Efficacy Analysis of Trastuzumab Combined With FLOT as Neoadjuvant Treatment of Human Epidermal Growth Factor Receptor 2 Positive Advanced Gastric Cancer

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This research aims to assess the efficacy of neoadjuvant trastuzumab with 5-fluorouracil, leucovorin, oxaliplatin and docetaxel for the treatment of human epidermal growth factor receptor 2 positive metastatic gastric cancer. To conduct the research, we recruited 80 patients having human epidermal growth factor receptor 2 positive advanced gastric cancers between January 2020 and December 2021 admitted to our institution and randomly allocated them to the control and observation groups, each with 40 cases. Patients in the 5-fluorouracil, leucovorin, oxaliplatin and docetaxel group served as controls, while those in the observation group underwent a combination of trastuzumab and 5-fluorouracil, leucovorin, oxaliplatin and docetaxel. The short-term curative outcome of patients after neoadjuvant therapy was evaluated; the levels of carcinoembryonic antigen, serum glycoprotein 19-9 and glycoprotein (carcinoembryonic antigen 72-4) were measured by chemiluminescence immunoassay. Side effects experienced by patients in both groups were recorded when they occurred during therapy. The disease control rate and objective response rate of the observation group were found to be statistically and clinically higher than those of the control group ($p<0.05$), per the findings of the short-term effectiveness assessment. After treatment, there was a notable reduction in serum carcinoembryonic antigen, carcinoembryonic antigen 19-9 and carcinoembryonic antigen 72-4 in both groups (both $p<0.05$) and the levels of carcinoembryonic antigen 72-4, carcinoembryonic antigen 19-9 and carcinoembryonic antigen in the observation group were considerably lower than the control group ($p<0.05$). There was no evident difference between the two patient groups in adverse reactions. Trastuzumab combined with 5-fluorouracil, leucovorin, oxaliplatin and docetaxel has high efficacy and safety in neoadjuvant therapy for human epidermal growth factor receptor 2-positive advanced gastric cancer patients and it can be popularized and applied as a new model of clinical treatment.

Key words: Trastuzumab, 5-fluorouracil, leucovorin, oxaliplatin, docetaxel, gastric cancer, neoadjuvant therapy

Gastric cancer is the 5th most common malignant tumor globally and poses a significant threat to human health. Statistics show that more than 1 million new cases are reported annually[1]. Currently, surgery is a successful therapy for gastric cancer. Gastric cancer has a high death rate since its early signs are rarely noticeable. As a consequence, most patients are detected in the disease's intermediate to late stages, after the time frame for surgical therapy has been over. Patients with advanced gastric cancer are often treated with chemotherapy and it has greatly contributed to the improvement of both the disease-free survival rate and overall survival rate for these patients[2]. Neoadjuvant therapy is expected to reduce the tumor burden of gastric cancer before the operation, minimize the clinical phase of gastric cancer, improve the possibility of radical surgery and provide systemic treatment for tumors in advance. Meanwhile, neoadjuvant therapy is also currently a clinical research hotspot, which evaluates the effectiveness of chemotherapy regimens and provides a reference for the formulation of postoperative chemotherapy. In addition to its roles in normal cell development, tumor cell proliferation and metastasis, Human Epidermal Growth Factor Receptor 2 (HER-2) also plays a significant role in gastric carcinogenesis. Since HER-2 overexpression or

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amplification is associated with a poor prognosis in gastric cancer, it is being studied as a possible prognostic factor and therapeutic target[3]. Trastuzumab is a targeted therapy drug that inhibits HER-2 gene expression and inhibits tumor growth and metastasis[4]. Trastuzumab has been shown to be effective in the first-line treatment of patients with advanced gastric cancer that has spread to other parts of the body; however, more research is needed to determine whether the drug is also effective or not when used in conjunction with chemotherapy in the neoadjuvant treatment of these patients. This study aims to help clinicians make better-informed decisions by analyzing the efficacy of trastuzumab in combination with 5-Fluorouracil, Leucovorin, Oxaliplatin and Docetaxel (FLOT) for the neoadjuvant therapy of HER-2 positive advanced gastric cancers. Between January 2020 and December 2021, 80 patients with advanced gastric cancer that screened positive for HER-2 were hospitalized to our hospital's Department of Medical Oncology and Surgery, where our multidisciplinary team examined their treatment options. These patients required preoperative chemotherapy and were chosen as research subjects. They were randomly assigned to the observation and control groups, each of which had 40 cases. Control group have 14 female and 26 male patients; age ranges 40 y-71 y, average (53.32±5.06) y old. Observation group have 18 female and 22 male patients; age ranges 42 y-70 y, average (55.11±4.62) y old. The comparison of the medical records of the two groups is shown in Table 1. Inclusion criteria includes advanced gastric cancer diagnosed after gastroscopic pathology and imaging examination, Immunohistochemical (IHC) IHC (2+) or HER-2 (3+) and Fluorescence *In Situ* Hybridization (FISH) positive; no distant metastasis; no prior targeted therapy or chemotherapy; complete clinical data and provided consent. Exclusion criteria includes patients with severe complications such as gastrointestinal bleeding, gastrointestinal obstruction or perforation; patients with abnormal blood routine or kidney, liver and other organ dysfunction; patients with other tumors or peripheral nerves systemic diseases, severe primary disorders of the kidney, cerebrovascular and cardiovascular, liver and hematopoietic systems or mental illness. In the control group, 40 patients received FLOT treatment. On the 1st d, docetaxel injection of 50 mg/m^2, oxaliplatin injection of 85 mg/m^2, calcium folinate for injection of 200 mg/m^2, 5-fluorouracil injection of 2600 mg/m^2 were pumped continuously, 1 time/day, intravenous infusion for 2 h/time, repeated medication in the 2nd w, 2 w as a cycle, 4 cycles of treatment. Trastuzumab combined with the FLOT regimen was given to 40 individuals in the observation group. The FLOT protocol was identical to the control group. The medication method of trastuzumab was as follows; on the 1st d, the first intravenous infusion of trastuzumab 8 mg/kg once a day, administrated by 6 mg/kg dosage, 3 w as a cycle and 3 treatment cycles. The enhanced CT examination of the upper abdomen within 1 w before neoadjuvant treatment was used as the baseline image and the enhanced CT of the upper abdomen was re-examined after neoadjuvant treatment to investigate the effectiveness. Preoperative therapy efficacy was compared between the two groups using the Response Evaluation Criteria in Solid Tumors (RECIST) 1.0, which classifies patient's tumor responses as Progressing Disease (PD), Partial Response (PR), Stable Disease (SD) or in Complete Response (CR). Disease Control Rate (DCR)=(CR+PR+SD)/total number of cases×100 % and Objective Response Rate (ORR)=(CR+PR)/total number of cases×100 %. Fasting venous blood samples (5 ml) were taken from patients before and after therapy to determine tumor marker concentrations in the serum, centrifuging the blood at 3000 rpm for 10 min to separate the serum and then storing the serum at -20°. Serum concentrations of Carbohydrate Antigen (CA) 19-9, CA72-4 and Carcinoembryonic Antigen (CEA) were measured using chemiluminescent immunoassay. Keep records frequency of adverse medication reactions in the two patient groups while they are receiving therapy. Statistical Package for the Social Sciences (SPSS) 22.0 was used for the statistical analysis of the data. The adoption rate (%) of count data was used and Fisher's test was used to do group comparisons; measurement findings were shown as mean±standard deviation (x±s). A significant difference exists between groups if the significance threshold is less than 0.05. There was a statistically significant ($p<0.05$) increase in ORR and DCR in the observation group than the control as shown in Table 2. None of the pretreatment differences in CA72-4, CA19-9 or CEA serum concentrations were significant ($p>0.05$). The CA19-9, CEA and CA72-4 serum levels were all reduced after treatment and the difference between the two groups was statistically significant (all $p<0.05$). However, the levels of CA72-4, CA19-9 and CEA were all considerably lower in the observation group. Table 3 displays data from the placebo group ($p<0.05$). Most of the adverse reactions in the two groups were grade I-II, including nausea and vomiting, anemia, leukopenia,

thrombocytopenia and fatigue. As can be shown in Table 4, there was no significant difference in the frequency of adverse reactions between the two groups (p>0.05). Early gastric cancer usually lacks typical clinical manifestations and about 70 % of patients are in locally advanced or advanced stage at first diagnosis. Surgical treatment alone has a poor curative effect on locally advanced gastric cancer. Even with D2 radical resection, the 5 y survival rate after surgery remains below 50 %[5]. Neoadjuvant therapy can reduce the invasion or compression of tumor cells to surrounding tissues, reduce the primary lesion's size and facilitate the realization of R0 resection. In addition, preoperative tumor cells have rich blood supply and high sensitivity to chemotherapy drugs. Neoadjuvant therapy can kill some malignant cells, minimize the risk of intraoperative dissemination and metastasis, prolong disease-free survival and bring survival benefits to patients[6]. Therefore, it is particularly important to choose efficient and safe neoadjuvant chemotherapy. HER2 positivity in gastric cancer ranges from 12 % to 20 %[7]. HER2-positive advanced gastric cancer has a high degree of malignancy, unique biological behavior, early metastasis and recurrence and is not sensitive to conventional chemotherapy[8]. Trastuzumab role as a first-line curative for HER2-positive advanced gastric cancer was demonstrated by the trastuzumab for gastric cancer study[9]. Combining it with neoadjuvant chemotherapy has shown promising results in studies involving patients with HER2-positive, late-stage gastric cancer, with a pathological CR (pCR) rate of 8 %-21.4 % [10-12]. Earlier studies have demonstrated that the addition of trastuzumab to FLOT in the perioperative cure of HER2-positive advanced gastric cancer patients can remarkably increase the pCR rate and the R0 resection rate reaches 90 %[13]. The FLOT treatment consists of docetaxel, oxaliplatin, 5-fluorouracil, and leucovorin. The FLOT4 study published in 2016 confirmed that compared with traditional epirubicin, cisplatin and 5-FU or epirubicin, cisplatin and capecitabine treatment, the efficacy and overall survival rate of FLOT chemotherapy for advanced gastric cancer was significantly improved[14]. To analyze the efficacy of trastuzumab combined with FLOT on neoadjuvant therapy for HER2-positive late gastric cancer, 80 patients were included in this study for a comparative study. The results showed that patients in the control group who got FLOT alone had a lower DCR and ORR compared to those in the observation group who received trastuzumab coupled with FLOT and tumor markers (CA19-9, CEA and CA72-4). Combining FLOT with trastuzumab significantly improved efficacy, since the frequency of adverse events among patients was not substantially greater and the level was considerably lower than in the control group. As a targeted therapy drug, trastuzumab can antagonize the biological functions mediated by HER-2, inhibit the progression of cell cycle and the transcription and expression of HER-2 and prevent angiogenesis, thereby promoting the development of new effects of adjuvant chemotherapy. At the same time, the progress and efficacy of the disease can be judged according to the variations in serum tumor marker levels, which will help to adjust the follow-up treatment plan to better improve the prognosis. In summary, trastuzumab combined with the FLOT regimen has high efficacy and safety in neoadjuvant therapy for HER2-positive advanced gastric cancer patients and it can be popularized and applied as a new model of clinical treatment.

TABLE 1: DEMOGRAPHICS AND OTHER GENERAL DETAILS ABOUT THE TWO GROUPS

Pathological data	Control group	Observation group	p
Age	53. 32±5.06	55.11±4.62	0.1025
Gender			0.4939
Female	14	18	
Male	26	22	
Tumor location			0.5985
Gastric antrum	22	20	
Gastric fundus	5	4	
Gastric body	8	9	
Whole stomach	5	7	
Degree of differentiation			0.8027
Medium-advanced	10	12	
Poor	30	28	
Clinical stage			0.5458
II	5	8	
III	35	32	

TABLE 2: THE TWO PATIENT GROUP'S COMPARISON RESPONSE TO THERAPY IN THE SHORT TERM (n (%), n=40)

Group	CR	PR	SD	PD	ORR	DCR
Control group	1 (2.50)	8 (20.00)	17 (42.50)	14 (35.00)	9 (22.50)	26 (65.00)
Observation group	4 (10.0)	15 (37.50)	16 (40.00)	5 (12.50)	19 (47.50)	35 (87.50)
p	-	-	-	-	0.0270	0.0307

TABLE 3: COMPARISON OF THE LEVELS OF A SERUM TUMOR MARKER IN THE TWO GROUPS (x±s, n=40) BEFORE AND AFTER THERAPY

Group	CA19-9 (U/ml)		CEA (mg/l)		CA72-4 (U/ml)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	62.65±7.26	37.51±5.94*	59.02±11.07	24.19±5.38*	9.54±3.42	4.26±1.13*
Control group	64.16±7.94	48.92±6.28*	57.68±10.56	30.56±6.28*	10.05±3.68	5.64±1.25*
t	0.8877	8.348	0.554	4.872	0.642	5.18
p	0.3775	<0.001	0.5812	<0.001	0.5227	<0.001

TABLE 4: COMPARISON OF THE ADVERSE EFFECTS SEEN BY THE TWO GROUPS (n (%), n=40)

Adverse Reaction	Control group			Observation group			p
	I-II	III-IV	Total incidence	I-II	III-IV	Total incidence	
Nausea and vomiting	15 (37.50)	0 (0.00)	15 (37.50)	18 (45.00)	0 (0.00)	18 (45.00)	0.65
Diarrhea	3 (7.50)	0 (0.00)	3 (7.50)	5 (12.50)	0 (0.00)	5 (12.50)	0.7119
Peripheral neurotoxicity	13 (32.50)	0 (0.00)	13 (32.50)	16 (40.00)	1 (2.50)	17 (42.50)	0.4888
Anemia	7 (17.50)	0 (0.00)	7 (17.50)	6 (15.00)	0 (0.00)	6 (15.00)	>0.9999
Leukopenia	18 (45.00)	2 (5.00)	20 (50.00)	21 (52.50)	3 (7.50)	24 (60.00)	0.5005
Thrombocytopenia	8 (20.00)	0 (0.00)	8 (20.00)	6 (15.00)	0 (0.00)	6 (15.00)	0.7695
Fatigue	6 (15.00)	0 (0.00)	6 (15.00)	8 (20.00)	0 (0.00)	8 (20.00)	0.7695

Author's contributions:

Kangzhong Wu and Yinyuan zheng have contributed equally to this work.

Conflict of interests:

The authors declared no conflict of interests.

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