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ABOUT COVER

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Clinical Trials Study

Safety and efficacy of a programmed cell death 1 inhibitor combined with oxaliplatin plus S-1 in patients with Borrmann large type III and IV gastric cancers

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Abstract

BACKGROUND

Gastric cancer (GC) is the fifth most common and the fourth most lethal malignant tumour in the world. Most patients are already in the advanced stage when they are diagnosed, which also leads to poor overall survival. The effect of postoperative adjuvant chemotherapy for advanced GC is unsatisfactory with a high rate of distant metastasis and local recurrence.

AIM

To investigate the safety and efficacy of a programmed cell death 1 (PD-1) inhibitor combined with oxaliplatin and S-1 (SOX) in the treatment of Borrmann large type III and IV GCs.

METHODS

A retrospective analysis (IRB-2022-371) was performed on 89 patients with Borrmann large type III and IV GCs who received neoadjuvant therapy (NAT) from January 2020 to December 2021. According to the different neoadjuvant treatment regimens, the patients were divided into the SOX group (61 patients) and the PD-1 + SOX (P-SOX) group (28 patients).

RESULTS
The pathological response (tumor regression grade 0/1) in the P-SOX group was significantly higher than that in the SOX group (42.86% *vs* 18.03%, *P* = 0.013). The incidence of ypN0 in the P-SOX group was higher than that in the SOX group (39.29% *vs* 19.67%, *P* = 0.05). The use of PD-1 inhibitors was an independent factor affecting tumor regression grade. Meanwhile, the use of PD-1 did not increase postoperative complications or the adverse effects of NAT.

CONCLUSION
A PD-1 inhibitor combined with SOX could significantly improve the rate of tumour regression during NAT for patients with Borrmann large type III and IV GCs.

Key Words: Neoadjuvant therapy; Immunotherapy; Gastric cancer; Borrmann type; Tumor regression grade

Core Tip: Borrmann type III and IV gastric cancers (GCs) generally have a poor prognosis. JCOG0501 failed to demonstrate the efficacy of a preoperative neoa-djuvant chemotherapy regimen (S-1 plus cisplatin) in patients with type IV or large type III GC. For these patients, we explored the possibility of chemotherapy combined with immunotherapy. The results showed that programmed cell death 1 inhibitors combined with oxaliplatin and S-1 significantly increased Tumor regression rate during neoadjuvant therapy in patients with type III and type IV GC. At the same time, chemotherapy side effects and surgical complications did not increase.

INTRODUCTION

Gastric cancer (GC) is the fifth most common and the fourth most lethal malignant tumour in the world[1]. The morbidity of GC is insidious. Due to the lack of typical symptoms and an effective screening plan[2], most patients are already in the advanced stage when they are diagnosed, which also leads to poor overall survival (OS). Surgery has always been the core treatment for GC. The radical gastrectomy is suitable for patients with early GC, and the effect of postoperative adjuvant chemotherapy for advanced GC is unsatisfactory with a high rate of distant metastasis and local recurrence[3].

In recent years, the results of the Medical Research Council Adjuvant Gastric Infusional Chemotherapy and Fédération Nationale des Centres de Lutte contre le Cancer (FFCD9703) clinical trials, which confirmed that neoadjuvant therapy (NAT) can improve the 5-year OS of patients with GC compared with surgical treatment alone, have established the important role of NAT in the treatment of advanced GC[4,5]. NAT can improve OS by reducing the tumour volume, achieving tumour degradation and eliminating micrometastases as early as possible to increase the probability of R0 resection by chemotherapy before surgery[6,7]. Since 2008, NAT has been recommended as a first-line treatment for locally advanced GC in the National Comprehensive Cancer Network guidelines. However, only approximately 20%-45% of patients with GC can benefit from NAT[8].

For the past few years, The Cancer Genome Atlas Program classification has been developed in GC, which including Epstein-Barr virus positive GC (EBV+ GC), microsatellite instability (MSI), genomic stability, and chromosomal instability [9]. According to recent research, GC patients who had MSI-high (MSI-H) or EBV+ status were the best candidates for immunotherapy. KRAS mutation-carrying GC MSI-H GC patients had a better prognosis than microsatelite instability-stable (MSS) GC patients, according to Rodriquenz *et al*[10]. These may be brought on by MSI-H GC patients' high mutational load and hypermethylation. Additionally, patients with MSI-H status had a higher overall response rate than those with MSS status, according to the results of the KEYNOTE-059 clinical trials[11]. Pietrantonio *et al*[12] found that MSI-H GC patients who got anti-programmed cell death 1 (PD-1) therapy had a greater OS rate than those who just received chemotherapy, proving that MSI patients are more responsive to immunotherapy. Additionally, pembrolizumab was given the go-ahead to treat patients with metastatic GC who had programmed death ligand 1 (PD-L1) positive status or deficient mismatch repair/MSI-H status[13]. A theoretical foundation for using EBV as a biomarker of immunotherapy response has been established by studies that demonstrate that EBV+ GC has distinct molecular characteristics and that PD-L1 is typically overexpressed in such people[14]. The survival rate of EBV+ GC patients was greater than that of EBV- GC, according to Camargo *et al*[15], indicating that EBV positivity may be a prognostic indication for bettering GC patients. The effectiveness of immunotherapy for EBV+ GC was supported by Liu *et al*[16], they discovery that PD-L1 was expressed in 59.3% of GC patients and was related with both MSI and EBV positivity. This makes it possible to do more study on these patients.

Borrmann large type III and IV GCs are usually characterized by a low early diagnosis rate, easy metastasis, poor prognosis and high mortality[17]. The role of NAT in Borrmann large type III and IV GCs is still controversial. A phase III study, Japan Clinical Oncology Group Study (JCOG0501), failed to demonstrate the efficacy of a preoperative neoadjuvant chemotherapy regimen (S-1 plus cisplatin) in patients with type IV or large type III (≥ 8 cm maximum diameter) GC[18]. Therefore, the S-1/cisplatin regimen is not recommended for NAT of Borrmann IV GC in the Japanese guidelines for GC. With the advent of immune checkpoint inhibitors, immunotherapy has opened a new field of cancer treatment in recent years[19,20]. The CheckMate 649 study confirmed that untreated patients with HER2- advanced GC could benefit from treatment with chemotherapy combined with nivolumab compared with chemotherapy alone[21]. Chemotherapy combined with a PD-1 inhibitor was recommended by the Food and Drug Administration as the first-line treatment for advanced GC. However, there is no relevant study on whether NAT of platinum plus S-1 combined with a PD-1 inhibitor can improve the survival of type IV or large type III GC. Therefore, the purpose of this study was to investigate the efficacy and safety of a PD-1 inhibitor combined with platinum + S-1 in the treatment of Borrmann type IV and large type III GCs.

MATERIALS AND METHODS

Patient selection
This retrospective study (IRB-2022-371) included 89 Borrmann type III (> 8 cm in diameter) and IV GC patients who underwent NAT and radical gastrectomy at the Department of Gastric Surgery in the Cancer Hospital of Chinese Academy of Sciences from January 2020 to December 2021. The inclusion criteria were as follows: (1) The patient was confirmed as Borrmann type IV or large type III GC (large ulcerative aggressive GC with a diameter of more than 8 cm) by pathological examination *via* surgical samples; and (2) The patient had received standard NAT prior to surgery. The exclusion criteria were as follows: (1) Patients with other Borrmann types of GC; and (2) Patients with metastases from other tumour types. Medical records were reviewed for all included patients. Data on clinical characteristics, treatment regimens, and chemotherapy responses were collected. The study was approved by the Ethics Committee of the Cancer Hospital of the Chinese Academy of Sciences. The study conformed to the tenets outlined in the Declaration of Helsinki. All patients provided written informed consent to participate.

NAT
NAT was divided into two groups according to the difference of NAT: The oxaliplatin + S-1 (SOX) group and the PD-1 inhibitor + SOX (P-SOX) group. The following describes the SOX chemotherapeutic cycle: Oxaliplatin 130 mg/m^2 intravenous infusion on day 1 (patients who have severe hematological and biochemical or non-haematological toxicity may receive a lower dose of 100 mg/m^2, 80 mg/m^2, or 50 mg/m^2); S-1, surface area ≥ 1.5 m^2, 120 mg/d, < 1.25 m^2, 80 mg/d, surface area between 1.25 and 1.5 m^2, 100 mg/d, twice daily, on days 1 to 14. On day 22, the subsequent chemotherapy cycle was carried out. The treatment cycle combining PD-1 inhibitor, oxaliplatin, and S-1 was as follows: Day 1: 200 mg of intravenous PD-1 mAb; day 1: 130 mg/m^2 of intravenous oxaliplatin; days 1 to 14: S-1, surface area ≥ 1.5 m^2, 100 mg/d, < 1.25 m^2, 80 mg/d, surface area between 1.25 and 1.5 m^2, 100 mg/d, twice a day. The next chemotherapy was repeated on day 22.

Study endpoints
The primary endpoint of the study was the ratio of the tumor regression grade (TRG) 0/1. The secondary endpoints included ypTNM stage, total number of lymph nodes, number of positive lymph nodes, complete resection rate, surgical complications, and adverse reactions to NAT.

The tumour response regression score was defined according to the recommendations of the Society of American Pathologists as follows: (1) No residual cancer cells were defined as TRG 0; (2) Single cells or small groups of cells were defined as TRG 1; (3) Residual cancer with desmoplastic response was defined as TRG 2; and (4) Minimal evidence of tumour response was defined as TRG 3[22-24]. The results were reviewed by two independent pathologists blinded to the clinical data. If the results for the same sample were inconsistent, the pathologists discussed the final score. Pathological complete response was defined as the absence of invasive disease within the submitted gross lesions and histologically negative nodules and was assessed based on central review.

Evaluation of the treatment effect
The radiologists followed the guidelines of the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 to determine the radiation response to neoadjuvant chemotherapy[25]. The response rates were independently assessed by two specialized radiologists, and the final results were determined after reviewing the results of both groups. Postoperative complications were defined as events occurring within 30 d of surgery, and their severity was assessed according to the Clavien-Dindo classification system[26,27]. The adverse reactions to chemotherapy were based on the WHO score. For patients with grade 3 or more serious adverse reactions, the dose or timing of the drug should be adjusted.

Statistical methods
All of the data were analysed by SPSS software (SPSS, Chicago, IL, United States), version 22.0. The χ^2 test or Fisher's exact test was used for comparisons of categorical variables. The independent sample *t* test or Mann-Whitney *U* test was

used for comparisons of continuous variables. Univariate logistic regression analysis was used to analyse the clinicopath-ological data of TRG (0/1). *P* < 0.05 was considered statistically significant. *P* < 0.1 was considered marginally significant.

RESULTS

Clinical characteristics

A total of 89 patients were included in the study, including 61 patients in the SOX group and 28 patients in the P-SOX group (Supplementary Table 1). There were no significant differences in age, sex, body mass index, tumour location, ypTNM stage, cTNM stage, TRG, neoadjuvant cycle, operation mode, or adverse chemotherapy reactions between the two groups (*P* > 0.05). There was a statistically significant difference in carbohydrate antigen (CA)125 at the first diagnosis (32.14% *vs* 14.75%, *P* = 0.034). However, after NAT, there was no statistically significant difference in CA125 (3.57% *vs* 4.92%, *P* = 0.835) (Table 1).

Table 1 Demographic data before surgery

Baseline variable	P-SOX group (*n* = 28)	SOX group (*n* = 61)	χ^2	*P* value
Gender			0.080	0.777
Male	21 (75%)	44 (72.58%)		
Female	7 (25%)	17 (27.42%)		
Age			0.107	0.743
< 60	10 (35.71%)	24 (38.71%)		
≥ 60	18 (64.29%)	37 (61.29%)		
BMI			1.684	0.431
< 18.5	4 (14.29%)	10 (16.39%)		
18.5-23	19 (67.86%)	33 (54.10%)		
≥ 23	5 (17.86%)	18 (29.51%)		
Tumor location			2.101	0.350
Upper	6 (21.43%)	15 (24.59%)		
Middle	12 (42.86%)	33 (54.10%)		
Lower	10 (35.71%)	13 (21.31%)		
cT stage			0.297	0.586
T1/T2	5 (8.06%)	14 (22.58%)		
T3/T4	23 (37.10%)	47 (77.42%)		
cN stage			1.099	0.295
N0	3 (10.71%)	12 (19.67%)		
N1-N3	25 (89.29%)	49 (80.32%)		
cM stage			0.670	0.413
0	23 (82.14%)	54 (88.91%)		
1	5 (17.86%)	7 (11.29%)		
cTNM stage			0.351	0.554
I and II	7 (11.29%)	19 (32.26%)		
III and IV	21 (33.87%)	42 (67.74%)		
Neoadjuvant cycle			0.053	0.817
≤ 3	20 (71.43%)	45 (72.58%)		
> 3	8 (28.57%)	16 (27.42%)		
Operation mode			0.149	0.700

Open surgery	25 (89.29%)	56 (91.94%)		
Laparoscopy	3 (10.71%)	5 (8.06%)		
Adverse chemotherapy reaction			0.610	0.435
Yes	6 (21.43%)	9 (14.52%)		
No	22 (78.57%)	52 (85.24%)		
Differentiation			1.140	0.286
Well and middle	5 (17.86%)	6 (9.84%)		
Poor and under-differentiated	23 (82.14%)	55 (90.16%)		
Borrmann type			0.279	0.597
Big III	15 (53.58%)	29 (47.54%)		
IV	13 (46.43%)	32 (52.46%)		
AFP[1] (ng/mL)			0.566	0.452
≤ 8.1	20 (71.43%)	43 (70.49%)		
> 8.1	2 (7.14%)	8 (13.11%)		
Unknown	6 (21.43%)	10 (16.39%)		
CEA[1] (ng/mL)			0.123	0.726
≤ 5	16 (57.14%)	35 (57.38%)		
> 5	6 (21.43%)	16 (26.23%)		
Unknown	6 (21.43%)	10 (16.39%)		
CA199[1] (U/mL)			0.123	0.726
≤ 37	16 (57.14%)	35 (57.38%)		
> 37	6 (21.43%)	16 (26.23%)		
Unknown	6 (21.43%)	10 (16.39%)		
CA724[1] (U/mL)			0.432	0.511
≤ 6.9	12 (42.86%)	32 (52.46%)		
> 6.9	10 (35.71%)	19 (31.15%)		
Unknown	6 (21.43%)	10 (16.39%)		
CA125[1] (U/mL)			4.477	0.034[a]
≤ 35	13 (46.43%)	42 (68.85%)		
> 35	9 (32.14%)	9 (14.75%)		
Unknown	6 (21.43%)	10 (16.39%)		
CA50[1] (U/mL)			0.003	0.956
≤ 25	18 (64.29%)	42 (68.85%)		
> 25	4 (14.29%)	9 (14.75%)		
Unknown	6 (21.43%)	10 (16.39%)		
Leukemia[1]			0.228	0.892
≤ 3.5	1 (3.57%)	3 (4.92%)		
3.5-9.5	19 (67.86%)	43 (70.49%)		
> 9.5	3 (10.71%)	5 (8.20%)		
Unknown	5 (8.20%)	10 (16.39%)		
HGB[1]			0.473	0.492
≤ 130	18 (64.29%)	36 (59.02%)		
130-175	5 (8.20%)	15 (24.59%)		

> 175	0	0		
Unknown	5 (8.20%)	10 (16.39%)		
Platelets[1]			0.806	0.668
≤ 125	2 (7.14%)	2 (3.28%)		
125-350	16 (57.14%)	39 (63.93%)		
> 350	5 (8.20%)	10 (16.39%)		
Unknown	5 (8.20%)	10 (16.39%)		
Neutrophils[1]			0.667	0.716
≤ 1.8	1 (3.57%)	4 (6.56%)		
1.8-6.3	18 (64.29%)	41 (67.21%)		
> 6.3	4 (14.29%)	6 (9.84%)		
Unknown	5 (8.20%)	10 (16.39%)		
Lymphocytes[1]			0.084	0.772
≤ 1.1	8 (28.57%)	16 (26.23%)		
1.1-3.2	15 (53.57%)	35 (57.38%)		
> 3.2	0	0		
Unknown	5 (8.20%)	10 (16.39%)		
AFP[2] (ng/mL)			0.078	0.781
≤ 8.1	20 (71.43%)	46 (75.41%)		
> 8.1	4 (14.29%)	11 (18.03%)		
Unknown	4 (14.29%)	4 (6.56%)		
CEA[2] (ng/mL)			2.806	0.094
≤ 5	22 (78.57%)	43 (70.49%)		
> 5	2 (7.14%)	14 (22.95%)		
Unknown	4 (14.29%)	4 (6.56%)		
CA199[2] (U/mL)			0.507	0.476
≤ 37	22 (78.57%)	49 (80.33%)		
> 37	2 (7.14%)	8 (13.11%)		
Unknown	4 (14.29%)	4 (6.56%)		
CA724[2] (U/mL)			2.034	0.154
≤ 6.9	18 (64.29%)	32 (52.46%)		
> 6.9	6 (21.43%)	23 (37.70%)		
Unknown	4 (14.29%)	6 (9.84%)		
CA125[2] (U/mL)			0.043	0.835
≤ 35	23 (82.14%)	54 (88.52%)		
> 35	1 (3.57%)	3 (4.92%)		
Unknown	4 (14.29%)	4 (6.56%)		
CA50[2] (U/mL)			0.583	0.445
≤ 25	22 (78.57%)	47 (77.05%)		
> 25	2 (7.14%)	8 (13.11%)		
Unknown	4 (14.29%)	6 (9.84%)		
Leukemia[2]			1.181	0.554
≤ 3.5	7 (25%)	12 (19.67%)		

3.5-9.5	16 (57.14%)	43 (70.49%)		
> 9.5	3 (10.71%)	4 (6.56%)		
Unknown	2 (7.14%)	2 (3.28%)		
HGB[2]			0.662	0.416
≤ 130	23 (82.14%)	48 (78.69%)		
130-175	3 (10.71%)	11 (18.03%)		
Unknown	2 (7.14%)	2 (3.28%)		
Platelets[2]			0.614	0.433
≤ 125	7 (25%)	21 (34.43%)		
> 125	19 (67.86%)	38 (62.30%)		
Unknown	2 (7.14%)	2 (3.23%)		
Neutrophils[2]			0.730	0.673
≤ 1.8	6 (21.43%)	13 (21.31%)		
1.8-6.3	17 (60.71%)	42 (68.85%)		
> 6.3	3 (10.71%)	4 (6.56%)		
Unknown	2 (7.14%)	2 (3.23%)		

[1]Tumor markers at first diagnosis.

[2]Preoperative tumor markers.

[a]Statistically significant ($P < 0.05$).

SOX: S-1 + oxaliplatin; P-SOX: Programmed cell death 1 + S-1 + oxaliplatin; BMI: Body mass index; AFP: Alpha-fetoprotein; CEA: Carcinoembryonic antigen; CA199: Carbohydrate antigen199; HGB: Hemoglobin; cTNM: Clinical tumor node metastasis.

Pathological response

There were significant differences in TRG grade (0 + 1) and ypN0 between the P-SOX group and the SOX group (P = 0.013, P = 0.05). There were no significant differences between the P-SOX group and the SOX group in ypT0, ypM0, or ypTNM stage (P > 0.05) (Table 2). We performed univariate analysis and found that the factors affecting TRG (0 + 1) included PD-1 use, nerve invasion and lymphovascular invasion (P < 0.1). Further multivariate analysis showed that tumour type and nerve invasion were associated risk factors [risk ratio (RR) = 2.131, 95% confidence interval (CI): 0.882-23.12, P = 0.070; odds ratio (OR) = 1.683, 95%CI: 0.910-7.684, P = 0.074], and the use of PD-1 inhibitors was an independent protective factor (RR = 0.421, 95%CI: 0.090-0.740, P = 0.012) (Supplementary Table 2). Univariate analysis of factors affecting lymph node stage (ypN0) showed that tumour type, nerve invasion, and use of PD-1 inhibitors were associated factors. Multivariate analysis showed that use of PD-1 inhibitors was an independent protective factor (RR = 0.501, 95%CI: 0.041-1.193, P = 0.074) (Supplementary Table 3).

Surgical factors

There were no significant differences between the P-SOX group and the SOX group in terms of surgical method, R0 resection, nerve invasion or vascular tumour thrombus (P > 0.05). The total number of lymph nodes and number of positive lymph nodes in the SOX group were greater than those in the SOX group, but there was no significant difference between the two groups (P > 0.05) (Table 3).

Postoperative complications

The total postoperative complication rate was 10.11%, the incidence of grade II complications was 7.87%, the incidence of grade III complications was 2.25%, and there were no grade IV or V complications. There was no significant difference in the incidence of postoperative complications between the P-SOX group and the SOX group (P > 0.05). There were no significant differences in the incidences of postoperative fever, pneumonia, abdominal infection, and anastomotic leakage or the postoperative hospital stay between the two groups (P > 0.05). The postoperative bleeding rate in the P-SOX group was lower than that in the SOX group (P = 0.02) (Table 4).

Adverse reactions of therapy

We analysed adverse reactions associated with NAT and found that the most common adverse reactions (grades 3 and 4) were decreased white blood cell count, decreased neutrophil count, and decreased hemoglobin. The platelet count in the P-SOX group (14.29%) was significantly lower than that in the SOX group (4.92%), but there was no significant difference between the two groups (P > 0.05). The P-SOX group and the SOX group showed no significant differences in the decrease in white blood cell count, neutrophil count or hemoglobin (P > 0.05). There was no significant difference in other grade 3 and 4 chemotherapy complications between the two groups (P > 0.05) (Table 5).

Table 2 Differences in response among the two groups

Baseline variable	P-SOX group (*n* = 28)	SOX group (*n* = 61)	*P* value
TRG			0.038
TRG0	4 (14.29%)	3 (4.92%)	
TRG1	8 (28.57%)	8 (13.11%)	
TRG2	13 (46.43%)	30 (49.18%)	
TRG3	3 (10.71%)	20 (32.79%)	
Subgroup analysis			0.013[a]
TRG0/TRG1	12 (42.86%)	11 (18.03%)	
TRG2/TRG3	16 (57.14%)	50 (81.97%)	
ypT stage			0.272
0	4 (14.29%)	2 (3.23%)	
1	1 (3.57%)	3 (4.92%)	
2	6 (21.43%)	8 (13.11%)	
3	2 (7.14%)	5 (8.20%)	
4	15 (53.57%)	43 (70.49%)	
ypN stage			0.130
0	11 (39.29%)	12 (19.67%)	
1	5 (8.20%)	7 (11.48%)	
2	5 (8.20%)	15 (24.59%)	
3	7 (25%)	27 (44.26%)	
ypM stage			0.099
	26 (92.86%)	48 (78.69%)	
	2 (7.14%)	13 (21.31%)	
ypTNM stage			0.196
pCR	4 (14.29%)	3 (4.92%)	
I	4 (14.29%)	3 (4.92%)	
II	4 (14.29%)	12 (19.67%)	
III	13 (46.43%)	29 (47.54%)	
IV	3 (10.71%)	14 (22.95%)	
ypT stage			0.055
T0	4 (14.29%)	2 (3.28%)	
T1-T4	24 (85.71%)	59 (96.72%)	
ypN stage			0.05[a]
N0	11 (39.29%)	12 (19.67%)	
N1-N3	17 (60.71%)	49 (80.33%)	
ypTNM stage			0.130
pCR	4 (14.29%)	3 (4.92%)	
I-IV	24 (85.71%)	58 (95.08%)	

[a]Statistically significant (*P* < 0.05).

SOX: S-1 + oxaliplatin; P-SOX: Programmed cell death 1 + S-1 + oxaliplatin; pCR: Pathological complete response; TRG: Tumor regression grade.

Table 3 Clinicopathological results after surgery

Baseline variable	P-SOX group (*n* = 28)	SOX group (*n* = 61)	x^2	*P* value
Surgical approach			0.149	0.700
Laparoscopy	25 (89.29%)	56 (91.80%)		
Open	3 (10.71%)	5 (8.20%)		
Extent of resection			0.041	0.840
R0	23 (82.14%)	49 (80.33%)		
R1	5 (17.86%)	12 (19.67%)		
Nerve invasion			0.634	0.426
No	14 (50%)	25 (40.98%)		
Yes	14 (50%)	36 (59.01%)		
Vessel invasion			0.214	0.644
No	12 (42.86%)	23 (37.70%)		
Yes	16 (57.14%)	38 (62.30%)		
Harvested lymph nodes				0.354
Median	27.85 ± 10.27	31.45 ± 12.48		
Positive lymph nodes				0.254
Median	4.71 ± 5.52	7.04 ± 8.84		

SOX: S-1 + oxaliplatin; P-SOX: Programmed cell death 1 + S-1 + oxaliplatin.

Table 4 Postoperative complications

Baseline variable	P-SOX group (*n* = 28)	SOX group (*n* = 61)	*P* value
Total	5 (17.86%)	4 (6.56%)	0.101
Clavien-Dindo grading			
Grade I-II	4	3	0.127
Fever	2	1	0.182
Lung infection	2	1	0.182
Pancreatic leakage	0	1	> 0.99
Cardiac insufficiency	0	1	> 0.99
Grade III	1	1	> 0.99
Anastomotic leakage	1	1	0.568
Grade IV	0	0	NA
Grade V	0	0	NA
Postoperative bleeding	94.82 ± 70.91	136.97 ± 119.59	0.020[a]
Postoperative hospital stay	11.42 ± 5.67	11.20 ± 4.57	0.964

[a]Statistically significant ($P < 0.05$).
SOX: S-1 + oxaliplatin; P-SOX: Programmed cell death 1 + S-1 + oxaliplatin; NA: Not available.

Changes in blood indexes before and after chemotherapy

We compared the changes in tumour indexes and blood indexes between the P-SOX and SOX groups after the first diagnosis and after NAT. The results showed that the tumour indexes CA125 and alpha-fetoprotein were significantly different before and after treatment in the P-SOX and SOX groups ($P < 0.05$), but there were no significant differences in CA724, CA50, carcinoembryonic antigen, or CA19-9 before and after treatment ($P > 0.05$). There was a statistically significant difference in platelet count before and after treatment in the P-SOX group ($P < 0.05$), but there was no

Table 5 Neoadjuvant treatment adverse effects

Baseline variable	P-SOX group (*n* = 28)	SOX group (*n* = 61)	χ^2	*P* value
WHO grading				
0	7 (25%)	16 (26.23%)	0.015	0.902
I	8 (28.57%)	21 (34.43%)	0.299	0.584
II	9 (32.14%)	15 (24.59%)	0.566	0.456
III	4 (14.29%)	9 (14.75%)	0.003	0.954
IV	0	0		
WBC decreased			0.023	0.881
Grade 0, 1	24 (85.71%)	53 (86.88%)		
Grade 2, 3, 4	4 (14.29%)	8 (13.11%)		
HGB decreased			0.026	0.873
Grade 0, 1	22 (78.57%)	47 (77.05%)		
Grade 2, 3, 4	6 (21.43%)	14 (22.95%)		
Platelet count decreased			2.324	0.127
Grade 0, 1	24 (85.71%)	58 (95.08%)		
Grade 2, 3, 4	4 (14.29%)	3 (4.92%)		
Neutrophil count decreased			0.140	0.708
Grade 0, 1	24 (85.71%)	54 (88.52%)		
Grade 2, 3, 4	4 (14.29%)	7 (11.48%)		
Other adverse effects			0.458	0.499
Grade 0, 1	25 (89.29%)	59 (96.72%)		
Grade 2, 3, 4	3 (10.71%)	2 (3.28%)		

SOX: S-1 + oxaliplatin; P-SOX: Programmed cell death 1 + S-1 + oxaliplatin; WBC: White blood count; HGB: Hemoglobin.

significant difference in white blood cell count, hemoglobin, or neutrophil count (*P* > 0.05). The white blood cell, hemoglobin, platelet and neutrophil counts in the SOX group decreased significantly before and after treatment, and the difference was statistically significant (*P* < 0.05). This finding indicates that P-SOX may be a safer treatment regimen for individuals (Table 6).

DISCUSSION

Borrmann type IV GC, which includes linitis plastica and scirrhous-type cancer, has the unique characteristics of diffuse infiltration in the gastric wall, easy metastasis to the peritoneum, and poor prognosis even after D2 gastrectomy[28]. Previous studies have shown that patients with Borrmann type IV or large type III GC have a very poor prognosis, with a 3-year OS of only 28.9%[29]. Many studies have reported that perioperative chemotherapy, especially NAT, can significantly improve the prognosis of patients with advanced GC[30,31]. However, the role of NAT in Borrmann type IV GC is still in dispute. The JCOG0501 study in Japan evaluated the effect of neoadjuvant chemotherapy with S-1/cisplatin on the survival of patients with Borrmann type IV or large type III GC. The results showed that NAT did not significantly improve the prognosis of patients with Borrmann type IV or large type III GC, and there was no significant difference in the 3-year OS between patients who received adjuvant chemotherapy alone and those who received NAT (62.4% *vs* 60.9%). Therefore, the S-1/cisplatin regimen is not recommended for NAT in Borrmann type IV or large type III GC in the Japanese guidelines for GC. Chemotherapy based on the platinum/fluorouracil regimen failed to effectively improve the OS of patients with Borrmann type IV GC, possibly because poorly differentiated GC cells or peritoneal metastases were not sensitive to this chemotherapy regimen. Therefore, it is urgent to find safe and effective treatments to improve the OS of these patients.

Different from traditional therapies, immunotherapy achieves antitumor effects by activating the body's own immune system and removing immunosuppression. It has been suggested that immunotherapy can enhance the response of T cells to tumour antigens and the ability to detect and kill the deposition of micrometastases that have spread beyond the excised tumour[32,33]. Currently, immunotherapy is gradually playing an increasingly important role in the treatment of

Table 6 Comparison of tumor indexes between programmed cell death 1 + S-1 + oxaliplatin group and S-1 + oxaliplatin group before and after chemotherapy

	P-SOX group (*n* = 28)			SOX group (*n* = 61)		
	First diagnosed	Preoperative	*P* value	First diagnosed	Preoperative	*P* value
AFP (ng/mL)			0.019[a]			0.002[a]
≤ 8.1	20 (71.43%)	20 (71.43%)		43 (70.49%)	46 (75.41%)	
> 8.1	2 (7.14%)	4 (14.29%)		8 (13.11%)	11 (18.03%)	
Unknown	6 (21.43%)	4 (14.29%)		10 (16.39%)	4 (6.56%)	
CEA (ng/mL)			0.211			0.405
≤ 5	16 (57.14%)	22 (57.14%)		35 (57.38%)	43 (70.49%)	
> 5	6 (21.43%)	2 (21.43%)		16 (26.23%)	14 (22.95%)	
Unknown	6 (21.43%)	4 (14.29%)		10 (16.39%)	4 (6.56%)	
CA199 (U/mL)			0.232			0.181
≤ 37	16 (57.14%)	22 (57.14%)		36 (59.02%)	49 (80.33%)	
> 37	6 (21.43%)	2 (21.43%)		15 (24.59%)	8 (13.11%)	
Unknown	6 (21.43%)	4 (14.29%)		10 (16.39%)	4 (6.56%)	
CA724 (U/mL)			0.356			0.552
≤ 6.9	12 (42.86%)	18 (42.86%)		32 (52.46%)	32 (52.46%)	
> 6.9	10 (35.71%)	6 (35.71%)		19 (31.15%)	23 (37.70%)	
Unknown	6 (21.43%)	4 (14.29%)		10 (16.39%)	6 (9.84%)	
CA125 (U/mL)			0.005[a]			0.023[a]
≤ 35	13 (46.43%)	23 (82.14%)		42 (68.85%)	54 (88.52%)	
> 35	9 (32.14%)	1 (3.57%)		9 (14.75%)	3 (4.92%)	
Unknown	6 (21.43%)	4 (14.29%)		10 (16.39%)	4 (6.56%)	
CA50 (U/mL)			0.301			0.915
≤ 25	18 (64.29%)	22 (64.29%)		42 (68.85%)	47 (77.05%)	
> 25	4 (14.29%)	2 (14.29%)		9 (14.75%)	8 (13.11%)	
Unknown	6 (21.43%)	4 (14.29%)		10 (16.39%)	6 (9.84%)	
Leukemia			0.366			0.005[a]
≤ 3.5	1 (3.57%)	7 (25%)		3 (4.92%)	12 (19.67%)	
3.5-9.5	19 (67.86%)	16 (57.14%)		43 (70.49%)	43 (70.49%)	
> 9.5	3 (10.71%)	3 (10.71%)		5 (8.20%)	4 (6.56%)	
Unknown	5 (8.20%)	2 (7.14%)		10 (16.39%)	2 (3.28%)	
HGB			0.094			0.045[a]
≤ 130	18 (64.29%)	23 (82.14%)		36 (59.02%)	48 (78.69%)	
130-175	5 (8.20%)	3 (10.71%)		15 (24.59%)	11 (18.03%)	
> 175	0	0		0	0	
Unknown	5 (8.20%)	2 (7.14%)		10 (16.39%)	2 (3.28%)	
Platelets			0.001[a]			0.001[a]
≤ 125	2 (7.14%)	7 (25%)		2 (3.28%)	21 (34.43%)	
125-350	16 (57.14%)	19 (67.86%)		39 (63.93%)	35 (57.38%)	
> 350	5 (8.20%)	0		10 (16.39%)	3 (4.92%)	
Unknown	5 (8.20%)	2 (7.14%)		10 (16.39%)	2 (3.28%)	

Neutrophils			0.077			0.005[a]
≤ 1.8	1 (3.57%)	6 (21.43%)		4 (6.56%)	13 (21.31%)	
1.9-6.3	18 (64.29%)	17 (60.71%)		41 (67.21%)	42 (68.85%)	
> 6.3	4 (14.29%)	3 (10.71%)		6 (9.84%)	4 (6.56%)	
Unknown	5 (8.20%)	2 (7.14%)		10 (16.39%)	2 (3.28%)	

[a]Statistically significant ($P < 0.05$).

SOX: S-1 + oxaliplatin; P-SOX: Programmed cell death 1 + S-1 + oxaliplatin; AFP: Alpha-fetoprotein; CEA: Carcinoembryonic antigen; CA199: Carbohydrate antigen199; HGB: Hemoglobin.

GC. Kang *et al*[34] found that nivolumab as a third-line therapy significantly prolonged OS in patients with advanced GC. The KEYNOTE-062 clinical trial, a phase III study of pembrolizumab in advanced or metastatic gastric adenocarcinoma, showed that treatment with pembrolizumab significantly improved OS in patients with strongly PD-L1-positive tumours (combined positive score ≥ 10)[35]. The NCT03472365 clinical trial evaluated the efficacy of camrelizumab combined with chemotherapy (oxaliplatin and capecitabine) in the treatment of advanced GC and found that the treatment regimen of the PD-1 inhibitor combined with platinum and 5-fluorouracil can effectively improve the survival and prognosis of patients[36]. Moreover, with the published results of the CheckMate 649 study, which confirmed that untreated patients with HER2- advanced GC could benefit from the treatment of chemotherapy combined with nivolumab compared with chemotherapy alone, chemotherapy with immunotherapy was recommended as the first-line treatment for advanced or metastatic GC[21]. This study is the first to investigate the safety and efficacy of immunotherapy combined with platinum plus S-1 in the treatment of Borrmann large type III and type IV GCs. Our results confirmed that the good response rate (TRG 0 and TRG 1) to NAT was 42.86% in the P-SOX group, while the good response rate (TRG 0 and TRG 1) to NAT was 18.03% in the SOX group. There was a significant difference between the two groups. TRG plays an important role in evaluating the chemotherapy response in NAT; it was determined to be an independent factor affecting the prognosis of GC, and patients with complete tumour regression usually have a better prognosis[37]. Previous studies have demonstrated that immunotherapy can reduce the TRG classification[38]. In addition, the yp N0 rate in the P-SOX group was higher than that in the SOX group. Further multivariate analysis confirmed that the use of PD-1 inhibitors was an independent factor affecting TRG. This indicates that chemotherapy combined with PD-1 inhibitors may improve the prognosis of patients with Borrmann large type III and type IV GCs.

In addition, in terms of adverse reactions and postoperative complications after NAT, there was no significant difference in the adverse reactions to chemotherapy between the P-SOX group and the SOX group in this study. The total postoperative complication rate was 10.11%, the incidence of grade II complications was 7.87%, the incidence of grade III complications was 2.25%, and there were no grade IV or V complications. The P-SOX group had less surgical blood loss than the SOX group, and the remaining postoperative complications were not significantly different. This is similar to the results reported by Lin *et al*[27], which also indicates that PD-1 inhibitors combined with platinum plus S-1 treatment does not lead to an increase in the adverse reactions of chemotherapy in patients. Moreover, it reduces postoperative adverse reactions in patients.

However, this study also has several limitations. First, although there was no statistically significant difference in clinical data between the two groups, the bias could not be completely eliminated. Second, the numbers of samples in the two groups were relatively small, especially the number of patients in the P-SOX group, and large sample prospective clinical studies are needed to further confirm our findings. Additionally, PD-L1 expression was not measured, and differences in the combined positive score may have influenced the results of this study.

In conclusion, we demonstrated that a PD-1 inhibitor combined with oxaliplatin + S-1 can significantly improve the TRG ratio (TRG 0/1) of Borrmann large type III and IV GCs. This treatment plan does not increase postoperative complications or adverse reactions related to NAT. The results of this study must be confirmed by further prospective trials.

CONCLUSION

A PD-1 inhibitor combined with chemotherapy could significantly improve the rate of tumour regression during NAT for patients with Borrmann large type III and IV GCs without increasing the number of adverse reactions to chemotherapy compared with chemotherapy alone.

ARTICLE HIGHLIGHTS

Research background

Gastric cancer (GC) is the fifth most common and fourth deadliest malignancy in the world. Due to the lack of typical symptoms and an effective screening program, most patients are already at an advanced stage when diagnosed, which also leads to poor overall survival. Surgery has always been the core treatment of the gastrointestinal tract. Radical

gastrectomy is suitable for patients with early GC. Postoperative adjuvant chemotherapy for advanced GC is not satisfactory, with high rate of distant metastasis and local recurrence.

Research motivation

Borrmann major type III and IV GCs are generally characterized by low early diagnosis rate, easy metastasis, poor prognosis, and high mortality. The objective of this study was to investigate the efficacy and safety of programmed cell death 1 (PD-1) inhibitors combined with platinum + S-1 in the treatment of Borrmann type IV and large type III GC.

Research objectives

To investigate the safety and efficacy of PD-1 inhibitor combined with oxaliplatin and S-1 (SOX) in the treatment of Borrmann large type III and IV GC.

Research methods

A retrospective analysis (IRB-2022-371) was performed on 89 patients with Borrmann III who received neoadjuvant therapy (NAT) between January 2020 and December 2021. Patients with type I and type IV GC were retrospectively analyzed. According to different neoadjuvant treatment regimens, patients were divided into SOX group (61 cases) and PD-1 + SOX (P-SOX) group (28 cases).

Research results

The pathological response (tumor regression grade 0/1) in P-SOX group was significantly higher than that in SOX group (42.86% *vs* 18.03%, $P = 0.013$). The incidence of ypN0 in P-SOX group was higher than that in SOX group (39.29% *vs* 19.67%, $P = 0.05$). The use of PD-1 inhibitors was an independent factor affecting tumor regression grade. At the same time, the use of PD-1 did not increase postoperative complications or adverse effects of NAT.

Research conclusions

PD-1 inhibitors combined with SOX significantly improved the rate of tumor regression during NAT in Borrmann's large type III and IV GC patients.

Research perspectives

To find new treatment options to improve the prognosis of patients with Borrmann large type III and IV GC.

FOOTNOTES

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