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Clinical efficacy and safety of adjuvant immunotherapy (Tislelizumab) plus chemotherapy *vs.* adjuvant chemotherapy alone in lymph node-positive patients with gastric cancer after D2 radical resection: a prospective, 2-arm, phase II study

J.-W. SHI[1,2], Y. ZHOU[1,2], S. WU[1,2]

[1]The Affiliated Yixing Clinical School of Medical School of Yangzhou University, Yangzhou University, Jiangsu, China
[2]Department of Oncology, Yixing Hospital Affiliated to Medical College of Yangzhou University, Yangzhou University, Jiangsu, China

Abstract. – OBJECTIVE: This study aims to investigate the effectiveness and safety of adjuvant Tislelizumab (BeiGene China Co., Ltd, Changping District, Beijing, China) in combination with chemotherapy for patients with localized lymph node-positive disease following D2 (extended lymphadenectomy) radical gastrectomy for gastric cancer.

PATIENTS AND METHODS: Patients with lymph node-positive gastric cancer who underwent D2 radical gastrectomy at Yixing People's Hospital between April 2021 and June 2022 were selected and enrolled in the study. They were divided into the study group, which received immunotherapy (Tislelizumab) in combination with chemotherapy (XELOX regimen: Xeloda plus Oxaliplatin), or the control group, which received chemotherapy alone (XELOX regimen). Adverse events, disease-free survival (DFS), and overall survival (OS) were observed. This study was registered on ClinicalTrials.gov (ClinicalTrials.gov Identifier: NCT05844371).

RESULTS: The one-year disease-free survival (DFS) rate was 81.82% in the study group compared to 71.43% in the control group. Although the DFS rate tended to be higher in the study group, the difference did not reach statistical significance (p=0.388, HR=0.573, 95% CI: 0.161-2.032). Patients in both groups tolerated the treatment well. Both groups exhibited similar rates of neutropenia, hemoglobin depletion, gastrointestinal reactions, abnormal liver function, and peripheral neuritis. The majority of adverse events in both groups were grade 1-2, with only hypothyroidism showing a significant difference (p=0.021). The only statistically significant difference in grade 3-4 adverse events was thrombocytopenia (p=0.048). All adverse reactions were effectively managed with symptomatic treatment.

CONCLUSIONS: The addition of adjuvant PD-1 inhibitor (Tislelizumab) to XELOX therapy showed a favorable impact on the one-year disease-free survival (DFS) rate when compared to adjuvant XELOX chemotherapy alone in patients with regional lymph node-positive disease after D2 radical gastrectomy. Moreover, patients were able to tolerate the accompanying adverse effects, which were deemed safe.

Key Words:
Immunotherapy, Chemotherapy, Gastric cancer, D2 radical gastrectomy, Localized lymph node-positive.

Introduction

In China, gastric cancer accounts for approximately 479,000 new cases annually, thus ranking it as the third most prevalent malignant tumor in the country[1]. Around 374,000 individuals lost their lives to gastric cancer, placing it as the third-leading cause of death in terms of malignant tumors during that time. A significant number of patients are already in advanced stages at the time of diagnosis, with early gastric cancer representing only 10- 20% of cases and exhibiting a 5-year survival rate of fewer than 50%[2]. A limited group of individuals diagnosed with early gastric cancer hold the potential to achieve

Corresponding Author: Y. Zhou, MD; e-mail: dryanz@163.com

complete recovery through comprehensive treatment. The majority of therapies available for locally advanced gastric cancer rely on a combination of two drugs: Platinum, Fluorouracil, Paclitaxel, and Anthracycline. These regimens have shown promising results in extending patient survival to a certain degree[3]. Despite continuous advances in tumor treatment, the prognosis for locally advanced gastric cancer remains poor, emphasizing the urgent need for new therapies. Notably, the development and utilization of immune checkpoint inhibitors have demonstrated promising therapeutic effects across various malignancies, leading to the emergence of immune checkpoint-related signaling pathway intervention as a novel strategy for cancer treatment[4]. Currently, both domestic and foreign authorities consistently recommend the use of PD-1 monoclonal antibodies as a third-line treatment for gastric cancer. Tislelizumab, developed by BeiGene China Co., Ltd. (Changping District of Beijing, China), is a self-improving PD-1 monoclonal antibody that has been further optimized based on traditional PD-1 antibodies. Tislelizumab possesses a unique binding epitope and a binding surface on PD-1 that extensively overlaps with that of PD-L1 (Programmed cell death 1 ligand 1), enabling it to block PD-1 binding to PD-L1 effectively. Furthermore, Tislelizumab demonstrates remarkable binding kinetics, exhibiting a slower rate of dissociation from PD-1 and a high affinity[5]. By specifically targeting the constant region of antibodies that bind to Fc-γ effector receptors, Tislelizumab has been ingeniously engineered to evade binding to Fc-γ-R (Fc-γ Receptors) on macrophages. As a result, it effectively inhibits antibody-dependent cell-mediated phagocytosis (ADCP), thereby sidestepping any potential compromise in antitumor efficacy caused by a decrease in T cell abundance[6,7]. BGB-A317-205 was a meticulously designed open-label, non-randomized phase II study[8] aimed at assessing the effectiveness of Tislelizumab in tandem with chemotherapy among Chinese patients grappling with advanced gastric/gastroesophageal adenocarcinoma. The findings showcased that the amalgamation of Tislelizumab and chemotherapy was generally well-received bypatients diagnosed with gastric cancer (GC) / gastroesophageal junction cancer (GEJ), exhibiting an Objective Response Rate (ORR) of 47% and a Disease Control Rate (DCR) of 80%. Currently, there are limited reports on the effectiveness and safety of combining programmed death-1 (PD-1) inhibitors with chemotherapy in the postoperative adjuvant treatment of gastric cancer. Therefore, this prospective, two-arm, nonrandomized study aims to investigate the efficacy and safety of combining the PD-1 inhibitor Tislelizumab with chemotherapy compared to chemotherapy alone in patients who have localized node-positive disease after undergoing D2 radical gastrectomy for gastric cancer. The goal is to offer guidance for clinical treatment selection and introduce a novel approach to treating locally advanced gastric cancer, with the ultimate hope of improving the survival prognosis for patients with this condition. This study has undergone review and approval by the ethics committee of Yixing People's Hospital, with the ethics review number AF/SC-05/1.0.

Patients and Methods

Case Selection and General Information

Lymph node-positive patients who underwent D2 radical gastrectomy for gastric cancer treatment at Yixing People's Hospital between April 2021 and June 2022 were included in this study. The inclusion criteria were as follows: (1) patients with a good bone marrow reserve, including leukocyte count $\geq 4\times10^9$/L, neutrophil count $\geq 1.5\times10^9$/L, platelet count $\geq 100\times10^9$/L, and hemoglobin level ≥90 g/L. (2) Patients with unremarkable cardiopulmonary function. (3) Patients with normal liver and kidney function, such as creatinine ≤1.5×Upper Limit of Normal (ULN) or a calculated serum creatinine clearance ≥50 ml/min (calculated according to the Cockcroft Gault formula), albumin ≥30 g/L, and total bilirubin ≤1.5×ULN, as well as Alanine Aminotransferase (ALT) / Aspartate Aminotransferase (AST) ≤2×ULN. (4) Patients with an international normalized ratio/activated partial thromboplastin time ≤1.5×ULN. (5) Patients aged 18 years or older, with a Karnfsky Performance Status (KPS) score ≥80, and patients with little impact on prognosis from bone marrow status, liver and kidney function, and cardiopulmonary function. The exclusion criteria were as follows: patients with a previous history of immunodeficiency, acquired or congenital immunodeficiency diseases, or organ transplantation; patients with preexisting thyroid dysfunction that cannot be maintained within the normal range despite medical therapy; pregnant or lactating women; patients with

a history of substance abuse or mental disorders who are unable to abstain. A total of 43 patients who met the inclusion criteria were enrolled in either the study group, which received immunization (Tislelizumab) combined with chemotherapy (XELOX regimen), or the control group, which received chemotherapy alone (XELOX regimen). The study was conducted in accordance with the Declaration of Helsinki, and all enrolled patients provided signed informed consent approved by the ethics committee (Figure 1). The detailed clinical baseline characteristics of the two groups are presented in Table I, and the baseline characteristics were generally balanced. Adenocarcinoma was found in all patients through postoperative pathology. All tables and figures can be found at the end of the text or in supplementary materials.

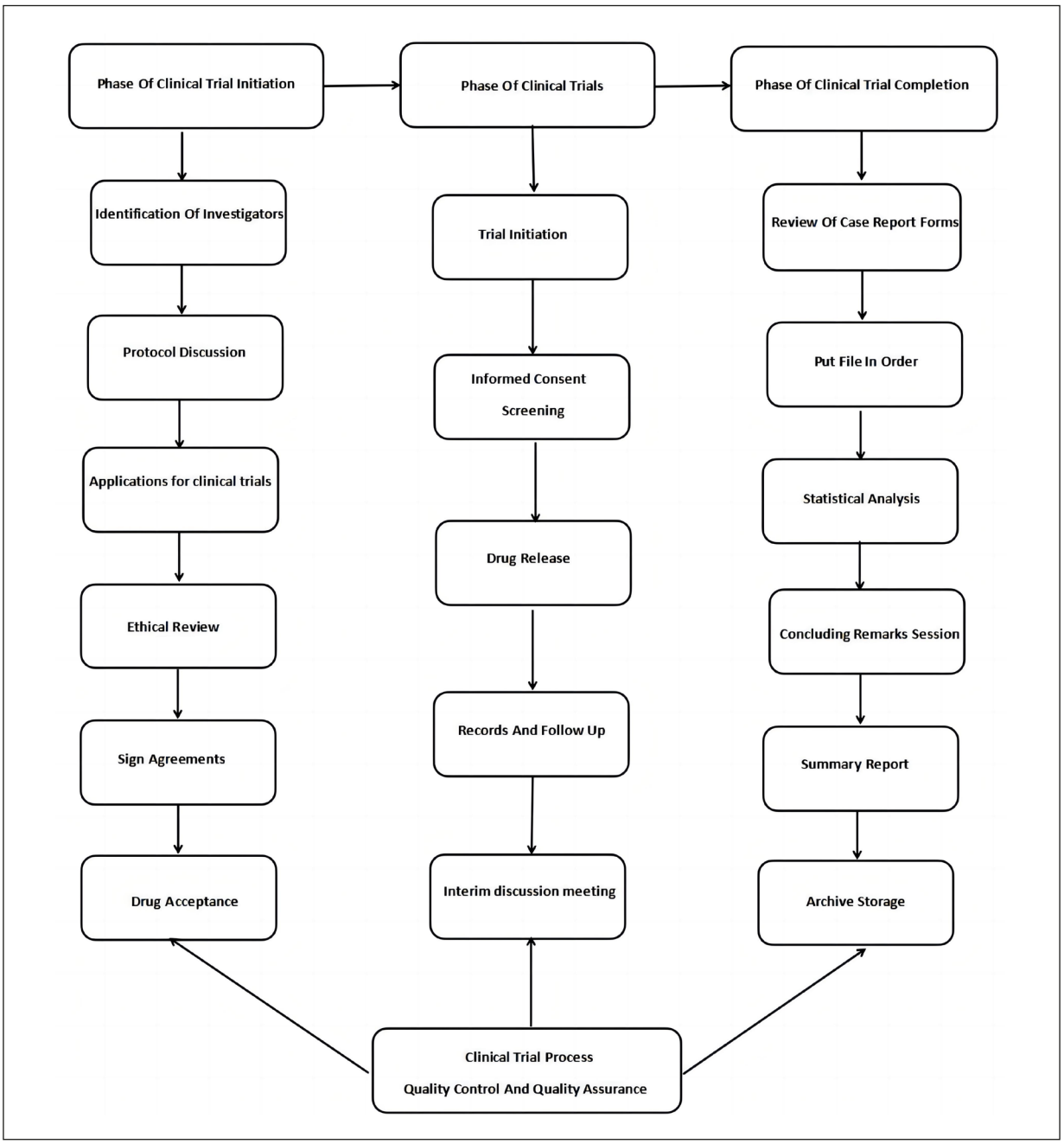

Figure 1. Flow chart of study participants.

Table I. Baseline characteristics of the patients in the two groups.

Clinical features	N	Study group (n=22)	Control group (n=21)	*p*-value
Sex				0.721
Male	34	18	16	
Female	9	4	5	
Age (year)				> 0.999
< 65	19	10	9	
≥ 65	24	12	12	
ECOG score				0.488
0	33	18	15	
1	10	4	6	
Tumor site				0.795
Cardia	10	4	6	
Fundus of gastric	9	4	5	
Gastric body	10	6	4	
Lesser curvature side	14	8	6	
Clinical stages				0.513
IIA	6	2	4	
IIB	5	2	3	
IIIA	13	6	7	
IIIB	13	7	6	
IIIC	6	5	1	
T staging				0.528
T1	1	0	1	
T2	6	3	3	
T3	22	10	12	
T4	14	9	5	
N staging				0.788
N1	8	3	5	
N2	18	10	8	
N3	17	9	8	
Differentiated degree				> 0.999
Well and moderately differentiated	14	7	7	
Poorly differentiated	29	15	14	
Lauren type				0.618
Intestinal type	8	3	5	
Diffuse type	17	10	7	
Mixed type	18	9	9	
Nervous invasion				> 0.999
+	29	15	14	
-	14	7	7	
Vascular invasion				0.526
+	29	16	13	
-	14	6	8	

ECOG=Eastern Cooperative Oncology Group. DFS=Disease-free Survival. T=Primary Tumor. N=Regional Lymph Node.

Treatment Protocol

Patients with lymph node-positive gastric cancer who underwent D2 radical surgery were carefully selected for this study. Those who had contraindications to chemotherapy and immune checkpoint inhibitor treatment were excluded. Treatment was initiated within 3-6 weeks after obtaining the patient's consent. In the study group, patients received chemotherapy with the Oxaliplatin + Xeloda regimen. This involved administering Oxaliplatin at a dose of 130 mg/m^2 on day 1, while Xeloda tablets (Roche Pharma Ltd, Basel, Switzerland) were given at a dose of 1,000 mg/m^2 twice daily from day 1 to day 14, with a 21-day repetition cycle. Additionally, Tislelizumab was administered at a dose of 200 mg every 3 weeks. After completing 6 cycles of chemotherapy, patients continued with Tislelizumab monotherapy at the same dosage for up to 1 year. The control group underwent 6 cycles of Oxaliplatin + Xeloda chemotherapy. In the event of grade 3-4 adverse events occurring during treatment,

the drug dosage was reduced, or treatment was temporarily suspended until each index recovered. If adverse events persisted, the treatment was discontinued. Treatment was continued until disease progression, death, or the development of intolerable toxic effects.

Evaluating Indicator

After the initiation of treatment, patients in both groups underwent computed tomography (CT) based efficacy assessments every three cycles. The adverse effects testing methods included blood routine, liver and kidney function, thyroid function, and Eastern Cooperative Oncology Group (ECOG) score, among others.

Assessment of efficacy

Disease-free survival (DFS) is defined as the time from surgical resection to the occurrence of disease recurrence. Overall survival (OS) is defined as the time from disease onset to death resulting from any cause.

Adverse effects

The Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 was utilized for evaluating the acute toxic side effects experienced by patients. The primary acute toxic effects encompass myelosuppression (such as leukopenia, neutropenia, thrombocytopenia, and decreased hemoglobin), inflammation related to immunotherapy (such as myocarditis, pneumonia, encephalitis, hepatitis, and enteritis), as well as hyperthyroidism or hypothyroidism, abnormal liver function, abnormal renal function, gastrointestinal reactions, diarrhea, and changes in body mass, among others.

Follow-up

All 43 patients were successfully treated at the Department of Oncology of Yixing People's Hospital. Throughout their treatment, their conditions were meticulously documented. Following their outpatient visits, regular follow-up sessions were conducted both in person and over the phone. The diligent follow-up process continued for a complete period of 12 months, ensuring comprehensive monitoring of all patients.

Statistical Analysis

SPSS 26.0 (IBM Corp., Armonk, NY, USA) software was used to analyze all data in this study. Categorical data were presented as either the number of cases or percentage, while meteorological data were transformed into categorical data using the critical point. The χ^2 test or Fisher's exact test was used to calculate the efficacy and incidence of adverse effects in both groups. Survival analysis was conducted using the Kaplan-Meier method, and survival curves were plotted. The log-rank method was employed to compare outcomes between groups. Cox regression models were utilized to analyze factors influencing survival. All results were considered statistically significant at $p<0.05$.

Results

Survival Analysis

All patients were followed for up to 12 months. In the study group, four patients experienced recurrence, resulting in a 1-year disease-free survival (DFS) rate of 81.82%. In the control group, six patients had recurrences, yielding a 1-year DFS rate of 71.43%. The comparison between the two groups revealed no significant difference in the 1-year DFS rate, with a p-value of 0.388 (HR=0.573, 95% CI: 0.161-2.032) (Figure 2). The results suggest a potential improvement in the 1-year DFS rate for patients who received both Tislelizumab and XELOX chemotherapy compared to those who solely underwent XELOX chemotherapy. However, this difference did not reach statistical significance. When analyzing

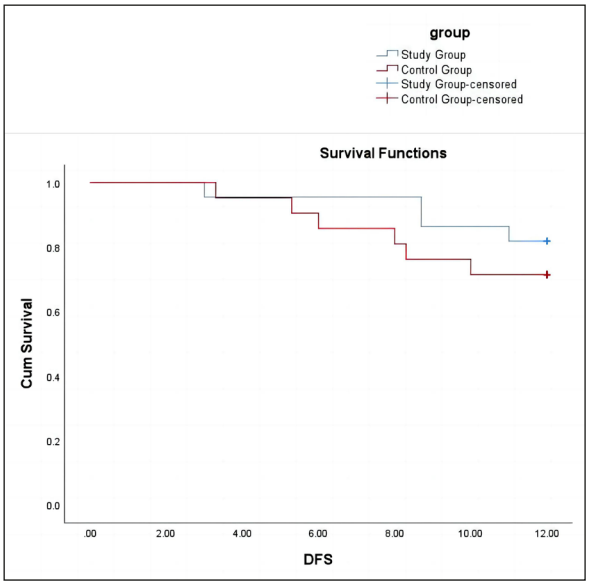

Figure 2. 1-year DFS survival curves in the study and control groups. DFS= Disease-free Survival.

various subgroups, including age, ECOG score, sex, tumor site, and differentiated degree, the study group consistently demonstrated a higher 1-year DFS rate compared to the control group. Nevertheless, these differences were not statistically significant (p>0.05) (Figure 3).

Analysis of Prognostic Factors

The univariate analysis indicated that ECOG score, N stage, and Lauren classification significantly affected the prognosis of the patients in terms of DFS. In addition, the multivariate analysis confirmed that ECOG score and N stage were independent prognostic factors for DFS in patients. The statistical significance (p<0.05) of these findings is presented in Table II.

Comparison of Adverse Effects

The adverse effects observed in both groups were predominantly grade 1 to 2, with the only statistically significant difference being the occurrence of hypothyroidism (p=0.021). For grade 3-4 adverse events, the only statistically significant difference was observed in thrombocytopenia (p=0.048). No significant difference was found between the two groups in terms of other adverse effects (p>0.05) (Table III). Symptomatic management effectively controlled each adverse event, and no deaths related to serious adverse effects were reported in any of the patients.

Discussion

Gastric cancer has emerged as one of the deadliest malignancies, posing a grave threat to human well-being[9]. Surgery is considered the primary treatment for gastric cancer, and clinical practice commonly employs postoperative adjuvant chemotherapy. This approach is widely rec-

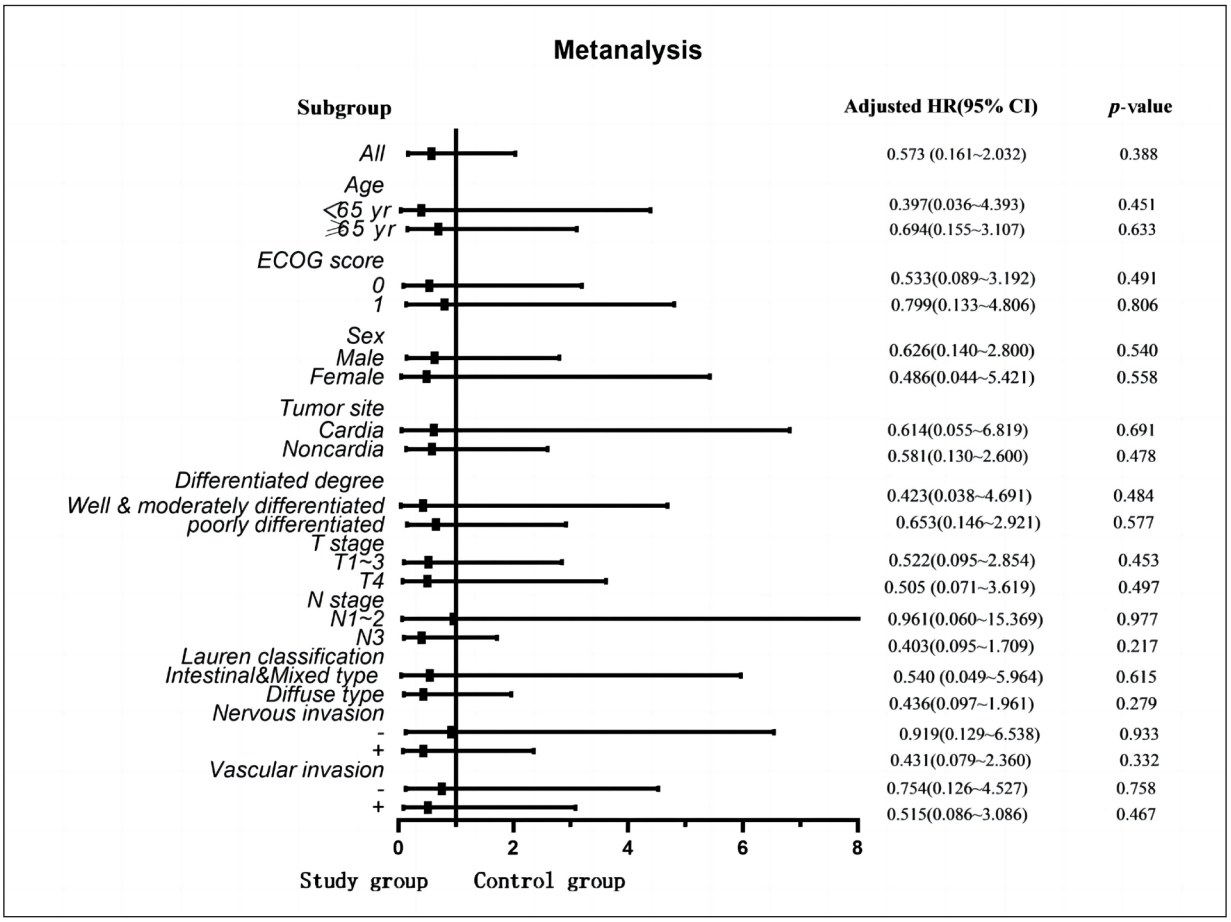

Figure 3. Comparison of 1-year DFS between the two treatment regimens in different subgroups of patients. All=all patients in the study. ECOG=Eastern Cooperative Oncology Group. DFS=Disease-free Survival. T=Primary Tumor. N=Regional Lymph Node.

Table II. Prognostic factors for 1-year DFS in both groups.

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Male *vs.* Female	0.586 (0.151-2.271)	0.440		
< 65 y *vs.* ≥ 65 y	0.526 (0.136-2.035)	0.352		
ECOG score 0 *vs.* 1	0.275 (0.080-0.952)	0.042	0.202 (0.056-0.732)	0.015
Cardia tumors *vs.* Noncardia tumors	1.525 (0.394-5.900)	0.541		
Stage - *vs.* Stage -	0.725 (0.154-3.415)	0.684		
T1-2 *vs.* T3-4	0.538 (0.068-4.249)	0.557		
N1-2 *vs.* N3	0.128 (0.027-0.602)	0.009	0.177 (0.033-0.949)	0.043
Well and moderately differentiated *vs.* poorly differentiated	0.855 (0.221-3.309)	0.821		
Intestinal and Mixed type *vs.* Diffuse type	0.242 (0.062-0.941)	0.041	0.376 (0.084-1.691)	0.202
Nervous invasion - *vs.* +	0.789 (0.222-2.797)	0.713		
Vascular invasion - *vs.* +	0.488 (0.141-1.688)	0.257		

ECOG=Eastern Cooperative Oncology Group. DFS=Disease-free Survival. T=Primary Tumor. N=Regional Lymph Node.

ognized for its ability to greatly enhance patient outcomes[10,11]. The CLASSIC study demonstrated a notable extension in Disease-Free Survival (DFS) and Overall Survival (OS) among gastric cancer patients who underwent adjuvant chemotherapy using XELOX[12]. The XELOX regimen has been widely recommended by major guidelines as the standard postoperative chemotherapy for patients with stage II/III disease[13]. In the realm of treating patients with advanced gastric cancer, there has been a significant shift from traditional chemotherapy to molecularly precise targeted therapy. This advancement has swiftly ushered in the era of immunotherapy. Moreover, the conventional notion of solely eliminating tumors has evolved into one that emphasizes the combination of immune regulation and tumor management. Consequently, these revolutionary changes have led to prolonged patient survival and improved overall quality of life[14,15]. The 2020 edition of the Chinese Society of Clinical Oncology guidelines have made a Grade-I recommendation for nivolumab as a third-line therapy for patients with advanced metastatic gastric cancer. Immunotherapy has significantly transformed the treatment approach for advanced gastric cancer, constantly expanding its application. Nonetheless, the prognosis for locally advanced gastric cancer remains bleak, with a high incidence of postoperative recurrence and metastasis. Particularly, patients in stage III of the disease have a 5-year survival rate of no more than 40%[16]. There is an urgent need for new treatments that can enhance outcomes

Table III. Comparison of the incidence of adverse effects between the study and control groups [n (%)].

	Grade 1-2			Grade 3-4		
Adverse effects	Study group (n = 22)	Control group (n = 21)	*p*-value	Study group (n = 22)	Control group (n = 21)	*p*-value
Neutropenia	9 (40.91)	12 (57.14)	0.366	2 (9.09)	1 (4.76)	> 0.999
Thrombocytopenia	7 (31.82)	5 (23.81)	0.736	5 (22.73)	0	0.048
Hemoglobin decreased	8 (36.36)	10 (47.62)	0.543	4 (18.18)	2 (9.52)	0.664
Gastrointestinal responses	5 (22.73)	7 (33.33)	0.510	3 (13.64)	1 (4.76)	0.607
Abnormal liver function	7 (31.82)	5 (23.81)	0.736	1 (4.55)	0	> 0.999
pneumonia	0	0	-	0	0	-
Hypothyroidism	6 (22.27)	0	0.021	0	0	-
Islet dysfunction	1 (4.55)	0	> 0.999	0	0	-
Hand foot syndrome	2 (9.09)	0	0.488	1 (4.55)	0	> 0.999
Peripheral neuritis	5 (22.73)	3 (14.29)	0.698	2 (9.09)	0	0.488

for patients grappling with locally advanced gastric cancer. The objective of this prospective, non-randomized study was to assess the effectiveness and safety of combining PD-1 inhibitor (Tislelizumab) with chemotherapy compared to chemotherapy alone in patients who underwent D2 radical gastrectomy for gastric cancer and had localized lymph node-positive disease. The study found that the 1-year disease-free survival (DFS) rates were 81.82% in the study group and 71.43% in the control group. These findings indicate that the addition of Tislelizumab to XELOX regimen chemotherapy as adjuvant treatment leads to improved 1-year DFS in patients with lymph node-positive disease after D2 radical resection for gastric cancer (HR=0.573, 95% CI: 0.161-2.032). However, it should be noted that the difference between the study and control groups was not statistically significant (p=0.388), potentially due to the relatively delayed postoperative staging in the study group.

In this study, both univariate and multivariate analyses highlighted ECOG score 1 and N3 stages as independent poor prognostic factors for the disease-free survival (DFS) of patients.

In the present study, both the Tislelizumab plus XELOX group and the XELOX alone group exhibited good tolerability. The most commonly observed adverse event was myelosuppression. There were similar incidences of neutropenia, hemoglobin reduction, gastrointestinal reaction, abnormal liver function, and peripheral neuritis between the two groups, with no statistically significant differences. Most adverse reactions in both groups were mild to moderate (grade 1 to 2). Among these, hypothyroidism was more frequent in the study group than in the control group (22.27% *vs*. 0%, p=0.021). Among grade 3 to 4 adverse events, thrombocytopenia occurred more frequently in the study group than in the control group (22.73% *vs*. 0%, p=0.048). Symptomatic management effectively controlled all adverse effects, and no patient experienced any relevant deaths due to serious adverse effects.

Conclusions

This study demonstrated that the combination of PD-1 inhibitor Tislelizumab with XELOX chemotherapy significantly enhanced the 1-year disease-free survival (DFS) rate in patients with localized lymph node-positive disease after D2 radical gastrectomy for gastric cancer, compared to XELOX chemotherapy alone. Moreover, both treatment regimens exhibited favorable tolerability profiles in patients. Nonetheless, it is important to acknowledge certain limitations of the present study. Firstly, being a single-center prospective study, the sample size was relatively small. Secondly, the follow-up was conducted *via* telephone, and not all patients underwent testing for potential biomarkers. These factors may impact the representativeness of the data and introduce recall bias, influencing the interpretation of outcomes. Consequently, additional prospective clinical studies with larger sample sizes are necessary to validate these findings and draw more conclusive results.

In conclusion, the combination of PD-1 inhibitor (Tislelizumab) and XELOX chemotherapy is demonstrated to be superior to XELOX chemotherapy alone in the treatment of patients with localized lymph node-positive gastric cancer after D2 radical gastrectomy. Moreover, the 1-year disease-free survival (DFS) rate of the patients is found to be beneficial, and the adverse safety profile is deemed manageable. As a result, these findings warrant further clinical promotion and application. However, it is crucial to conduct future studies with larger prospective multicenter samples to provide additional evidence to confirm the efficacy and safety of this research protocol.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Authors' Contribution

Yan Zhou contributed to the conception and design of the study. Shuang Wu contributed to the statistical analysis. All authors contributed to the article and approved the submitted version.

ORCID ID
Jiawei Shi: 0009-0000-3281-6141.

Data Availability
The datasets generated during and analyzed during the current study are available from the corresponding author on reasonable request.

Informed Consent
This study was performed in accordance with the Declaration of Helsinki. The patients provided their written informed consent to participate in this study.

Ethics Approval
This study involving human participants was reviewed and approved by the institutional review boards and Ethics Committees of Yixing People's Hospital and Medical College of Yangzhou University (acceptance code: AF/SC-05/1.0).

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