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Original Article

A clinical exploration of neoadjuvant chemotherapy with tegafur, gimeracil, and oteracil potassium capsules combined with oxaliplatin for advanced gastric cancer

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Abstract: Background: Advanced gastric cancer refers to tumor invasion into the gastric muscularis propria or even the layer beyond, and has low early gastric cancer diagnosis rate. Purpose: To determine the clinical efficacy and side effects of neoadjuvant chemotherapy with tegafur, gimeracil, and oteracil potassium capsules (TGOP) combined with oxaliplatin (SOX regimen) in patients with advanced gastric cancer. Methods: We evaluated 25 patients with advanced gastric cancer who were admitted and treated with neoadjuvant chemotherapy with the SOX regimen (intravenous injection of 130 mg/m^2 oxaliplatin on day 1 followed by oral administration of 60 mg TGOP twice daily on days 1-14), every 3 weeks. The clinical efficacy and side effects of the SOX regimen were evaluated after two courses of treatment, before surgery. Results: Of the 25 patients enrolled in this study, 23 completed two courses of neoadjuvant chemotherapy, and of these, 12 achieved downstaging as determined by the clinical TNM stage, resulting in a total response rate of 52.2%. The 23 patients underwent surgery, with 22 receiving radical resection (95.7%). Among these 23 patients, R0 resection was achieved in 16 (69.6%) and pathological complete remission was observed in one. Conclusion: Neoadjuvant chemotherapy with TGOP combined with oxaliplatin was effective for advanced gastric cancer and had tolerable side effects.

Keywords: Gastric cancer, neoadjuvant chemotherapy, TGOP, oxaliplatin

Introduction

Gastric cancer accounts for 8% of new cancer cases and 10% of cancer-related deaths worldwide, as reported by the World Health Organization. The incidence of gastric cancer is high in East Asia, especially in China, with 46.8% of new cases and 47.8% of deaths worldwide being reported from China [1]. Advanced gastric cancer refers to tumor invasion into the gastric muscularis propria or even the layer beyond. The rate of early gastric cancer diagnosis is only approximately 10%, with most patients being diagnosed at advanced stages [2]. To date, surgical resection has been the only option for curative treatment. However, patients with advanced gastric cancer (stage III and IV) have large tumors that adhere closely to the tissue of surrounding organs and may have existing micrometastatic foci. Therefore, it is often difficult to achieve radical resection with surgery alone, and tumor recurrence after surgery is noted in most patients. Further, postoperative chemotherapy has very limited effects on prolonging the survival of patients [3]. Therefore, actively controlling the micrometastasis foci, to achieve biological radical resection, and improving the surgical resection rate, particularly the radical resection rate, are currently two goals aimed at improving the prognosis of gastric cancer patients.

The main purpose of neoadjuvant chemotherapy, also known as preoperative chemotherapy, is preoperative downstaging, in addition to reducing tumor burden, so as to improve the radical resection rate, and thereby, prognosis. The MAGIC trial [4] was the first phase III randomized controlled clinical trial that confirmed the benefit of perioperative chemotherapy in patients with gastric cancer, with the 5-year survival rate improving from 23% to 36% in gas-

Table 1. The adverse reaction caused by neoadjuvant chemotherapy

Adverse reactions	Cases (%)	Adverse reaction grades			
		I	II	III	IV
Hematologic toxicity					
Leukopenia	7 (30.4%)	3	2	2	0
Lower hemoglobin	11 (47.8%)	5	3	3	0
Thrombocytopenia	10 (43.5%)	7	3	0	0
Reduced neutrophil	22 (95.7%)	7	11	4	0
Non-hematologic toxicity					
Nausea and vomiting	15 (62.2%)	7	5	3	0
Diarrhea	8 (34.8%)	5	1	2	0
Stomatitis	3 (13.0%)	2	1	0	0
Skin	14 (60.9%)	9	2	3	0

tric cancer patients who received perioperative chemotherapy with epirubicin, cisplatin, and 5-fluorouracil. In recent years, neoadjuvant chemotherapy has received increasing attention as a comprehensive treatment method for gastric cancer, and has been included in the treatment recommendations for stage T2 and higher gastric cancer in the National Comprehensive Cancer Network Clinical Practice Guidelines for gastric cancer in 2010. However, to date, no standard neoadjuvant chemotherapy for gastric cancer has been established [5].

Oxaliplatin is a third-generation platinum drug that has shown efficacy in various cell lines that were resistant to cisplatin and even 5-fluorouracil [6]. The combination of oxaliplatin and other cytotoxic drugs has been widely used as adjuvant treatment for colorectal and gastric cancer. Tegafur, gimeracil, and oteracil potassium capsules (TGOP), in the ratio of 1:0.4:1, are newly developed for oral chemotherapy. Tegafur is a 5-fluorouracil prodrug with excellent oral bioavailability and can be converted to 5-fluorouracil in vivo. Gimeracil is a dihydropyrimidine dehydrogenase inhibitor that inhibits the dihydropyrimidine dehydrogenase-dependent catabolism of 5-fluorouracil, thus helping to maintain an effective concentration of 5-fluorouracil in blood and tumor tissues for a long time-mimicking the effect of continuous 5-fluorouracil infusion. Oteracil potassium is a gastrointestinal mucosal protective agent that blocks 5-fluorouracil phosphorylation and alters 5-fluorouracil distribution in the gastrointestinal tract, thereby reducing the toxic effects of 5-fluorouracil [7]. The efficacy of single-drug use in the treatment of advanced gastric cancer is reported to be 20-40% [8-10], and therefore, we hypothesized that the combination of tegafur, gimeracil, and oteracil potassium with oxaliplatin (the SOX regimen) could be a potential neoadjuvant chemotherapy option for advanced gastric cancer. Accordingly, this study aimed to explore the clinical efficacy and side effects of neoadjuvant chemotherapy with the SOX regimen in patients with advanced gastric cancer.

Materials and methods

Eligibility criteria

Twenty-five patients with advanced gastric cancer who were admitted to the second section of the Surgical Department between January 2009 and December 2010 were enrolled in this study. All patients had received a pathological diagnosis before surgery and had consented to the receipt of neoadjuvant chemotherapy with the SOX regimen. The inclusion criteria were a gastric cancer diagnosis based on endoscopic biopsy; stage III or IV ($T_{3\text{-}4}N_{any}M_0$) gastric cancer without distant metastasis, as determined by preoperative abdominal computed tomography or B ultrasonic examination (Union for International Cancer Control staging of gastric cancer, 6th edition); normal results on preoperative blood tests; age less than 75 years; no prior anti-tumor therapy; and information on the purposes, schedules, and side effects of the neoadjuvant chemotherapy provided to the family members of the patients. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of the First People's Hospital of Yongkang. Written informed consent was obtained from all participants.

Neoadjuvant chemotherapy with the SOX regimen

All patients received neoadjuvant chemotherapy with the SOX regimen. Briefly, the regimen comprised intravenous injection of 130 mg/m^2 oxaliplatin on day 1, followed by oral administration of 60 mg TGOP (Weikangda; Lunan Pharmaceutical Co., China) twice daily on days 1-4, every 3 weeks. Two weeks after the completion of the second course of treatment, endoscopy, B ultrasonic examination, and

Table 2. Surgery and pathological data

Surgery	Cases (%)
R0 radical cure	16 (69.6%)
R1 + R2	7 (30.4%)
Surgery approach	
Distal stomach resection + D2/3 lymphadenectom	10 (43.5%)
Full stomach resection + D1 lymphadenectomy	3 (13%)
Full stomach resection + D2/3 lymphadenectomy	9 (39.1%)
Unresectable	1 (4.3%)
Pathologically staging	
I	1 (4.3%)
II	4 (17.4%)
III	9 (39.1%)
IV	8 (34.8%)
Pathological complete remission	1 (4.3%)
T staging	
Tx	2 (8.7%)
T1	0
T2	3 (13%)
T3	13 (56.5%)
T4	5 (21.7%)
N staging	
N0	3 (13%)
N1	10 (43.5%)
N2	6 (26.1%)
N3	3 (13%)
Nx	1 (4.3%)

abdominal computed tomography were performed again. Surgery was performed after comparing imaging results before and after neoadjuvant treatment.

Evaluation of efficacy and side effects

Efficacy was evaluated according to the Response Evaluation Criteria in Solid Tumors [11]. Abdominal computed tomography was used to measure tumor size before and after neoadjuvant chemotherapy, to evaluate complete response (CR), partial response (PR), progressive disease (PD), and stable disease (SD). Chemotherapy-related toxicity was assessed according to the common standards for adverse reactions (Common Terminology Criteria for Adverse Events v3.0) [12].

Surgery

The surgical approach was selected according to tumor location and death of invasion. Patients underwent distal stomach resection, full stomach resection, or combined organ resection, together with routine D2 lymphadenectomy.

Statistical analysis

All statistical analysis was carried out using SPSS17.0 software (SPSS Inc., Chicago, IL, USA). Survival analyses were performed using the Kaplan-Meier method, and survival rates were analyzed using the log-rank test.

Results

Patient characteristics

The study population comprised 20 male and five female patients, aged 31 to 74 years, with a median age of 51 years. All 25 patients received preoperative chemotherapy; 23 (92%) completed two courses of neoadjuvant chemotherapy and then underwent surgery. Of the remaining two patients who did not complete two courses of chemotherapy, one consulted another hospital after one course of chemotherapy and the other could not tolerate the adverse reactions after one course of chemotherapy (this patient underwent surgery after one course).

Efficacy

Efficacy was evaluated by comparing tumor sizes before and after chemotherapy, determined by endoscopy, computed tomography, and other imaging modalities. The response to neoadjuvant chemotherapy was CR in two cases (8.7%), PR in 10 cases (43.5%), SD in seven cases (30.4%), and PD in four cases (17.4%). Thus, the response rate (CR + PR) was 52.2%. Only one patient (4.3%) achieved pathological complete remission.

Safety

The 23 patients who received two courses of neoadjuvant chemotherapy experience varying degrees of nausea, vomiting, fatigue, leukopenia, thrombocytopenia, peripheral sensory neurotoxicity, and other adverse reactions. These could be managed with symptomatic treat-

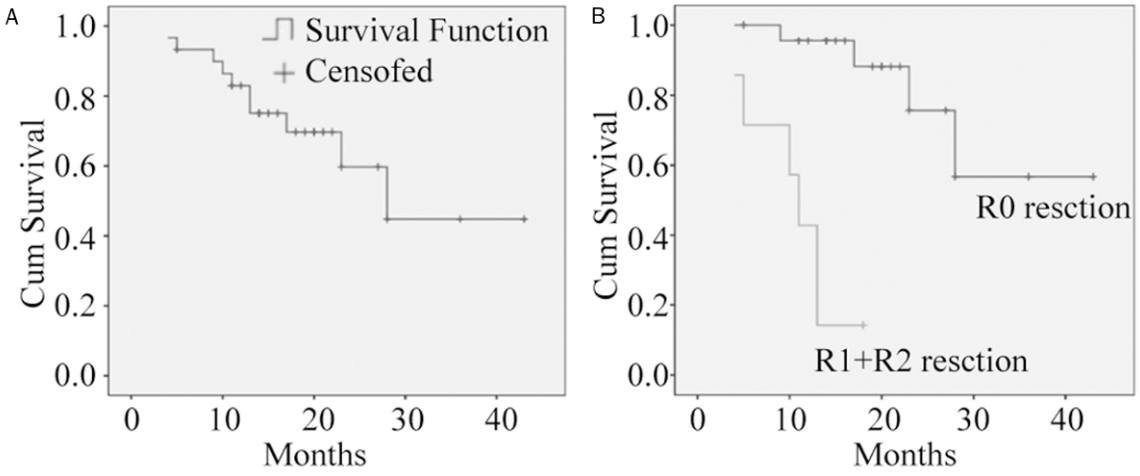

Figure 1. Survival analysis of gastric cancer patients. A. Overall survival of patients with gastric cancer. B. Survival curves of patients undergoing different surgery approaches.

ment, and surgery was possible thereafter. There were no grade 4 hematologic or non-hematologic adverse reactions or deaths due to the chemotherapy (**Table 1**).

Resection

Twenty-three patients underwent surgery. Excluding one patient in whom extensive peritoneal metastasis was detected after laparotomy, radical gastrectomy was achieved in 22 patients. Among these patients, R0 resection was achieved in 16 (69.6%) and pathological complete remission was observed in one (**Table 2**).

Survival analysis

All 23 patients who underwent surgical treatment were followed-up at outpatient clinics and be telephone until February 2013. The follow-up period ranged from 4 to 38 months. Eleven patients were alive at the time of study completion. The 1-year and 2-year survival rates were 82.7% and 59.7%, respectively (**Figure 1A**). R0 resection was significantly associated with patient prognosis ($P < 0.001$, **Figure 1B**).

Discussion

Gastric cancer is a common gastrointestinal malignancy in China, where advanced gastric cancer accounts for a higher proportion of cases and is associated with a low 5-year survival rate of 20.8% to 36.8% [13]. Even if the scope of surgical resection and lymph node dissection were expanded, a biologically significant radical cure with surgery alone would be difficult in most patients. Therefore, two important objectives in improving the prognosis of patients with advanced gastric cancer are actively seeking alternative means for tumor treatment and improvement of the resection rate, especially the rate of radical resection. Neoadjuvant chemotherapy refers to systemic chemotherapy administered before surgery and radiotherapy. It was first introduced for the treatment for gastric cancer by Wilke et al in 1989 [14]. As neoadjuvant chemotherapy for gastric cancer has gained recognition in recent years, clinical studies in this area of research are being undertaken aggressively to evaluate different chemotherapy regimens and drugs, particularly some new drugs. A body of clinical evidence shows that neoadjuvant chemotherapy can downstage tumors, increase the rate of radical resection, and improve patient survival, without increasing the incidence of surgical complications [15-18]. To date, no standard neoadjuvant chemotherapy regimen has been established for gastric cancer, although docetaxel, cisplatin, and 5-fluorouracil; epirubicin, cisplatin, and 5-fluorouracil; pirarubicin, cisplatin, 5-fluorouracil; and cisplatin and 5-fluorouracil have been shown to downstage advanced gastric cancer [4, 19-21].

Oxaliplatin is a third-generation platinum drug that inhibits a variety of tumor types without any renal toxicity. Its combination with 5-fluorouracil has obvious synergetic effects. At the

2007 American Society of Clinical Oncology conference, Moon et al [22] reported the use of FOLFOX7 as neoadjuvant treatment for gastric cancer, which yielded a clinical response rate of 58% and an R0 resection rate of 52%. Another study suggests that the survival benefit with neoadjuvant chemotherapy is more significant in cases of upper stomach cancer [23].

TGOP, an oral drug composition, includes tegafur, a precursor of 5-fluorouracil, and two novel regulatory drugs, gimeracil and oteracil potassium in an appropriate ratio. It is associated with excellent oral bioavailability, resulting in a stable plasma concentration when taken every 12 h. Continuous administration for 14 days is consistent with its time-dependent pharmacological characteristics. Thus, it is an ideal alternative to the continuous intravenous infusion of 5-fluorouracil. Several clinical trials have confirmed its broad application as chemotherapy for gastrointestinal cancer [9]. Currently, oral TGOP is the standard treatment for gastric cancer in Japan [24].

In this study, the pre-chemotherapy staging of all enrolled patients was stage III/IV, and radical resection would be difficult to achieve in most patients. After SOX neoadjuvant chemotherapy, approximately 17.4% of patients showed disease progression, and the R0 resection rate was 69.6% among the 23 patients who completed two courses of neoadjuvant chemotherapy. The survival rate was higher among those in whom R0 resection was achieved than in those with non-R0 resection. The overall clinical efficacy was slightly higher than in the JACCRDGC-01 study, where S-1 plus cisplatin was used as neoadjuvant chemotherapy [25], which reported a pathological response rate of 39%. This might be explained by the fact that the JACCRDGC-01 study included only one cycle of chemotherapy whereas we used two cycles of chemotherapy. The radical resection rate in our study was lower than that in the France FNCLCC ACCORD 07-FFCD 9703 study (84%, France) [21] and similar to that in the MAGIC trial (39%) [14]. The adverse events in this study were also less frequent, with no grade 4 adverse reactions being observed. Therefore, the preoperative neoadjuvant chemotherapy used in this study could effectively control tumor growth, inhibit its progress, and greatly improve the R0 resection rate in patients with advanced gastric cancer, with side effects that were tolerable by most patients.

In summary, the SOX regimen exhibited good clinical efficacy, low toxicity, and improvement in the R0 resection rate in cases of advanced gastric cancer, thus improving short-term survival. Therefore, this regimen could be considered a high-potential neoadjuvant chemotherapy regimen. However, the efficacy and safety of new treatment depended on lots of factors such as patient's age, gender, nutrition status, stage of disease, existed complication, etc. This study mainly compared the survival rate and adverse effects, without considering other contributors. Therefore, the results of this study might have partial bias, which should be overcome in further studies. In addition, this study only included a small sample size, had no control group, and lacked long-term follow-up, the efficacy of the SOX regimen needs to be evaluated further.

Disclosure of conflict of interest

None.

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