Medicine®

CLINICAL TRIAL/EXPERIMENTAL STUDY

OPEN

A Phase II Study of Sequential Capecitabine Plus Oxaliplatin Followed by Docetaxel Plus Capecitabine in Patients With Unresectable Gastric Adenocarcinoma

The TCOG 3211 Clinical Trial

Ming-Huang Chen, MD, PhD, Johnson Lin, MD, Chin-Fu Hsiao, PhD, Yan-Shen Shan, MD, PhD, Yeu-Chin Chen, MD, Li-Tzong Chen, MD, PhD, Tsang-Wu Liu, MD, Chung-Pin Li, MD, PhD, and Yee Chao

Abstract: Fluorouracil and platinum are considered the standard treatment options for advanced gastric cancer. Docetaxel is also an effective agent and it shows no cross-resistance with fluorouracil and platinum. The combination treatment of docetaxel with fluorouracil and platinum has been explored, but it demonstrated intolerable toxicities. An alternative approach in the first-line treatment of gastric adenocarcinoma may be to use these agents sequentially. We aimed to evaluate the activity and safety profile of sequential chemotherapy with capecitabine plus oxaliplatin, followed by docetaxel plus capecitabine in the first-line treatment of unresectable gastric cancer.

We conducted a phase II study of sequential first-line chemotherapy in advanced gastric cancer. Treatment consisted of 6 cycles of capecitabine plus oxaliplatin (capecitabine 1000 mg/m^2 bid on days 1–10 and oxaliplatin 85 mg/m^2 on day 1, every 2 weeks), followed by 4 cycles of docetaxel plus capecitabine (docetaxel 30 mg/m^2 on days 1 and 8, capecitabine 825 mg/m^2 bid on days 1–14, every 3 weeks). The primary end-point was the objective response rate.

Fifty-one patients were enrolled: median age, 63 years; male/female: 37/14. The main grade 3 to 4 toxicities were a decreased absolute neutrophil count (25.4%), diarrhea (9.8%), and hand-foot syndrome (15.7%). The objective response rate was 61.7%. The median progression-free survival and overall survival were 8.6 and 11.0 months, respectively. Six patients (11.8%) received surgery after chemotherapy and 5 are still disease-free.

This sequential treatment demonstrated feasibility with a favorable safety profile and produced encouraging results in terms of activity and efficacy.

(*Medicine* 95(3):e2565)

Editor: Patrick Wall.
Received: October 26, 2015; revised: December 18, 2015; accepted: December 28, 2015.
From the School of Medicine, National Yang-Ming University (M-H C, C-P L, YC) National Yang-Ming University (M-HC); Department of Oncology, Taipei Veterans General Hospital (M-HC); Division of Hematology and Oncology, Department of Medicine, Mackay Memorial Hospital, Taipei (JL); Institute of Population Health Sciences, National Health Research Institutes, Miaoli (C-FH); Department of Surgery, National Cheng Kung University Hospital, National Cheng Kung University, Tainan (Y-SS); Division of Hematology and Oncology, Department of Medicine, Tri-Service General Hospital, Taipei (Y-CC); National Institute of Cancer Research, National Health Research Institutes, Tainan City (L-TC, T-WL); Division of Gastroenterology and Hepatology, Department of Medicine (C-PL); and Department of Oncology, Taipei Veterans General Hospital, Taipei, Taiwan (C-PL, YC).
Correspondence: Yee Chao, Department of Oncology, Taipei Veterans General Hospital, 201, Section 2, Shi-pai Road, Taipei, Taiwan (e-mail: ychao@vghtpe.gov.tw).
Chung-Pin Li, Division of Gastroenterology and Hepatology, Department of Medicine, Taipei Veterans General Hospital, 201, Section 2, Shi-Pai Road, Taipei, Taiwan (e-mail: cpli@vghtpe.gov.tw).
Novelty & impact statements: a phase II trial which enrolled 51 patients to clarify the safety and efficacy of XELOX followed by TX in unresectable gastric cancer patients. We found it is effective, well-tolerated, convenient, and practical for advanced gastric cancer patients in daily practice
Human rights statement and informed consent: all procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Informed consent or substitute for it was obtained from all patients for being included in the study.
Funding: the study was supported by the Taiwan Cancer Clinic Foundation, the Szu-Yuan Research Foundation of International Medicine, and the Chong Hin Loon Memorial Cancer; also by the National Research Program for Biopharmaceuticals (100CT202).
The authors have no conflicts of interest to disclose.

ISSN: 0025-7974
DOI: 10.1097/MD.0000000000002565

INTRODUCTION

Gastric cancer (GC) is the fourth most common cancer and the third most common cause of cancer-related death worldwide.[1] Surgery is the only curative modality. However, many patients are initially diagnosed with locally advanced or metastatic disease. The cancer has a high recurrence rate after surgery, especially for advanced disease.[2] For these patients, systemic chemotherapy has been shown to improve quality of life and survival compared with best supportive care.[3]

One meta-analysis study of 11 gastric cancer trials found that combination chemotherapy resulted in better overall survival (OS) compared with single-agent chemotherapy.[4] There is still no well-established standard regimen, but doublet chemotherapy, including fluoropyrimidine (5-FU) and platinum, is widely used in worldwide clinical trials. Docetaxel is another effective agent in the treatment of GC. In the phase III TAX-V325 trial, the addition of docetaxel to 5-FU and cisplatin (DCF regimen) improved response rate, time to progression, and survival compared with 5-FU and cisplatin (CF).[5] However, the DCF regimen is associated with increased toxicity, especially myelosuppression and infection, and it is not widely used in clinical practice. Several modifications of the DCF regimen have been developed to increase the tolerability of the regimen while maintaining the same level of activity.[6–10]

An alternative way to include these active agents in the first-line treatment of advanced GC is to use them sequentially. Sequential schedules may maximize the dose-intensity of each single agent and avoid the overlapping toxicity of concomitant agents. Three studies using sequential strategies to treat advanced GC have been reported.[11–13] All studies showed that sequential therapies produced good treatment efficacy with manageable toxicities.

In the REAL2 study, capecitabine, the oral pro-drug form of 5-FU, has already shown the same efficacy as 5-FU, cisplatin or oxaliplatin.[14] Capecitabine is an oral chemotherapy, which is more convenient than continuous 5-FU infusion. Oxaliplatin is an alkylating agent and is a third-generation platinum. Compared with cisplatin, oxaliplatin has shown more favorable safety profiles. In our previous study, we showed that a modified biweekly capecitabine and oxaliplatin (XELOX) regimen is a practical and effective regimen in the treatment of GC.[15,16] Lo et al and Giordano et al also showed that docetaxel and capecitabine (TX) is a well-tolerated, easily administrated regimen in advanced GC.[17,18] Therefore, we conducted a phase II study to investigate the efficacy and feasibility of the sequential administration of the XELOX regimen followed by the TX regimen in patients with GC.

MATERIAL AND METHODS

Study Design

This trial was a multicenter, open label, single-arm phase II study evaluating sequential chemotherapy with the XELOX regimen followed by the TX regimen (NCT01558011). The primary end-point was the objective response rate (ORR), and the secondary end-points were OS, progression-free survival (PFS), and assessment of toxicity. The study was approved by the Institutional Review Board of each participating center or the competent authority and the Ethics Committee. The study was conducted in full accordance with the International Conference on Harmonization Good Clinical Practice guidelines and the Declaration of Helsinki. All patients provided written informed consent before entering the study.

Eligibility

Patients were enrolled from the following medical centers: Taipei Veterans General Hospital, Mackay Memorial Hospital, National Health Research Institutes, National Cheng Kung University Hospital, and Tri-Service General Hospital. Patients with pathologically proven unresectable recurrent or metastatic gastric adenocarcinoma were assessed for eligibility. The major inclusion criteria were as follows: at least 1 measurable disease; age $>$ 20 years; an Eastern Cooperative Oncology GROUP (ECOG) performance status (PS) of 0 to 2; adequate bone marrow function (defined by a leukocyte count of $\geq$4000 leukocytes/μL, an absolute neutrophil count of $\geq$1500 neutrophils/μL, a platelet count of $\geq$100,000 platelets/μL, and a serum hemoglobin level of $\geq$9 g/dL); adequate renal function (serum creatinine level at least 1.5-fold lower than the reference value); and adequate hepatic function (bilirubin level at least 2-fold lower than the reference value and aspartate aminotransferase and alanine aminotransferase levels at least 2.5-fold lower than the reference value). Prior radiotherapy was permitted if it was not administered to the target lesions evaluated in this study and if it had been completed at least 2 weeks prior to the patient's enrollment into the study. Patients who had completed adjuvant chemotherapy at least 6 months before recruitment were enrolled. Patients with brain metastasis or those who could not take study medication orally were excluded. Patients whose tumor samples revealed overexpression of the HER-2/neu protein (3+) by immunohistochemical (IHC) staining were also excluded.

Treatment Schedule

Eligible patients received oral capecitabine (Xeloda®; Roche, Basel, Switzerland) - 1000 mg/m^2 twice daily on days 1 to 10 every 2 weeks, plus oxaliplatin (Eloxatin®, Sanofi-Aventis, Paris, France) 85 mg/m^2 (2 h IV infusion) on day 1 (XELOX regimen) every 2 weeks for 6 cycles (Figure 1). Patients were allowed to rest for 1 week after XELOX treatment. Then the treatment was shifted to docetaxel (Taxotere®, Sanofi-Aventis, Paris, France) 30 mg/m^2 (a 30-min intravenous infusion) on days 1 and 8, plus oral capecitabine 825 mg/m^2 twice daily on days 1 to 14 (TX regimen) every 3 weeks for 4 cycles. After completing all planned regimens, a further regimen was independently decided by the investigator. Prophylactic dexamethasone was prescribed to prevent any potential hypersensitivity reactions to docetaxel. The standard antiemetic prophylaxis of intravenously administered 5-HT3 antagonists was administered before chemotherapy. Granulocyte colony-stimulating factor was administered to treat neutropenic events; however, prophylactic granulocyte colony-stimulating factor and prophylactic antibiotics were not administered to patients who had experienced a neutropenic event in the previous cycle.

Response and Toxicity Evaluation

The response to therapy was assessed by the radiological evaluation of any measurable lesion every 8 weeks based on Response Evaluation Criteria In Solid Tumors version 1.1[19] using computed tomography; it was determined by an independent response review committee. After discontinuation of the study treatment, patients were followed up every 3 months until disease progression or death. Toxicity was evaluated and recorded according to version 4.0 of the Common Terminology Criteria for Adverse Events of the National Cancer Institute. All of the patients were included in the toxicity assessment. For the toxicity analysis, the data indicating the worst toxicity for each patient from all of the chemotherapy cycles were used.

Statistical Analysis

According to Simon's optimal 2-stage design,[20] 16 patients were required for enrollment to test the null hypothesis that the true ORR is 40% versus the alternative hypothesis that the true ORR is at least 60%, at a significance level of 0.05 with a power of 80%. If 8 or more responses were observed among 16 patients

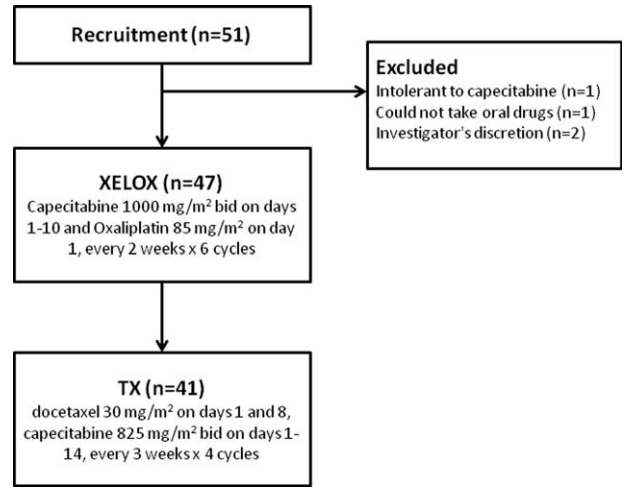

FIGURE 1. The Consolidated Standards of Reporting Trials (CONSORT) diagram depicting the trajectory of the trial. CONSORT = Consolidated Standards of Reporting Trials.

in the first stage, the study was continued with 30 additional patients included. As the dropout rate was assumed 10%, the number of patients necessary for recruitment into the study was calculated to be 51.

The perprotocol (PP) population excluded those patients who received treatment of <1 cycle for reasons other than disease progression or death or those who received <50% of the anticipated treatment during the first 6 weeks of the trial. The response and toxicity data were described using simple descriptive statistics. PFS was calculated from the first day of treatment until the first day of documented disease progression or death from any cause. PFS was censored at the date of the last follow-up visit for the patients who were still alive and had no documented disease progression. OS was calculated from the first day of treatment until the day of death. PFS and OS were estimated using the Kaplan–Meier method.

RESULTS

Patient Characteristics

From March 2012 to Sep 2014, 51 patients were enrolled in this study. The patient characteristics were shown in Table 1. The median age was 63 years (range 32–83 years). Thirty-seven patients (72.5%) were men, and most patients (98%) had ECOG PS of 0 or 1. Twenty-eight patients (54.9%) had poorly differentiated adenocarcinoma. Four patients (7.8%) had received adjuvant chemotherapy. Forty-two patients (82.4%) had metastatic disease and the most common metastatic sites were the distant lymph nodes (62.7%), liver (39.2%), and peritoneum (33.3%). Forty-three patients (84.3%) had low-level HER2 protein expression (IHC staining 0 or 1+) in their tissue samples.

TABLE 1. Patient Characteristics

	N	(%)
No. of enrolled patients	51	
Median age (range, year)	63	(32–83)
Gender		
Male	37	(72.5)
Female	14	(27.5)
ECOG performance status		
0	15	(29.4)
1	35	(68.6)
2	1	(2.0)
Prior adjuvant chemotherapy		
No	47	(92.2)
Yes	4	(7.8)
T stage		
1 + 2	4	(7.8)
3	19	(37.3)
4	27	(52.9)
X	1	(2.0)
N stage		
0	5	(9.8)
1	9	(17.6)
2	9	(17.6)
3	28	(54.9)
M stage		
0	9	(17.6)
1	42	(82.4)
Differentiation		
Moderately	14	(27.5)
Poorly	28	(54.9)
Unknown	9	(17.6)
Site(s) of involvement		
Primary site/stomach	40	(78.4)
Regional lymph nodes	36	(70.6)
Distant lymph nodes	32	(62.7)
Peritoneum	17	(33.3)
Lung	9	(17.6)
Bone	2	(3.9)
Liver	20	(39.2)
Others	17	(33.3)
HER-2/neu expression		
Negative	17	(33.3)
1 +	26	(51.0)
2 +	8	(15.7)

ECOG = Eastern Cooperative Oncology Group.

Treatment Delivery

Out of the 51 patients, 4 patients received only 1 cycle of the XELOX regimen and were excluded from analysis by PP population (Table 2). Forty-three patients (84.3%) completed 6 cycles of the XELOX regimen, with a median of 6 cycles (range 1–6 cycles). Among these patients, 42 patients (82.4%) then proceeded to receive the TX regimen. A total of 31 patients (60.8%) completed 4 cycles of the TX regimen; the median was 4 cycles (range 0–4 cycles).

Efficacy

Of the 51 patients, 47 were eligible for response evaluation. Four patients were not available for response evaluation: 1 was intolerant to capecitabine, 1 had disease progression and could not take oral drugs, and 2 patients were excluded at the investigator's discretion. Tumor responses are summarized in Table 3. During the XELOX regimen period, 25 patients (53.2%) achieved a partial response, 21 patients (44.7%) had stable disease, and 1 patient (2.7%) had disease progression. During the TX period, 8 patients (19.5%) achieved a partial response, 27 patients (65.9%) had stable disease, and 6 patients (14.6%) had disease progression. Overall, 29 patients (61.7%) achieved a partial response and 18 patients (38.3%) had stable disease. Among 8 patients who had response during the TX period, 5 patients had partial response, 2 patients had stable disease, and 1 patient had progressive disease during the XELOX period. The median PFS was 8.6 months (95% confidence interval [CI] 5.6–13.7 months, Figure 2), and the median OS was 11.0 months (95% CI 9.6–14.5 months, Figure 3). The median follow-up time was 10.1 months. Six patients (11.8%) completed treatment and their tumors became resectable. They underwent surgery and 5 of these patients were still alive with disease-free status during their last follow-up.

Safety

Safety was assessed in 51 patients; the adverse events are listed in Table 4. In the XELOX period, the most common grade 3/4 adverse event was hand-foot syndrome (9.8%). In the TX period, the most common grade 3/4 adverse events were neutropenia (28.5%), leucopenia (14.3%), and hand-foot syndrome (9.5%). Overall, the most common grade 3/4 adverse events were neutropenia (25.4%), leucopenia (11.8%), diarrhea (9.8%), and hand-foot syndrome (15.7%). Other toxicities were

TABLE 2. Cycles of Treatment and Follow-Up Time

	N	(%)
No. enrolled patients	51	
Median total cycles of XELOX regimens (range)	6	(1–6)
Cycles of XELOX regimen		
1	4	(7.8)
3	1	(2.0)
5	3	(5.9)
6	43	(84.3)
Median total cycles of TX regimens (range)	4	(0–4)
Cycles of TX regimen		
0	9	(17.6)
1	1	(2.0)
2	7	(13.7)
3	3	(5.9)
4	31	(60.8)
Median follow-up time (months) (range)	10.1	(1.6–28.6)

TX = docetaxel and capecitabine; XELOX = capecitabine and oxaliplatin.

usually mild and manageable. Grade 3 toxicities with a frequency of 5% or more included oral mucositis (5.9%), nausea (5.9%), fatigue (5.9%), and thrombocytopenia (5.9%). No grade 3/4 peripheral neuropathy was observed in this study.

DISCUSSION

The prognosis of advanced gastric cancer is still dismal. For gastric cancer patients with unresectable tumors, systemic chemotherapy is the cornerstone of treatment, and it shows improved survival compared with best supportive care.[3] Several novel drugs have been developed in recent years. One of the most important drugs is docetaxel, which was recently approved as a first-line treatment on the basis of the TAX-V325 trial.[5] In this pivotal trial, the DCF regimen proved superior to the CF regimen; it showed improved time to progression (5.6 vs 3.7 months, respectively; $P < 0.001$), response rate (37% vs 25%, respectively; $P = 0.01$), and OS (9.2 vs 8.6 months, respectively; $P = 0.02$). However, the regimen is limited in clinical practice due to severe hematologic toxicity. When we consider that the aim of the treatment in advanced gastric cancer patients is generally palliative, the tolerability of the treatment is a very important issue. Therefore, we sequentially administered capecitabine, oxaliplatin, and docetaxel in order to increase the tolerability of this combination.

This is the first phase II study investigating the sequential therapy of the XELOX regimen followed by the TX regimen in the treatment of advanced gastric cancer. The 61.7% overall response rate of the evaluable patients, the PFS of 8.6 months and the median survival of 11 months are not inferior to the results of the other phase III clinical trials of the current reference regimens, including DCF, EOX, XP and TS1+cisplatin.[5,21–24] In these trials, the objective tumor response rate and the median survival ranged from 29% to 47% and from 8.6 to 11.1 months, respectively. The results are also not inferior

TABLE 3. Best Response Rate According to Response Evaluation Criteria In Solid Tumors (RECIST)

	XELOX Period		TX Period		Overall	
	N	(%)	N	(%)	N	(%)
No. of evaluable patients	47		41		47	
Complete response	0	(0)	0	(0)	0	(0)
Partial response	25	(53.2)	8	(19.5)	29	(61.7)
Stable disease	21	(44.7)	27	(65.9)	18	(38.3)
Progressive disease	1	(2.1)	6	(14.6)	0	(0.0)

Four patients are unevaluable.
TX = docetaxel and capecitabine; XELOX = capecitabine and oxaliplatin.

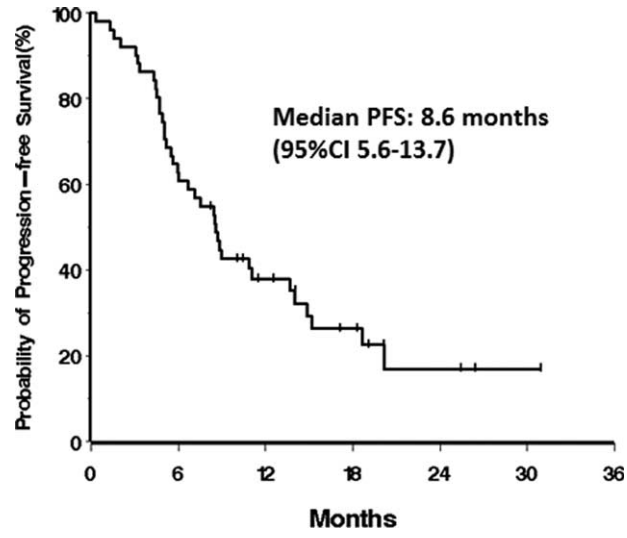

FIGURE 2. Kaplan–Meier curves for progression-free survival of 47 advanced gastric cancer patients.

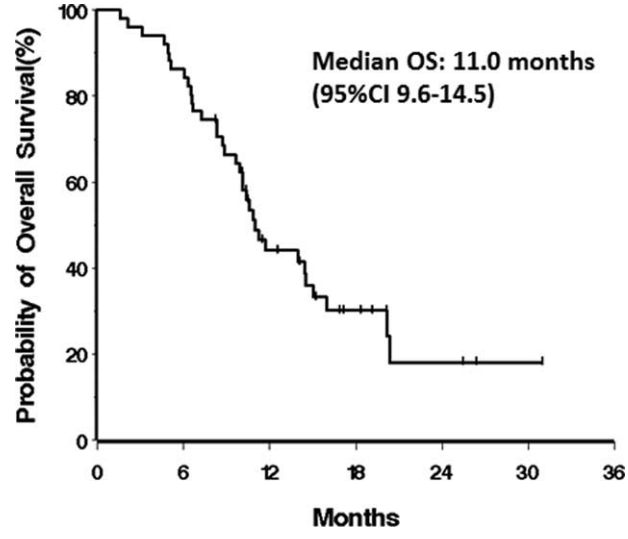

FIGURE 3. Kaplan–Meier curves for overall survival of 47 advanced gastric cancer patients.

TABLE 4. Toxicities According to Treatment

	XELOX (N = 51)			TX (N = 42)			Overall (N = 51)		
	N (%)			N (%)			N (%)		
Grade	**1/2**	**3**	**4**	**1/2**	**3**	**4**	**1/2**	**3**	**4**
Hematology toxicity									
Leucopenia	23(45)	0(0)	0(0)	29(69)	6(14)	0(0)	33(65)	6(12)	0(0)
Neutropenia	26(51)	1(2)	0(0)	22(52)	8(19)	4(10)	25(49)	9(18)	4(8)
Anemia	9(18)	0(0)	1(2)	13(31)	0(0)	0(0)	16(31)	0(0)	1(2)
Thrombocytopenia	30(59)	2(4)	1(2)	26(62)	1(2)	0(0)	33(65)	3(6)	1(2)
Nonhematology toxicity									
Constipation	2(4)	0(0)	0(0)	1(2)	0(0)	0(0)	3(6)	0(0)	0(0)
Diarrhea	9(18)	2(4)	0(0)	9(21)	3(7)	0(0)	12(24)	5(10)	0(0)
Oral mucositis	7(14)	1(2)	0(0)	21(50)	2(5)	0(0)	22(43)	3(6)	0(0)
Nausea	17(33)	3(6)	0(0)	10(24)	0(0)	0(0)	21(41)	3(6)	0(0)
Vomiting	14(27)	2(4)	0(0)	2(5)	0(0)	0(0)	14(27)	2(4)	0(0)
Limbs edema	2(4)	0(0)	0(0)	2(5)	0(0)	0(0)	3(6)	0(0)	0(0)
Fatigue	21(41)	1(2)	0(0)	24(57)	2(5)	0(0)	30(59)	3(6)	0(0)
AST increased	3(6)	0(0)	0(0)	1(2)	0(0)	0(0)	3(6)	0(0)	0(0)
ALT increased	3(6)	0(0)	0(0)	2(5)	0(0)	0(0)	5(10)	0(0)	0(0)
TB increased	0(0)	0(0)	0(0)	1(2)	0(0)	0(0)	1(2)	0(0)	0(0)
Cr increased	0(0)	1(2)	1(2)	1(2)	0(0)	0(0)	1(2)	1(2)	1(2)
Anorexia	21(41)	1(2)	0(0)	15(36)	0(0)	0(0)	27(53)	1(2)	0(0)
Dizziness	2(4)	0(0)	0(0)	0(0)	0(0)	0(0)	2(4)	0(0)	0(0)
Paresthesia	4(8)	0(0)	0(0)	4(10)	0(0)	0(0)	5(10)	0(0)	0(0)
Peripheral sensory neuropathy	11(22)	0(0)	0(0)	24(57)	0(0)	0(0)	27(53)	0(0)	0(0)
Epistaxis	0(0)	0(0)	0(0)	3(7)	0(0)	0(0)	3(6)	0(0)	0(0)
Alopecia	3(6)	0(0)	0(0)	30(71)	0(0)	0(0)	31(61)	0(0)	0(0)
Nail discoloration	3(6)	0(0)	0(0)	10(24)	0(0)	0(0)	11(22)	0(0)	0(0)
Nail loss	1(2)	0(0)	0(0)	4(10)	0(0)	0(0)	4(8)	0(0)	0(0)
Hand-foot syndrome	17(33)	5(10)	0(0)	21(50)	4(10)	0(0)	24(47)	8(16)	0(0)

ALT = aminotransferase, AST = aspartate aminotransferase and alanine, Cr = creatinine, TB = total bilirubin, TX = docetaxel and capecitabine, XELOX = capecitabine and oxaliplatin.

to the results of docetaxel-based phase II/III studies,[5–10] in which the objective tumor response rate and median survival ranged from 21% to 54% and from 8.6 to 14.5 months, respectively.

In this study, the ORR in evaluable patients was 61.7%. Six patients whose gastric cancers were initially unresectable became resectable after receiving treatment (Table 5). Notably, 1 patient (case number 2) received operation was due to tumor rupture but the pathology showed pathologic complete remission. These patients underwent surgery and 5 of them are still alive with disease-free status. Because of the high ORR and disease control rate, this sequential chemoregimen may be considered for the neoadjuvant setting of gastric cancer. Further studies are warranted.

In the phase III TAX-V325 trial, the DCF regimen had better results than the CF regimen but it was associated with intolerable toxicity; 82% of patients experienced grade 3/4 neutropenia and 14.3% of patients experienced febrile neutropenia.[5] In other docetaxel-based chemoregimens,[5–10] the rate of grade 3/4 neutropenia was lower and ranged from 37.2% to 70%. In our study, the sequential therapy with XELOX followed by TX was well tolerated by most patients. The most common grade 3/4 side effects were neutropenia (28.5%), decreased white blood cell counts (14.2%), and hand-foot syndrome (9.5%). It is worth mentioning that no patient experienced febrile neutropenia or grade 3/4 peripheral sensory neuropathy, the most concerning adverse events associated with docetaxel and oxaliplatin. To the best of our knowledge, the rate of grade 3/4 neutropenia is lowest with docetaxel-based chemotherapy. Few grade 3/4 nonhematologic adverse events were observed; these included mucositis, nausea, vomiting, fatigue, and anorexia. The favorable results may be due to the sequential therapy, which may have avoided the overlapping toxicity of

TABLE 5. Patients Who Became Operable After Chemotherapy

Case Number	Initial Stage	Best Response	Outcome
1	T4bN2M1	PR	Expired
2	T3N3M0	PR (pathology CR)	Alive
3	T4N2M1	PR	Alive
4	T4aN3bM1	PR	Alive
5	T4N1M1	PR	Alive
6	T3N0M1	PR	Alive

PR = partial remission; CR = complete remission.

concomitant agents and reduced the exposure doses of each agent.

The administration of the sequential therapy with XELOX followed by TX was convenient and practical for the gastric cancer patients. Unlike the traditional DCF regimen which requires intravenous infusion of 5-FU for 5 days, the sequential therapy only required a 2-h infusion of oxaliplatin in the XELOX regimen and a 1-h infusion of docetaxel in the TX regimen. Reducing the length of time required for the intravenous infusion may also decrease the number central line infections. This regimen can easily be administered at outpatient clinics.

In conclusion, the sequential therapy of the XELOX regimen followed by the TX regimen is effective, well-tolerated, convenient, and practical for advanced gastric cancer patients in daily practice.

REFERENCES

1. Shen L, Shan YS, Hu HM, et al. Management of gastric cancer in Asia: resource-stratified guidelines. *Lancet Oncol.* 2013;14: e535–e547.
2. Kuo CY, Chao Y, Li CP. Update on treatment of gastric cancer. *J Chin Med Assoc.* 2014;77:345–353.
3. Wagner AD, Unverzagt S, Grothe W, et al. Chemotherapy for advanced gastric cancer. *Cochrane Database Syst Rev.* 2010;3:CD004064.
4. Wagner AD, Grothe W, Haerting J, et al. Chemotherapy in advanced gastric cancer: a systematic review and meta-analysis based on aggregate data. *J Clin Oncol.* 2006;24:2903–2909.
5. Van Cutsem E, Moiseyenko VM, Tjulandin S, et al. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. *J Clin Oncol.* 2006;24:4991–4997.
6. Li CP, Chen JS, Chen LT, et al. A phase II study of weekly docetaxel and cisplatin plus oral tegafur/uracil and leucovorin as first-line chemotherapy in patients with locally advanced or metastatic gastric cancer. *Br J Cancer.* 2010;103:1343–1348.
7. Van Cutsem E, Boni C, Tabernero J, et al. Docetaxel plus oxaliplatin with or without fluorouracil or capecitabine in metastatic or locally recurrent gastric cancer: a randomized phase II study. *Ann Oncol.* 2015;26:149–156.
8. Kim HS, Ryu MH, Zang DY, et al. Phase II study of docetaxel, oxaliplatin, and S-1 therapy in patients with metastatic gastric cancer. *Gastric Cancer.* 2015. in press.
9. Tebbutt NC, Cummins MM, Sourjina T, et al. Randomised, non-comparative phase II study of weekly docetaxel with cisplatin and 5-fluorouracil or with capecitabine in oesophagogastric cancer: the AGITG ATTAX trial. *Br J Cancer.* 2010;102:475–481.
10. Wang J, Xu R, Li J, et al. Randomized multicenter phase III study of a modified docetaxel and cisplatin plus fluorouracil regimen compared with cisplatin and fluorouracil as first-line therapy for advanced or locally recurrent gastric cancer. *Gastric Cancer.* 2016;19:234–244.
11. Catalano V, Vincenzi B, Giordani P, et al. Sequential chemotherapy with cisplatin, leucovorin, and 5-fluorouracil followed by docetaxel in previously untreated patients with metastatic gastric cancer: a phase II study. *Gastric Cancer.* 2012;15:419–426.
12. Gubanski M, Johnsson A, Fernebro E, et al. Randomized phase II study of sequential docetaxel and irinotecan with 5-fluorouracil/folinic acid (leucovorin) in patients with advanced gastric cancer: the GATAC trial. *Gastric Cancer.* 2010;13:155–161.
13. Petrioli R, Francini E, Roviello F, et al. Sequential treatment with epirubicin, oxaliplatin and 5FU (EOF) followed by docetaxel, oxaliplatin and 5FU (DOF) in patients with advanced gastric or gastroesophageal cancer: a single-institution experience. *Cancer Chemother Pharmacol.* 2015;75:941–947.
14. Okines AF, Norman AR, McCloud P, et al. Meta-analysis of the REAL-2 and ML17032 trials: evaluating capecitabine-based combination chemotherapy and infused 5-fluorouracil-based combination chemotherapy for the treatment of advanced oesophago-gastric cancer. *Ann Oncol.* 2009;20:1529–1534.
15. Chao Y, Hsieh JS, Yeh HT, et al. A multicenter phase II study of biweekly capecitabine in combination with oxaliplatin as first-line chemotherapy in patients with locally advanced or metastatic gastric cancer. *Cancer Chemother Pharmacol.* 2014;73:799–806.
16. Kuo YC, Liu HT, Lin YL, et al. Modified biweekly oxaliplatin and capecitabine for advanced gastric cancer: a retrospective analysis from a medical center. *Biomed J.* 2014;37:141–146.
17. Giordano KF, Jatoi A, Stella PJ, et al. Docetaxel and capecitabine in patients with metastatic adenocarcinoma of the stomach and gastroesophageal junction: a phase II study from the North Central Cancer Treatment Group. *Ann Oncol.* 2006;17:652–656.
18. Lo SS, Khorana AA, Javle M, et al. A phase II study of weekly docetaxel in combination with capecitabine in advanced gastric and gastroesophageal adenocarcinomas. *Oncology.* 2010;78:125–129.
19. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer.* 2009;45:228–247.
20. Simon R. Optimal two-stage designs for phase II clinical trials. *Control Clinical Trials.* 1989;10:1–10.
21. Dank M, Zaluski J, Barone C, et al. Randomized phase III study comparing irinotecan combined with 5-fluorouracil and folinic acid to cisplatin combined with 5-fluorouracil in chemotherapy naive patients with advanced adenocarcinoma of the stomach or esophagogastric junction. *Ann Oncol.* 2008;19:1450–1457.
22. Kang YK, Kang WK, Shin DB, et al. Capecitabine/cisplatin versus 5-fluorouracil/cisplatin as first-line therapy in patients with advanced gastric cancer: a randomised phase III noninferiority trial. *Ann Oncol.* 2009;20:666–673.
23. Ajani JA, Rodriguez W, Bodoky G, et al. Multicenter phase III comparison of cisplatin/S-1 with cisplatin/infusional fluorouracil in advanced gastric or gastroesophageal adenocarcinoma study: the FLAGS trial. *J Clin Oncol.* 2010;28:1547–1553.
24. Cunningham D, Starling N, Rao S, et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. *N Engl J Med.* 2008;358:36–46.