs to be explored for GC patients undergoing D2 dissection.

In this study, patients who received adjuvant chemotherapy with SOX had significantly better survival than those who underwent surgery alone. In the ACTS-GC trial and CLASSIC studies, both S-1 mono-therapy and oxaliplatin combined with capecitabine were confirmed to have a survival benefit for patients with GC after D2 dissection[7,8]. Moreover, SOX was shown to have a high response rate (55.7%) and disease control rate (85.2%) in advanced GC[18]. Therefore, adjuvant chemotherapy with SOX is reasonable for GC. A single-arm, phase 2 study revealed that adjuvant SOX treatment was manageable and safe with optimal dose reduction or delay in the initiation of a subsequent cycle in stage Ⅲ GC patients undergoing D2 or more extensive lymphadenectomy[10]. Most recently, Wang *et al*[19] reported DFS (75.9%) and OS (85.2%) for 3 years by adjuvant SOX chemotherapy for Chinese patients in GC. However, there had been no study that evaluated the survival benefit of adjuvant SOX chemotherapy over surgery alone in GC patients after D2 gastrectomy.

In this study, the survival rates of propensity score-matched patients were compared between adjuvant SOX chemotherapy and surgery alone, adjuvant SOX and XELOX chemotherapy. The results showed that compared with surgery alone, adjuvant SOX chemotherapy had survival benefit in terms of DFS and OS. The 12.9% estimated five-year DFS benefit rate in this study was almost similar to the results of the ACTS-GC trial and CLASSIC studies. In this present study, the 22.5% significant improvement in the estimated five-year OS with SOX regimen was probably related to the adjuvant chemotherapy itself and to the fact that some patients with relapse in the surgery alone group declined further antineoplastic therapy, whereas the patients in the adjuvant chemotherapy group remained to receive palliative therapy after relapse or due to more other comorbidities or competing causes of death in surgery alone patients. Our exploratory subgroup analysis showed the same survival benefits of adjuvant SOX chemotherapy in stage Ⅲ and elderly patients. These results were similar to those of the CLASSIC study, but were not consistent with those of the ACTS-GC clinical trial. These differences might suggest that adjuvant chemotherapy with a doublet regimen containing S-1 was superior to mono-therapy with S-1 in these patients.

In this study, the adverse events documented with SOX were similar with the reported safety profiles of SOX in a phase 2 adjuvant therapy study and a phase 3 palliative treatment study on GC[10,18]. The most

Table 4 Adverse events reported by ⩾ 10% of patients who received adjuvant S-1 plus oxaliplatin chemotherapy

Event	Adjuvant SOX (n = 124)					
	Grade 1	Grade 2	Grade 3	Grade 4	All grade	Grade 3 or 4
	No. of patients				%	
Leukopenia	46	18	8	3	60.5	8.9
Neutropenia	34	31	19	9	75	22.6
Anemia	35	3	1	1	32.3	1.6
Thrombocytopenia	22	18	7	0	37.9	5.6
Elevated total serum bilirubin level	23	2	1	0	21	0.8
Elevated AST/ALT level	53	5	1	1	48.4	1.6
Elevated ALP level	12	3	1	0	12.9	0.8
Nausea	41	19	4	-	51.6	3.2
Vomiting	17	16	4	0	29.8	3.2
Diarrhea	33	7	1	0	33.1	0.8
Peripheral sensory neuropathy	61	4	0	-	52.4	0

Grades of adverse events were defined according to the Common Terminology Criteria for Adverse Events (Version 4.0). SOX: S-1 plus oxaliplatin; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; -: Not available.

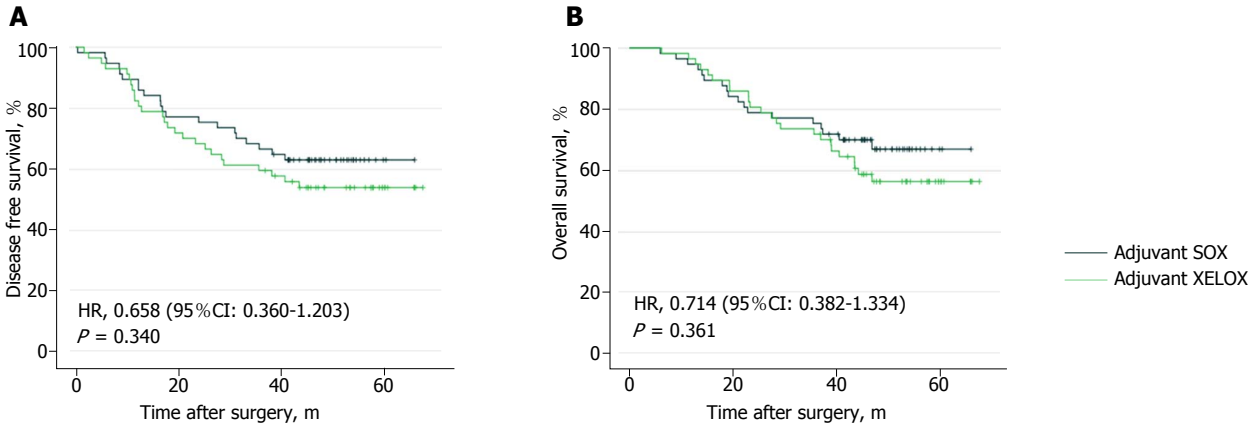

Figure 4 Kaplan-Meier curves for disease-free survival (A) and overall survival (B) between matched patients in the adjuvant S-1 plus oxaliplatin group and adjuvant capecitabine plus oxaliplatin group. SOX: S-1 plus oxaliplatin; XELOX: Capecitabine plus oxaliplatin; HR: Hazard ratio.

common adverse events were neutropenia, leukopenia, nausea, peripheral sensory neuropathy, and mild elevation of hepatic transaminases. Overall, the frequency of adverse events ⩾ grade 3 was less than 40%, suggesting that adjuvant SOX chemotherapy for GC after D2 radical gastrectomy was well tolerated.

The present study had several limitations. First, the baseline characteristics of the patients were different between both groups. Although we performed propensity score-matched analysis and multivariate regression to reduce biases, remnant heterogeneity between groups cannot be excluded. Second, although the entire study population was relatively large, the sample size of patients receiving adjuvant SOX or XELOX chemotherapy was not adequate for subgroup analyses according to each variable. Third, a majority of GC patients after D2 dissection in China were stage Ⅲ disease which can't benefit from S-1 monotherapy according to ACTS-GC trial; most of the patients in our study didn't receive S-1 monotherapy. We didn't analyze data about patients only receiving S-1 in our study. Forth, the definite relapse locations were not clear for part of the patients in our study, we didn't analyse the data about site of first relapse between patients received SOX or XELOX chemotherapy and those underwent surgery alone. Fifth, considering this study comprised Chinese patients, the dose of adjuvant SOX in other populations, especially Caucasians, remains to be further investigated because of the differences in the pharmacokinetics and toxicities of S-1 between Caucasian and Asian patients[20]. Moreover, the role of SOX in patients undergoing D1 dissection needs to be confirmed.

In conclusion, compared with surgery alone, adjuvant SOX regimen significantly improved the long-term survival of Chinese patients with stage ⅠB-ⅢC GC after D2 radical gastrectomy, with accepted side effects. It showed the similar DFS and OS outcomes with XELOX regimen which had become the standard adjuvant therapy nowadays. Therefore, SOX is likely to become a novel adjuvant chemotherapy regimen in GC. Several ongoing studies on the role of SOX for adjuvant chemotherapy in GC are expected to convey new and definite proofs in future[21-24].

ARTICLE HIGHLIGHTS

Research objectives

The main objectives of this retrospective study were to evaluate the safety and efficacy of S-1 plus oxaliplatin (SOX) as adjuvant chemotherapy for gastric cancer (GC) after D2 dissection.

Research methods

We collected patients with GC who underwent D2 gastrectomy from September 2009 to December 2011 in four Chinese institutions. Patients with stage IB-IIIC GC, who received adjuvant SOX treatment were matched by propensity scores with those who underwent surgery alone and those who conducted adjuvant capecitabine plus oxaliplatin (XELOX) regimen. We compared the estimated 5-year disease-free survival (DFS) and 5-year overall survival (OS) between the groups and analyzed adverse events in SOX patients.

Research results

In total, 867 GC patients were included for analysis. Among 124 patients treated with SOX regimen, 117 patients were matched to 234 patients who conducted surgery alone, and 57 patients were matched to 57 patients who received XELOX regimen. The estimated five-year DFS was 57.5% in the adjuvant SOX group and 44.6% in the surgery alone group (P = 0.001); and the estimated five-year OS was 68.3% and 45.8% (P < 0.001), respectively. Compared with XELOX regimen, SOX showed no significant difference in DFS and OS. The most common ⩾ 3 grade adverse events of SOX regimen were neutropenia (22.6%), leukopenia (8.9%) and thrombocytopenia (5.6%).

Research conclusions

This study showed that compared with surgery alone, adjuvant SOX regimen significantly improves the long-term survival and have acceptable toxicity in patients with stage ⅠB-ⅢC GC after D2 dissection.

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