ORIGINAL RESEARCH

Treatment Outcome and Safety of the TCX Regimen for Advanced Gastric Cancer: A Prospective Cohort Study

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Objective: To evaluate the outcome and safety of the paclitaxel, carboplatin, and capecitabine (TCX) regimen in patients with advanced gastric cancer.

Methods: Advanced gastric cancer patients received the TCX regimen for up to six cycles, which were 3 weeks apart. Paclitaxel (175 mg/m2) was given over a 3-hour infusion, followed by carboplatin in a 1-hour infusion on day 1. Capecitabine (850 mg/m2) was given orally twice daily from day 1 to day 14. Primary endpoints were progression-free survival (PFS) and overall survival (OS).

Results: Among 83 patients at stage IVa and IVb, the median PFS was 9.3 months; 6-month, 1-year, and 2-year PFS were 74.6%, 32.5%, and 14.4%, respectively. The median OS was 17.0 months; 6-month, 1-year, and 2-year OS were 97.5%, 68.7%, and 21.7%, respectively. In the multivariable Cox regression model, higher CEA was associated with poor OS. Common adverse events included hand-food syndrome (77.9%), peripheral neuropathy (63.2%), fatigue (68.7%), and nausea (54.2%).

Conclusion: The TCX regimen provided good survival and a better safety profile. More clinical trials are needed to confirm its treatment efficacy and safety, especially in comparison with other triplet regimens.

Keywords: paclitaxel, carboplatin, capecitabine, advanced gastric cancer, efficacy

Introduction

Gastric cancer is one of the most common cancers and the leading cause of death in Vietnam.[1] Around 87% of patients with gastric cancer are diagnosed at late stages.[2] While curative surgery (combined with chemotherapy as an adjuvant treatment) is effective in early-stage patients,[3] it is often not possible in late-stage patients; even if it is possible, recurrence and metastasis after surgery are common.[4] As a result, chemotherapy plays a key role at this stage. In addition to improving patient's symptoms and quality of life, chemotherapy also improves survival. In a 2017 systematic review of chemotherapy for advanced gastric cancer, the hazard of death in patients receiving chemotherapy was one-third of that in patients receiving best supportive care.[5] However, toxicity and efficacy should be considered when choosing any chemotherapy regimen.

Currently, no standard chemotherapy regimen has been globally approved for patients with advanced gastric cancer. Although the DCF (docetaxel, cisplatin and 5-fluorouracil) regimen has been found to improve survival and response rate, its hematological toxicities, such as febrile neutropenia, are common.[6–15] The TCX (paclitaxel, carboplatin, and capecitabine) regimen was developed with aim to reduce the toxicity and improve tolerability while maintaining treatment efficacy. In particular, paclitaxel has been linked to lower severe hematological toxicity compared to docetaxel regimens.[16–18] Carboplatin has been associated with less severe nausea/vomiting, thus is expected to improve tolerability and adherence.[19–21] Capecitabine is preferred to continuous infusion of 5-FU because it is more convenient, less costly, and associated with less severe hematological toxicity, including neutropenia and neutropenia febrile.[22] However, no trial

has been conducted to investigate the efficacy of the TCX regimen on advanced gastric cancer patients, with the exception of two studies on metastatic distal esophageal cancer and esophagogastric junction cancer.[23,24]

In Vietnam, ECF (epirubicin, cisplatin, and 5-fluorouracil), EOX (epirubicin, oxaliplatin, and capecitabine), DCF (docetaxel, cisplatin, and 5-fluorouracil), and DCX (docetaxel, cisplatin, and capecitabine) are commonly used for cancer patients at the late stages. The TCX regimen has been introduced in Vietnam since 2016, but no studies have been done to describe its treatment outcome on advanced gastric cancer. Therefore, in this study, we aimed to evaluate the treatment outcome and safety of the TCX regimen on patients with advanced gastric cancer.

Materials and Methods

Study Design

A prospective cohort study was conducted from January 2016 to February 2020 at Hanoi Oncology Hospital on 83 patients diagnosed with advanced gastric cancer and received TCX regimen for at least 3 cycles.

Patient Eligibility

Eligible patients were those with histologically proven advanced gastric cancer (stage IVa/IVb according to the eighth American Joint Committee on Cancer (ACJJ) staging system for gastric carcinoma[25] or metastatic cancer with a history of curative surgery) and an Eastern Cooperative Oncology Group Performance Status (ECOG PS) ≤2 who were planned to start TCX regimen within 4 weeks. Exclusion criteria were prior chemotherapy, HER2-positive gastric cancer, second cancer, a life expectancy of less than 3 months, altered mental status, absolute neutrophil count ≤1500 mm^3, platelet count ≤100,000 mm^3, insufficient liver function (total serum bilirubin >1.5 times the upper normal limit [UNL] or alanine transferase (ALT) >2.5 times or aspartate transferase (AST) >5 times the UNL in patients with liver metastasis), and insufficient renal function (serum creatinine level >1.25 mg/dl or creatinine clearance >60 mL/min). Figure 1 summarizes the screening, recruitment, and follow-up process of this study.

Treatment Schedule

Participants would receive the TCX regimen which includes paclitaxel, carboplatin, and capecitabine for up to six cycles, repeated every 3 weeks. Paclitaxel (175 mg/m^2) was given over a 3-hour infusion, followed by carboplatin (AUC 5) in a 1-hour infusion on day 1. Capecitabine (850 mg/m^2) was given orally twice a day from day 1 to day 14. All patients received a routine supportive treatment plan that included hydration with normal saline (at least 3 L/24 hours), dexamethasone, and 5-HT3 antagonists. Granulocyte colony stimulating factor (G-CSF) was not routinely given, although it was used as secondary prophylaxis and in subsequent courses if severe neutropenia or febrile neutropenia occurred.

Toxicity of the treatment regimen was evaluated based on the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.[26] The TCX regimen would be temporarily discontinued if one of the following toxicities occurred: hematological toxicity (grade 3 or higher), non-hematological toxicity (grade 4), serum creatinine >120 µmol/L, and clinical deterioration (ECOG PS >2). Chemotherapy was continued when the patient's condition improved (ECOG PS ≤2) and the toxic effects reduced to grade 2 or less. The treatment would be terminated if the patient did not improve within 2 weeks of supportive therapy. The subsequent treatment plan was decided by the treating physician based on the patient's condition.

Assessments

Per routine practice, patients were clinically examined at baseline, before each treatment cycle, and after the end of treatment. Evaluations included physical examination, medical history, physical examination, complete blood cell count, serum creatinine and urea, liver enzymes (AST/ALT), tumor markers (CEA [Carcinoembryonic antigen] and CA 72–4 [cancer antigen 72–4]), and computed tomography (CT). A comprehensive assessment was conducted before initiation of chemotherapy, then every 3 weeks, except for tumor markers and CT (at baseline and the end of cycles 3 and 6).

After the end of treatment, patients were followed up every 3 months for disease progression. Follow-up was conducted until 2 years since the beginning of treatment, death, or loss-to-follow-up, whichever came first. All the information has been recorded in detail in patient's medical charts.
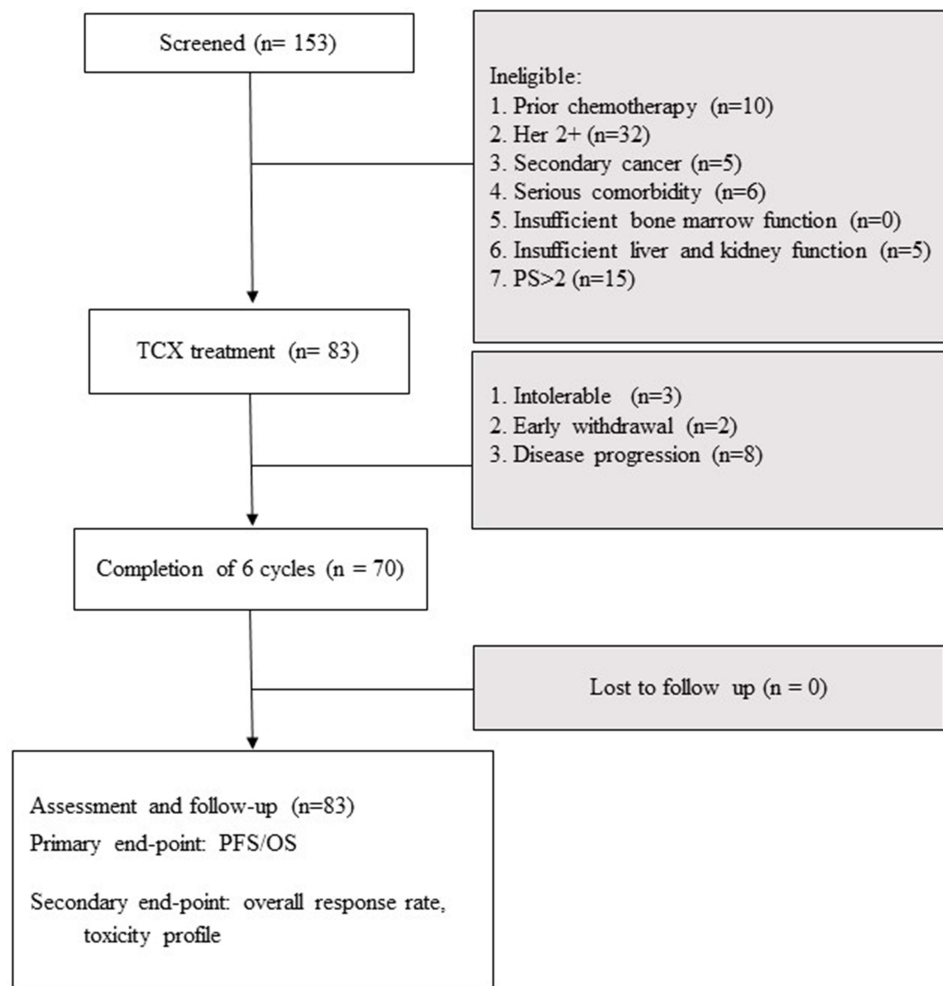
Figure 1 Study flow chart.

For patients who did not return for follow-up, we called the patients or their family to ask for their current status (ie, whether they were alive, whether their cancer had progressed, and the date of these events if they had occurred).

Study Outcomes

Progression-free survival (PFS) and overall survival (OS) were two primary endpoints in this study. PFS was defined as the time since the initiation of TCX regimen to the first documented disease progression or death, whichever came first. Disease progression was defined as (1) an increase in the sum of the longest diameter of target lesions of ≥20% or at least 5 mm, compared with that of the initiation of the treatment and/or (2) the progression of non-targeted lesions; and/or (3) the appearance of one or more new lesions. OS was defined as the time since the initiation of TCX regimen to death, administrative censoring, or the last date the patient was known to be alive (often in patients who were lost to follow-up).

Secondary outcomes included clinical improvement, tumor response, and safety. Clinical improvement was measured by the presence or absence of symptoms and signs at the end of the treatment course compared to baseline evaluation. The measured symptoms and signs included fatigue, abdominal pain, early satiety, anorexia, dysphagia, nausea, vomiting, weight loss, pyloric stenosis, and gastrointestinal bleeding. Tumor response was evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, which takes into account the responses in target and non-target lesions, as well as the formation of new lesions, in comparison to the prior evaluation. The elimination of all target and non-target lesions, normalization of tumor marker levels, and the absence of new lesions were considered complete response. A partial response was defined as a decrease in the sum of the longest diameter of target lesions by at

least 30% compared to baseline, the persistence of one or more non-target lesions without progression and/or the maintenance of tumor marker levels above normal limits, and absence of new lesions.

Safety of the regimen was evaluated by the presence of grade 3/4 adverse events (AEs) using the definitions of adverse events in CTCAE version 4.0. The monitored adverse events included nausea, fatigue, stomatitis, diarrhea, allergy, phlebitis, hand-foot syndrome, peripheral neuropathy, anemia (hemoglobin <8.0 g/dL or transfusion indicated), leukopenia (white cell count <2000/μL), thrombocytopenia (platelet count <50,000/mm^3), transaminitis (AST/ALT >100 UI/L), and hypercreatinemia (serum creatinine >300 mmol/L).

Sample Size
Sample size was calculated based on OS among esophagogastric cancer patients treated with TCX in a previous study.[23] Assuming a 2-year OS of 30%, a margin of error of 10%, and a confidence level of 95%, the minimum sample size was 81 patients. Accounting for 8% loss-to-follow-up, we planned to recruit 88 patients.

Statistical Analysis
Demographic and personal characteristics of the study participants were summarized by frequency and percentage for categorical variables, and median and IQR range for continuous variables.

Kaplan-Meier method was used to estimate the survival endpoints. We would report 6-month, 1-year, and 2-year PFS and OS. The Cox proportional-hazards regression model was used to determine factors associated with the survival outcomes. The candidates for the regression models were selected on the theoretical basis through literature review and clinical experience; factors that were not selected based on theory but associated with the outcomes of interest in the univariable analysis might also be included in the models.

For the clinical improvement endpoints, we compared the presence of symptoms and signs at baseline and after the end of treatment course using McNemar's test for paired dichotomous data. For the safety endpoints, AEs (any grade and grade 3/4) were reported for each cycle. Some AEs that were determined by the blood test results, such as anemia and hypercreatinemia, were recorded as continuous data. For these variables, we also examined the changes over cycles by the spaghetti plot and fitting generalized estimating equations.

All analyses were performed using Stata/BE 17 (StataCorp LLC, College Station, TX, US). An analysis with P-values of <0.05 was considered statistically significant.

Ethical Consideration
The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Hanoi Medical University under decision No. 05/06012017 dated January 06, 2017. Informed consent was obtained from the patients before participating in the study. The investigators were responsible for protecting the privacy and confidentiality of patients as per Vietnam's regulations and Good Clinical Practice.

Results
Participant Characteristics
A total of 83 patients were recruited in this study. At baseline, 77.1% were categorized as ECOG PS 0–1. Major metastatic sites were liver and peritoneum. Histopathologic types included moderately differentiated adenocarcinoma (37.3%), low differentiated adenocarcinoma (34.9%), and squamous cell carcinoma (27.7%) (Table 1).

Survival
Median PFS was 9.3 months; 6-month, 1-year, and 2-year PFS were 74.6%, 32.5%, and 14.4%, respectively. Median OS was 17.0 months; 6-month, 1-year, and 2-year OS were 97.5%, 68.7%, and 21.7%, respectively (Figure 2). The median OS and PFS was significantly longer in patients with CEA <5ng/mL group compared to those with CEA ≥5ng/mL (OS: 20.5 months vs 12.9 months; log-rank p = 0.014; PFS: 11.8 months vs 8.0 months, log-rank p = 0.02) (Figure 3).

Table 1 Baseline Characteristics (n = 83)

Characteristic	Result
Sex, n (%)	
Male	59 (71.1)
Female	24 (28.9)
Age (year), median (IQR)	58 (54–65)
BMI group, n (%)	
Underweight	22 (26.5)
Normal BMI	53 (63.9)
Overweight / obese	8 (9.6)
History of surgery before TCX, n (%)	
No surgery	51 (61.4)
Gastrectomy	16 (19.3)
Gastroenterostomy	16 (19.3)
ECOG PS, n (%)	
0	41 (49.4)
1	23 (27.7)
2	19 (22.9)
Clinical presentation, n (%)	
Abdominal pain	64 (77.1)
Weight loss	61 (73.5)
Anorexia	51 (61.4)
Fatigue	48 (57.8)
Early satiety	42 (50.6)
Pyloric stenosis	20 (24.1)
Nausea	13 (15.7)
Vomiting	13 (15.7)
Gastrointestinal bleeding	12 (14.5)
Dysphagia	1 (1.2)
Number of metastases, n (%)	
0	25 (30.1)
1	42 (50.6)
2–3	16 (19.3)
Site of metastasis, n (%)	
Liver	27 (32.5)
Peritoneum	22 (26.5)
Lung	6 (7.2)
Lymph nodes	18 (21.7)
Ovary	1 (1.2)
Supraclavicular lymph node	1 (1.2)
TNM stage, n (%)	
IVa	26 (31.3)
IVb	57 (68.7)
CEA ≥5 ng/mL, n (%)	44 (53.0)
CA 72–4 ≥5 UI/mL, n (%)	38 (45.8)
White cell count (/μL), median (IQR)	7.6 (6.1–8.6)
Hemoglobin level (g/L), median (IQR)	122.0 (105.0–134.0)
Platelet count (/mm3), median (IQR)	335.0 (254.0–403.0)
Creatinine (mmol/L), median (IQR)	76.0 (68.0–90.0)
AST, median (IQR)	24.0 (19.0–35.0)
ALT, median (IQR)	20.0 (15.0–29.0)

Abbreviations: IQR, interquartile range; ECOG PS, Eastern Cooperative Oncology Group Performance status; AST, aspartate transferase; ALT, alanine transferase; BMI, body mass index; TNM, tumor node metastasis; CEA, carcinoembryonic antigen; CA 72-4, cancer antigen 72-4; TCX, taxane carboplatin capecitabine.
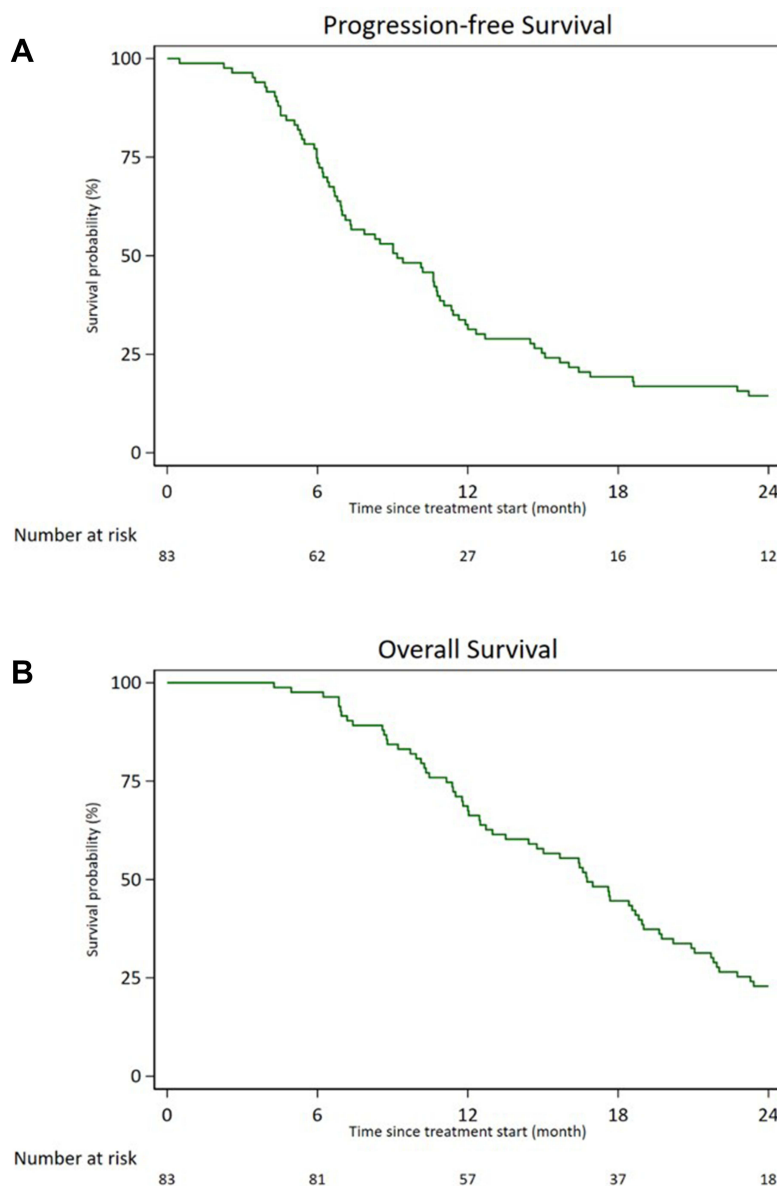
Figure 2 Kaplan-Meier estimates of (**A**) progression-free survival and (**B**) overall survival among the study participants (n = 83).

In the univariate analysis, factors associated with PFS included CEA (≥5ng/mL versus <5ng/mL; HR = 1.75; 95% CI: 1.08–2.82), metastatic status (M1 versus M0; HR = 1.77; 95% CI: 1.05–2.97), TNM stage (IVb versus IVa; HR = 1.82; 95% CI: 1.07–3.10), and liver metastasis (HR = 1.78; 95% CI: 1.09–2.89), but none of these was significant in the multivariable Cox model (Table 2). For OS, CEA (≥5ng/mL versus <5ng/mL; HR = 1.86; 95% CI: 1.12–3.07) were found to be associated in the univariable analysis and remained significant in the Cox model (HR = 1.89; 95% CI: 1.13–3.17).

Tumor Response and Clinical Improvement

A total of 466 TCX cycles were administered, and 70 out of 83 patients completed 6 cycles. Thirty-one patients (37.3%) had a partial response, and only four patients (4.8%) had a complete response. Eighteen patients (21.7%) had stable disease, while 30 patients (36.1%) had progressive disease (Table 3).

The prevalence of most of the signs and symptoms (including fatigue, abdominal pain, early satiety, poor eating, lose weight, pyloric stenosis and gastrointestinal bleeding) were reduced after the treatment course (Table 4). Fifteen patients
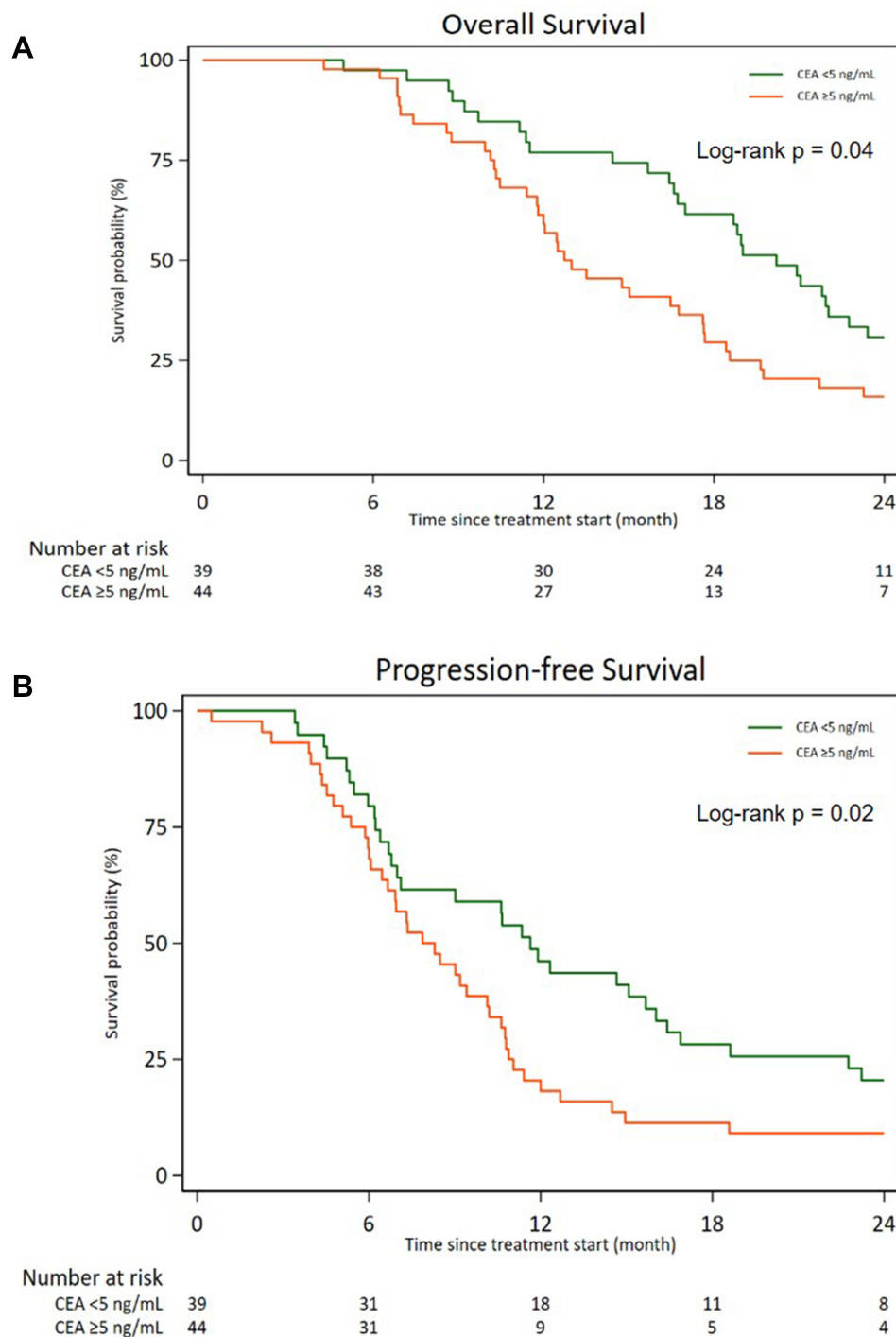
Figure 3 Kaplan-Meier estimates of (**A**) progression-free survival and (**B**) overall survival among the study participants, stratified by CEA levels (n = 83).

were candidates for curative surgery after TCX chemotherapy, in which three patients refused to participate in the procedure and were treated with second-line chemotherapy. Twelve patients underwent curative surgery (gastrectomy with lymph node dissection) and for all these patients, R0 resection was achieved; and no viable tumors were detected in resected lymph nodes (ypN0).

Table 2 Univariate and Multivariable Analysis of Factors Associated with Progression-Free Survival and Overall Survival Among the Study Participants (n = 83)

Variables	Progression-Free Survival (PFS)		Overall Survival (OS)	
	Univariate Analysis HR (95% CI)	Multivariable Analysis HR (95% CI)	Univariate Analysis HR (95% CI)	Multivariable Analysis HR (95% CI)
Clinicopathologic factors				
Age (≥55 versus <55)	1.33 (0.79–2.22)	1.53 (0.88–2.67)	1.17 (0.68–1.99)	0.79 (0.46–1.38)
Female	0.85 (0.51–1.42)	1.15 (0.68–1.96)	0.84 (0.49–1.45)	0.79 (0.46–1.37)
BMI (<18.5 versus ≥18.5)	0.84 (0.48–1.49)		1.19 (0.67–2.09)	
Performance status (2 versus <2)	1.02 (0.58–1.81)		0.78 (0.44–1.39)	
Histological type*	0.98 (0.61–1.59)		0.99 (0.59–1.67)	
CEA (≥5ng/mL versus <5ng/mL)	1.75 (1.08–2.82)	1.59 (0.97–2.62)	1.86 (1.12–3.07)	1.89 (1.13–3.17)
CA 72–4 (≥5ng/mL versus <5ng/mL)	1.08 (0.68–1.73)		1.28 (0.78–2.12)	
Tumor factors				
Tumor location				
Cardia				
Corpus	1.07 (0.33–3.46)		1.41 (0.43–4.55)	
Antrum	0.97 (0.54–1.75)		1.09 (0.59–2.05)	
Pretreatment tumor size (≥5cm versus <5cm)	1.01 (0.61–1.67)		1.07 (0.62–1.83)	
Tumor status (T4 versus T3 or less)	2.06 (0.89–4.78)		1.59 (0.68–3.71)	
Nodal status (N3 versus N2 or less)	0.65 (0.39–1.07)		0.91 (0.54–1.55)	
Metastatic status (M1 versus M0)	1.77 (1.05–2.97)	1.38 (0.76–2.50)	1.27 (0.75–2.16)	
TNM stage (IVb versus IVa)	1.82 (1.07–3.10)		1.33 (0.78–2.29)	1.15 (0.66–2.01)
Liver metastasis (yes versus no)	1.78 (1.09–2.89)	1.33 (0.75–2.34)	1.34 (0.80–2.25)	
Peritoneal metastasis (yes versus no)	0.96 (0.57–1.63)		1.14 (0.65–1.99)	

Notes: Indicators: *poorly differentiated adenocarcinoma and squamous cell carcinoma versus moderately differentiated adenocarcinoma.

Table 3 Tumor Response Rate Among the Study Participants (n = 83)

Response rate	n	%
Objective response rate	35	42.1
Partial response	31	37.3
Complete response	4	4.8
Stable disease	18	21.7
Progress disease	30	36.1

Toxicity

The most common non-hematological toxicity was hand-foot syndrome (HFS) (77.9%), peripheral neuropathy (63.2%), fatigue (68.7%), and nausea (54.2%). Grade 3–4 fatigue was observed in only one patient. Although 27.1% suffered from grade 3–4 neutropenia, there was no patient experienced febrile neutropenia. Grade 3–4 anemia and thrombocytopenia only occurred in 2 (2.4%) and 1 (1.2%) patients, respectively (Table 5). No treatment-related deaths were observed during the course of treatment. Patients had two hospital admissions (median), and most were admitted for only 1 day. The major cause of hospital admissions was severe neutropenia, in which patients received G-CSF as a subsequent course (Table 6). A total of 10 treatment-related serious adverse effects (SAE) were observed in the study, resulting in hospitalization/prolonged hospital stay. Of these, three patients had elevated AST/ALT which required administration of

Table 4 Clinical Improvement Among the Study Participants (n = 83)

Symptoms	At Baseline	After the Treatment Course	P-value
Fatigue	48	19	<0.001
Abdominal pain	64	35	<0.001
Early satiety	42	23	<0.001
Poor eating	51	26	<0.001
Difficulty swallowing	1	0	0.31
Nausea	13	9	0.21
Vomiting	13	9	0.21
Lose weight	61	19	<0.001
Pyloric stenosis	20	10	0.008
Gastrointestinal bleeding	12	4	0.005

Table 5 Hematologic and Nonhematologic Toxicities (n = 83)

Cycle	All Grades						Grade III/IV					
	1	2	3	4	5	6	1	2	3	4	5	6
Peripheral neuropathy	1 (1.2)	9 (10.8)	29 (34.9)	44 (58.7)	53 (73.6)	51 (75.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea	38 (45.8)	43 (51.8)	40 (48.2)	35 (46.7)	39 (54.2)	36 (52.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Allergy	1 (1.2)	1 (1.2)	1 (1.2)	0 (0.0)	1 (1.4)	2 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
HFS	0 (0.0)	14 (16.9)	34 (41.0)	46 (61.3)	50 (69.4)	53 (77.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fatigue	57 (68.7)	55 (66.3)	53 (63.9)	50 (65.8)	46 (63.9)	43 (63.2)	1 (1.2)	1 (1.2)	1 (1.2)	1 (1.3)	1 (1.4)	1 (1.5)
Diarrhea	9 (10.8)	31 (37.3)	27 (32.5)	23 (30.7)	22 (30.6)	30 (44.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stomatitis	5 (6.0)	4 (4.8)	6 (7.2)	13 (17.1)	16 (22.2)	10 (14.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Phlebitis	1 (1.2)	2 (2.4)	2 (2.4)	1 (1.3)	2 (2.8)	2 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Anemia	44 (53.0)	52 (62.7)	57 (68.7)	52 (69.3)	53 (73.6)	53 (75.7)	1 (1.2)	2 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)
Neutropenia	40 (48.2)	57 (68.7)	58 (69.9)	52 (69.3)	52 (72.2)	48 (68.6)	12 (14.5)	16 (19.3)	22 (26.5)	20 (26.7)	18 (25.0)	19 (27.1)
Thrombocytopenia	7 (8.4)	9 (10.8)	15 (18.1)	22 (29.3)	27 (37.5)	23 (32.9)	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)
Leukopenia	29 (34.9)	37 (44.6)	43 (51.8)	40 (53.3)	45 (62.5)	38 (54.3)	1 (1.2)	5 (6.0)	8 (9.6)	9 (12.0)	8 (11.1)	6 (8.6)

Abbreviation: HFS, Hand Foot Syndrome.

reamberin or glutathione, six had both severe anemia and neutropenia which required blood transfusion and G-CSF, and one had severe anemia which required blood transfusion.

Discussion

In this study, we examined the treatment outcome and safety of the TCX regimen on patients with advanced gastric cancer. We found that the median PFS and OS were 9.3 months and 17.0 months, respectively, and the objective response rate (ORR) was 42.1%. The TCX regimen was relatively safe and tolerable, with the incidence of grade 3–4 neutropenia was 27.1% and the completion of 6 cycles in majority of the patients.

Table 6 Administration Due to AEs, G-CSF Uses and Treatment Discontinuation

Administration (n =466 cycles)	
Administration due to all AEs, n (%)	193 (41.4)
Duration of administration (days), Median (IQR)	1 (1–4)
G-CSF uses (n = 466, cycles)	
As secondary prophylactic, Median (IQR)	3 (0–4)
As subsequent courses, Median (IQR)	2 (0–4)
Treatment discontinuation	
Number of patients completed 6 cycles, n (%)	70 (84.3)
Number of patients only completed 5 cycles, n (%)	2 (2.4)
Number of patients only completed 4 cycles, n (%)	3 (3.6)
Number of patients only completed 3 cycles, n (%)	8 (9.7)
Reason of discontinuation	
Intolerable	3
Early withdrawal	2
Disease progression	8

The survival outcomes in our study appear to be higher than that of other doublet and triplet chemotherapy regimens. For first-line doublet regimens, PFS did not exceed 6 months (3.7–6.0 months) and OS did not exceed 1 year (8.6–10.5 months).[12,27,28] For triplet regimens, survival was longer (PFS 5.0–7.4 months and OS 8.9–11.2 months) but still lower than in our study.[12,29–32] Among these, docetaxel-containing three-drug regimens increased response rates; however, the benefits of docetaxel-containing three-drug combinations (DCF and FLOT) were outweighed by their toxicity.[5] Due to concerns about toxicity, the National Comprehensive Cancer Network has recently removed the DCF regimen from the recommendation for first-line treatment for metastatic or locally advanced cancer, and suggested that dose-modified or other DCF modifications should be utilized as an alternative.[33] Based on this point, TCX was used in this study with the expectation to retain the same effectiveness while reducing the toxicity and increasing the tolerability of the regimen, thus, could be more suitable for the physical condition of patients with advanced gastric cancer. Although studies have yet to confirm the superiority of paclitaxel over docetaxel, there was evidence that suggests the difference in toxicity between these two, in monotherapy as well as combined regimens. Specifically, a 2006 study in South Korea showed that the PF (paclitaxel and 5-fluorouracil) regimen had fewer serious adverse effects than that of the DF (docetaxel and 5-fluorouracil) regimen.[17] In another study, neutropenia was more common in the DFL (docetaxel, 5-fluorouracil and leucovorin) regimen than that of the PFL regimen (paclitaxel, 5-fluorouracil and leucovorin) (71% versus 62%).[18] A Phase III clinical trial in 449 patients with metastatic breast cancer demonstrated a higher incidence of hematological and non-hematological toxicity in the docetaxel group compared to paclitaxel.[16] Despite its limited efficacy in esophageal and gastric cancer, with the single agent response rate of 5–10%,[34–36] carboplatin was associated with less severe nausea/vomiting and thus might improve tolerability and adherence. Thus, the use of carboplatin in the combination of docetaxel, carboplatin and fluorouracil was recommended as category 2B in the recent NCCN guidelines.[33] The introduction of oral capecitabine into the treatment regimen to replace the continuous infusion of 5-FU has demonstrated clinical benefits. The Real-2 multicenter clinical trial found that 5-FU infusion and capecitabine had similar effectiveness.[29] This substitution not only reduced the hematological toxicity as previously reported,[27,37,38] but also eliminated the requirement for hospitalization, as a central venous access device was no longer required. As expected, the ORR in our study were comparable to those of the DCF and its modification regimens (42.1% vs 25%–48.7%)[9,14,39–42] while the toxicity profile was more favorable.

In our study, higher CEA was associated with poor OS and PFS. As a membrane protein, CEA was associated with cell–cell adhesion and junction.[43] CEA has sialofucosylated glycoforms that act as selectin ligands and aid the metastasis of colon cancer cells.[44–47] In a retrospective cohort study that included 1596 gastric cancer patients, CEA was associated with chemokine signaling and immunology regulation, especially T cells and Th cells,[48] which have previously been shown to have a role in mediating cancer metastasis process.[49–51] Because CEA is involved in tumor metastasis, it may be linked to the prognosis of gastric cancer. In a meta-analysis that included 14,651 patients, increased pretreatment serum CEA levels nearly doubled the risk of mortality in patients with gastric cancer.[52] In a study on 615 Chinese patients with advanced gastric cancer, a CEA level of ≥8 ng/mL was associated with higher death risk compared to that of <8 ng/mL, and therefore, CEA has been incorporated into a prognostic scoring model for mortality risk stratification.[53] However, because other studies have indicated otherwise,[54–58] CEA is not considered an independent predictor for patients with gastric cancer, and curative approach should not be tailored based on CEA level.[25] However, the difference in mortality among levels of CEA should be considered by treating physicians, as patients could benefit from more intensive regimens (such as docetaxel-containing triplet regimen).

Our study reported a better safety profile of the TCX regimen. No patient died from treatment-related events. Non-hematologic and hematologic toxicities, albeit frequent, were mild and required neither intervention nor treatment discontinuation. Anemia is a common adverse effect in gastric cancer patients on chemotherapy. In addition to the adverse effect caused by the chemotherapy itself, anemia can also be aggravated by many factors such as gastrointestinal bleeding before admission, malnutrition, and vitamin B12 deficiency.[59] Only 27.1% of our patients had severe neutropenia (grade 3–4 AE), and no patient experienced febrile neutropenia. This incidence was much lower than that of a study on CF/DCF regimens (57% in patients treated with CF and 82% in DCF). Also, in this study, the incidence of febrile neutropenia was 29% and 12% in the DCF and CF arms, respectively, and treatment-related infections were the main cause of death in both arms.[12] A meta-analysis that included 482 randomized participants in three studies have reported the rate of treatment-related deaths (6.2%) and treatment discontinuation due to toxicity (17%) in patients treated with taxane-platinum-fluoropyrimidine combinations.[5] DCX (docetaxel, cisplatin and capecitabine), a modified regimen of DCF, had varied incidence of severe neutropenia and febrile neutropenia across studies (16–62% for severe neutropenia and 4.5–19% for febrile neutropenia).[37,38,60] Substituting docetaxel with paclitaxel, as well as the introduction of oral capecitabine as an alternative to intravenous 5-FU, may play a role in alleviating hematological toxicity, as shown in previous studies.[16–18,37,38,60]

To our knowledge, this is the first prospective cohort study evaluating the efficacy and toxicity of TCX regimen in patients with advanced stage cancer. The relatively small sample size, short follow-up period, and lack of a control group were the main disadvantages of this study. The results of our study need validating by prospective, randomized controlled clinical trials comparing TCX and other chemotherapy regimens in the treatment of advanced gastric cancer with a large number of participants.

Conclusions

The TCX regimen provided good survival and a better safety profile. Clinical trials are needed to confirm its treatment efficacy and safety, especially in comparison with other triplet regimens.

Disclosure

The authors report no conflicts of interest in this work.

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