

Retrospective Study

Evaluation of oxaliplatin and tiglio combination therapy in locally advanced gastric cancer

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Specialty type: Gastroenterology and hepatology**Provenance and peer review:** Unsolicited article; Externally peer reviewed.**Peer-review model:** Single blind**Peer-review report's classification****Scientific Quality:** Grade C**Novelty:** Grade B**Creativity or Innovation:** Grade B**Scientific Significance:** Grade B**P-Reviewer:** Vivolo R, Italy**Received:** March 5, 2024**Revised:** April 26, 2024**Accepted:** May 14, 2024**Published online:** June 27, 2024**Processing time:** 116 Days and 22.4 Hours**Teng Wang, Li-Yun Zhang**, Department of Gastroenterology, Xianyang Hospital, Yan'an University, Xianyang 712000, Shaanxi Province, China**Corresponding author:** Li-Yun Zhang, MM, Associate Chief Physician, Department of Gastroenterology, Xianyang Hospital, Yan'an University, Wenjin New Town Residential Area, Yingbin Avenue, Weicheng District, Xianyang 712000, Shaanxi Province, China.
zhangliyun0301111@163.com**Abstract****BACKGROUND**

Locally advanced gastric cancer (LAGC) is a common malignant tumor. In recent years, neoadjuvant chemotherapy has gradually become popular for the treatment of LAGC.

AIM

To investigate the efficacy of oxaliplatin combined with a tiglio neoadjuvant chemotherapy regimen *vs* a conventional chemotherapy regimen for LAGC.

METHODS

Ninety patients with LAGC were selected and randomly divided into control and study groups with 45 patients in each group, according to the numerical table method. The control group was treated with conventional chemotherapy, and the study group was treated with oxaliplatin combined with tiglio-neoadjuvant chemotherapy. The primary outcome measures were the clinical objective response rate (ORR) and surgical resection rate (SRR), whereas the secondary outcome measures were safety and Karnofsky Performance Status score.

RESULTS

The ORR in the study group was 80.00%, which was significantly higher than that of the control group (57.78%). In the study group, SRR was 75.56%, which was significantly higher than that of the control group (57.78%). There were 15.56% adverse reactions in the study group and 35.56% in the control group. These differences were statistically significant between the two groups.

CONCLUSION

The combination of oxaliplatin and tiglio before surgery as neoadjuvant chemotherapy for patients with LAGC can effectively improve the ORR and SRR and is safe.

Key Words: Locally advanced gastric cancer; Oxaliplatin and tiglo; Neoadjuvant chemotherapy; Surgical resection rate; Objective response rate; Clinical efficacy

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Core Tip: This study identified the following highlights. The objective response rate in the study was 80.00%, which was significantly higher than that of the control group (57.78%). In the study group, 75.56% of the tumors were resected, which was significantly higher than that of the control group (57.78%). There were 15.56% adverse reactions in the study group and 35.56% in the control group. These differences were statistically significant between the two groups.

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INTRODUCTION

According to the Global Cancer Statistics Report 2022, stomach cancer is the fifth most common malignancy worldwide and one of the leading causes of cancer-related deaths[1]. As of 2022, there were approximately 1089103 new cases of gastric cancer (GC) worldwide and approximately 768793 deaths[2]. GC is usually diagnosed at advanced stages in Chinese patients, and surgical resection remains the primary choice of treatment. However, in locally advanced GC (LAGC), only a small percentage of cases are surgically resected, and the proportion of radical resections is even low[3]. After exploratory laparotomy, the opportunity for surgery is often lost because the tumor invades adjacent organs, has extensive infiltration and metastasis, or only palliative resection can be performed, and the postoperative survival rate is low[4].

With the advancement of diagnostic and treatment technology in recent years, comprehensive treatment of GC has made some progress[5]. However, there is still a 20% 5-year survival rate for LAGC, and the postoperative recurrence rate and mortality rate remain high[6]. It is estimated that around 60% of the patients with GC will have local recurrence or distant metastasis even after radical resection (R0 resection)[7]. The proportion of patients with GC in stages II-III in our country is as high as 58.0%[8]. To improve the rate of R0 resection and reduce the incidence of postoperative recurrence and metastasis, the addition of neoadjuvant therapy undoubtedly brings new hope for the survival and benefits of patients with GC.

Studies have shown that neoadjuvant chemotherapy is a type of systemic chemotherapy for patients before surgery that plays a role in shrinking tumors and facilitating follow-up treatment[9,10]. Compared with conventional treatment, neoadjuvant chemotherapy has more significant clinical efficacy, higher drug safety, better disease control effects, and higher application value in advanced tumors[11,12]. Japan is advocating a chemotherapy regimen based on tiglo (S-1) [13]. Tiglo, a derivative of fluorouracil, is an oral anticancer agent with definite efficacy in the adjuvant treatment of GC. Five-year survival data from a Japanese trial of tiglo-assisted chemotherapy for GC confirmed an improvement in 5-year OS in patients receiving tiglo-assisted chemotherapy (71.7% vs 61.1%)[14]. However, due to the limited efficacy of single-drug chemotherapy, multi-drug combination regimens are often used clinically. In the ARTIST2 trial, it was shown that postoperative adjuvant (oxaliplatin + tiglo) or SOX + radiotherapy could effectively extend disease-free survival in D2-resectable stage II/ III GC patients compared to tiglo monotherapy[15]. Currently, regarding the neoadjuvant treatment of LAGC, a large-scale phase III clinical trial in China has confirmed the remarkable efficacy of the neoadjuvant scheme, and thus determined that oxaliplatin plus S-1 is the first choice for neoadjuvant chemotherapy of LAGC in China[16].

In this study, we compared the effectiveness of oxaliplatin combined with a tiglo neoadjuvant chemotherapy regimen to a conventional chemotherapy regimen for LAGC to further improve the clinical efficacy in patients with LAGC.

MATERIALS AND METHODS

General information

Ninety patients with clinically diagnosed LAGC between June 2022 and June 2023 were included in this study. Patients were randomly divided into a study group (45 patients) and a control group (45 patients). Both groups underwent B-ultrasonography and magnetic resonance imaging to detect abdominal lymph node metastasis, lesion infiltration, and organ metastasis. Upper gastrointestinal barium meal test revealed normal digestion.

Inclusion and exclusion criteria

The inclusion criteria[17] were as follows: pathologically diagnosed LAGC, aged between 18 and 75 years, did not receive chemotherapy or radiotherapy, no distant metastasis, signed the informed consent form, the expected survival time was

more than 6 months, and the Karnofsky Performance Status (KPS) score was > 60 points. The exclusion criteria were as follows: those whose physical signs did not meet the standards for chemotherapy, history of GC-related diagnosis and treatment, combined with other malignant tumors, and pregnant and lactating women.

Ethical approval

The hospital ethics committee approved informed consent forms for all chemotherapy patients.

Treatment methods

The 90 enrolled patients underwent routine and complete examinations, routine blood tests, liver and kidney function tests, electrocardiography, and cardiac ultrasonography. Antiemetics, stomach and liver protection, and other treatments were routinely administered before medication; specifically, 30 min before medication, patients were instructed to take intramuscular diphenhydramine and intravenously administered cimetidine (300.0 mg), and dexamethasone (7.5 mg) at 21:00 the previous night and 6 h in the morning of chemotherapy, and patients were administered antiemetic treatment with drugs, such as granisetron and metoclopramide.

In the control group, conventional chemotherapy was administered, that is, on the 1st d of chemotherapy, epirubicin 75 mg/m² + cisplatin 40 mg/m². The treatment course was 21 d.

The study group was treated with neoadjuvant chemotherapy[15], specifically, oxaliplatin and tiglo combined treatment, oxaliplatin intravenous infusion on the first day of treatment at an infusion dose of 130 mg/m² (the first day), and tiglo oral therapy at the same time at a dose of 80 mg/m² twice a day. Both groups were treated for 21 d, and the duration of treatment for both groups was more than two courses.

Observation indicators

Primary observation indicators: Evaluation of the objective response rate (ORR). According to RECIST1.0 standards[18]: (1) The tumor disappears completely and a complete response (CR) is achieved; (2) partial response (PR), the lesion shrinks by ≥ 50%; (3) the tumor is stable, and the lesions shrink by < 50% or increase by < 25%; and (4) tumor progression, with lesions increasing by ≥ 25%. The calculation method of clinical remission rate in each group is: (Complete remission + partial remission)/number of cases × 100%.

Surgical resection rate (SRR): Patients undergoing surgical resection/ total patients treated per group × 100%.

Secondary observation indicators: Adverse reactions: The incidence of adverse reactions in the two groups before and after treatment was analyzed. KPS scores: Before and after treatment, the KPS scores were compared between the two groups.

Statistical analysis

This group used SPSS 26.0 for the analysis and processing of the research data. Measurement data were expressed as (mean ± SD), *t*-tests were used to compare measurements, and count data were expressed as percentages (%). Chi-square tests were used to compare count data between groups, with *P* < 0.05 indicating statistically significant differences between the groups.

RESULTS

Comparison of general data

The research flowchart is presented in [Figure 1](#). A total of 25 men and 20 women participated in this study. Average age was 48.8 ± 9.5 years and body mass index (BMI) was 23.50 ± 3.12. Of these patients, 4 had diabetes, 18 had hypertension, 9 had hyperlipidemia, and 2 had arrhythmia; 16 were smokers and 20 were alcoholics. A total of 24 men and 21 women participated in this study. Their average age was 49.5 ± 9.8 years and BMI was 24.01 ± 2.85. Among them, 5 had diabetes, 14 had hypertension, 11 had hyperlipidemia, and 1 had arrhythmia; 18 were smokers and 22 were alcoholics. There were no statistically significant differences in the general information between the two groups during the study period (*P* > 0.05), indicating comparability. [Table 1](#) presents the results of the study.

Comparative analysis of recent treatment efficacy

Statistical analysis of the recent treatment efficacy in the two groups of patients revealed that among the 45 patients in the study group, 11 were classified as CR, 25 as PR, 6 cases as stable disease (SD), and 3 cases as progressive disease (PD). The ORR was 80.00% (36/45), and the disease control rate (DCR) was 93.33% (42/45). In the control group, there were 9 patients with CR, 17 with PR, 12 with SD, and 7 with PD. The ORR was 57.78% (26/45) and the DCR was 84.44% (38/45). The clinical efficacy was higher in the study group than that in the control group, and statistically significant differences were observed between the two groups (*P* < 0.05) ([Table 2](#)).

Comparison of the SRR

The study group had a significantly higher resection rate of 75.56% than that of the control group (57.78%). The differences between the groups were statistically significant (*P* < 0.05). The results are presented in [Figure 2A](#).

Table 1 Comparison of clinical data between the two groups

Index	Study group (n = 45)	Control group (n = 45)	χ^2/t	P value
Sex			0.044	0.832
Male	25	24		
Female	20	21		
Age (yr)	48.80 ± 9.50	49.50 ± 9.80	0.639	0.524
BMI (kg/m ²)	23.50 ± 3.12	24.01 ± 2.85	0.796	0.427
Complications (n)			0.795	0.672
Diabetes	4	5		
Hypertension	18	14		
Hyperlipidemia	9	11		
Arrhythmia	2	1		
Smoking history (n)			0.189	0.664
Yes	16	18		
No	29	27		
Drinking history (n)			0.179	0.673
Yes	20	22		
No	25	23		

BMI: Body mass index.

Table 2 Analysis of short-term efficacy of patients between two groups

Index	Study group (n = 45)		Control group (n = 45)		χ^2	P value
	n	%	n	%		
CR	11	24.44	9	20.00		
PR	25	55.56	17	37.78		
SD	6	13.33	12	26.67		
PD	3	6.67	7	15.56		
ORR (CR + PR)	36	80.00	26	57.78	11.519	0.011
DCR (CR + PR + SD)	42	93.33	38	84.44	4.215	0.016

CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease; ORR: Overall response Rate; DCR: Disease control rate.

Comparison of KPS scores

Compared with that before treatment, a significant improvement in KPS scores was observed in the study group ($P < 0.05$). The results are presented in [Figure 2B](#).

Comparison of adverse reactions

Based on the statistical results, 15.56% of the study group experienced adverse reactions compared to 35.56% of the control group ($P < 0.05$), indicating a statistically significant difference. as shown in [Table 3](#).

DISCUSSION

LAGC is a common malignant tumor in clinical practice. Most patients are asymptomatic in the early stages and are often treated at a later stage because of gastrointestinal reactions[19]. After gastroscopy and pathological examination, these tumors are often found in the middle and late stages, thus losing the best period for surgery[20]. Neoadjuvant chemotherapy has become a new treatment method for some patients with middle and advanced malignant tumors in

Table 3 Comparison of adverse reactions between the two groups

Index	Study group (n = 45)		Control group (n = 45)		χ^2	P value
	n	%	n	%		
Abnormal liver function	1	2.22	5	11.11		
Nausea and vomiting	3	6.67	6	13.33		
Diarrhoea	2	4.44	3	6.67		
Decreased white blood cells	1	2.22	2	4.44		
Total	7	15.56	16	35.56	10.512	< 0.001

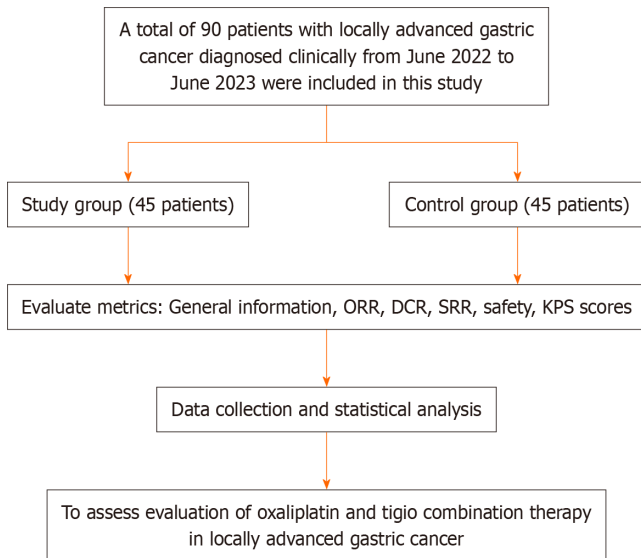


Figure 1 Flow chart. ORR: Overall response rate; DCR: Disease control rate; SRR: Surgical resection rate; KPS: Karnofsky Performance Status.

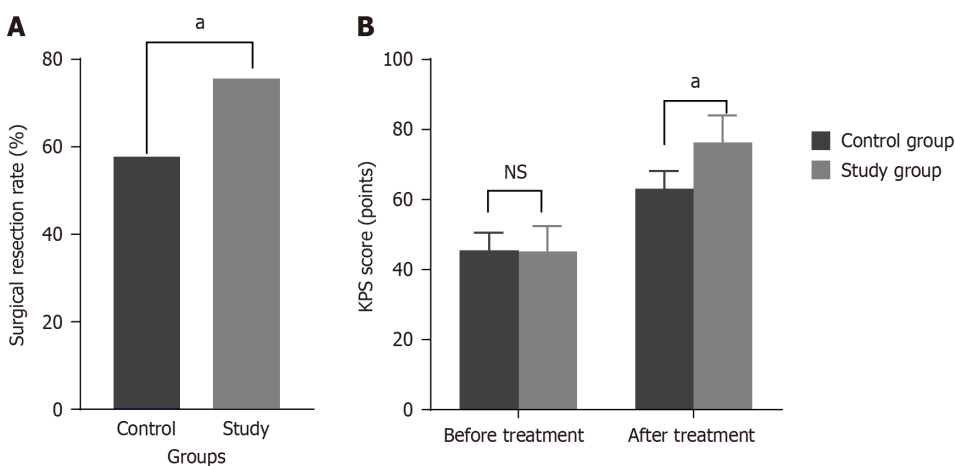


Figure 2 The surgical resection rate and Karnofsky Performance Status scores between the two groups. A: Surgical resection rate; B: Karnofsky Performance Status scores. KPS: Karnofsky Performance Status.

recent years, aiming to control and shrink the progression of the lesions through chemotherapy and then achieve therapeutic purpose through surgical treatment[21]. This type of therapy mainly uses a combination of two or three drugs; however, the number of drugs must be selected according to the patient’s body indicators and tolerance before treatment[22].

The results of this study showed that the ORR of the study group was 80.00% after treatment, which was significantly higher than that of the control group (57.78%) ($P < 0.05$). Compared with the control group, the study group had a resection rate of 75.56%, while the control group had a resection rate of 57.78%, and the two groups differed significantly

($P < 0.05$). This finding is consistent with those of the previous studies[23-25]. Analysis of the reasons: Compared with traditional chemotherapy methods, oxaliplatin and tiglo combined neoadjuvant chemotherapy regimen can effectively reduce focal diameter and control disease progression through the rational combination of multiple therapeutic drugs, thus further reducing the tumor stage of patients and providing a basis for the implementation of further treatment. In addition, neoadjuvant chemotherapy can have a good inhibitory effect on the metastasis and proliferation of cancer cells in patients, which can further improve the treatment effect, avoid the risk of patient prognosis recurrence, and improve the quality of life. However, in actual treatment, three drugs, two drugs, or single drugs should be carefully selected according to the physical strength and age of patients to reduce adverse reactions and improve the patient's quality of life.

According to this study, the study group experienced adverse reactions at a rate of 15.56% compared with the control group's 35.56%, which was statistically significant ($P < 0.05$). There was a significantly greater improvement in KPS score in the research group than that in the control group, with $P < 0.05$, which is in general agreement with the findings of Cui *et al*[26] and Dimpel *et al*[27]. This may be because the combined application of oxaliplatin and tiglo can play a synergistic role in enhancing the antitumor effect. Oxaliplatin is a platinum-based anticancer drug that inhibits DNA replication and transcription, thereby inhibiting the proliferation of tumor cells. Tiglo is an oral fluorouracil analog that inhibits the growth of tumor cells by inhibiting enzymes, such as thymidylate synthase, which interferes with DNA synthesis. The combined use of these two drugs is advantageous and improves their therapeutic effects. Simultaneously, the oral administration of tiglo is more convenient than intravenous administration, and its metabolites are less toxic to normal cells, which can reduce the incidence of adverse reactions.

Limitation

This study has several limitations. First, this was a single-center study, and a selection bias may have influenced the results. As a retrospective study, there were some limitations, such as the lack of a thorough research plan and information bias. Second, this study did not include indicators of blood drawing in patients before and after surgery. If more detailed biochemical indicators are available and their data statistics and analyses are performed, it may further explain why neoadjuvant chemotherapy does not increase the incidence of recent postoperative complications. Third, the sample size of this study was small, and the representation of the whole population was limited; therefore, this study still needs to be verified by a prospective study with a larger sample size.

CONCLUSION

In conclusion, for patients with LAGC, compared with conventional chemotherapy, oxaliplatin combined with tiglo as a preoperative neoadjuvant chemotherapy regimen can effectively increase the ORR and SRR, has certain safety, and improve its clinical therapeutic effect.

FOOTNOTES

Author contributions: Zhang LY designed this study, collected and analyzed the data; Wang T drafted the manuscript and gave final approval of the version to be published; Wang T and Zhang LY took part in this study as endoscopic operators or assistants.

Institutional review board statement: The study was reviewed and approved by the Medical Ethics Committee of Xianyang Hospital, Yan'an University (Approval No. 2023-299).

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

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