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A randomized phase II trial comparing capecitabine with oxaliplatin or docetaxel as first-line treatment in advanced gastric and gastroesophageal adenocarcinomas

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Abstract

Background: A combination of fluoropyrimidines and platinum is widely accepted as the standard first-line treatment for advanced gastric and gastroesophageal adenocarcinomas. However, the benefit compared with platinum-free chemotherapeutic regimens remains controversial. We compared the efficacy and safety of capecitabine with oxaliplatin or docetaxel, as first-line therapy in advanced gastric cancer.

Methods: Eligible patients were randomly assigned to receive either capecitabine and oxaliplatin (XELOX) (capecitabine 1,000 mg/m^2; twice daily for 14 days with oxaliplatin 130 mg/m^2 on day 1, every 21 days), or DX (capecitabine 1,000 mg/m^2; twice daily for 14 days with docetaxel 75 mg/m^2 on day 1, every 21 days). The primary endpoint was the objective response rate (ORR). Secondary endpoints included the disease control rate (DCR), progression-free survival, overall survival, and prespecified safety endpoints.

Results: Ninety patients were enrolled in the West China Hospital from April 2012 to August 2016; a total of 83 and 66 patients were eligible for safety and efficacy analyses, respectively. Between the XELOX and DX groups, ORR (24.2% vs 24.2%, $p = 1.000$), DCR (90.9% vs 75.8%, $p = 0.099$), progression-free survival (6.1m vs 4.1m, $p = 0.346$), and overall survival (8.8m vs 9.0m, $p = 0.973$) were similar. There was no significant difference in toxicity between the two regimens. The frequent grade 3 or higher toxicities in the XELOX and DX groups were peripheral neuropathy and hematological toxicity, respectively. Toxicity was tolerable; no treatment-related deaths occurred in either group.

Conclusions: The DX regimen was not superior to XELOX, but instead, similar. The platinum-containing regimen remains the preferred first-line option for advanced gastric and gastroesophageal adenocarcinomas, and DX might be considered as an alternative for patients unsuitable for platinum-containing chemotherapy.

Abbreviations: DCR = disease control rate, DX = docetaxel and capecitabin, ORR = objective response rate, OS = overall survival, PFS = progression-free survival, XELOX = capecitabine and oxaliplatin.

Keywords: advanced gastric cancer, capecitabine, chemotherapy, docetaxel, oxaliplatin

Editor: Guang Lei.

JH and MQ contributed equally to this work.

The protocol was approved by the Ethics Committee of West China Hospital.

All patients had signed informed consent.

All the authors listed have approved the manuscript that is enclosed.

All patients have given prior written consent.

Code availability was not applicable.

This work was supported by the Chinese Gastrointestinal Oncology Group (CGOG) Funding and the research and development important project of the Science and Technology Bureau in Sichuan (2018SZ0188).

The authors have no conflicts of interest to disclose.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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How to cite this article: Ni L, Zhang W, Chen Y, Leng W, Gou H, Hu J, Qiu M. A randomized phase II trial comparing capecitabine with oxaliplatin or docetaxel as first-line treatment in advanced gastric and gastroesophageal adenocarcinomas. Medicine 2021;100:17(e25493).

Received: 19 December 2020 / Received in final form: 17 March 2021 / Accepted: 19 March 2021

http://dx.doi.org/10.1097/MD.0000000000025493

1. Introduction

Gastric cancer is the fifth most common tumor in the world and the third leading cause of tumor-related deaths. Patients with inoperable locally advanced or metastatic gastric cancer have extremely poor outcomes, with 5-year survival rates of <5%. Palliative chemotherapy is the standard treatment for advanced gastric cancer, and 5-FU-based chemotherapy can significantly prolong survival and improve quality of life compared with best supportive care.[1]

Fluorouracil combined with platinum chemotherapy has become the standard first-line chemotherapy for advanced gastric cancer. The REAL2 study confirmed that capecitabine could replace 5-Fu, and oxaliplatin could replace cisplatin.[2] This comparison of multiple three-drug regimens found that groups using oxaliplatin or capecitabine, rather than cisplatin or 5-Fu, showed a trend toward longer overall survival and improved safety. Several phase II studies have shown the combination of capecitabine and oxaliplatin as effective, with an overall response rate of 22% to 42%, progression-free survival (PFS) from 4.0 to 5.8 months, and overall survival (OS) from 6.4 to 12.2 months.[3–6] However, platinum-containing regimens have a high rate of cumulative peripheral neurotoxicity and gastrointestinal toxicity, which may seriously affect patients' quality of life. Additionally, patients with platinum allergies are undoubtedly not suited for the capecitabine and oxaliplatin (XELOX) regimen.

Docetaxel monotherapy has demonstrated efficacy as second-line therapy for advanced gastric cancer.[7–9] The V325 study first confirmed that the DCF group (docetaxel, carboplatin and fluorouracil) as first-line therapy was superior to the carboplatin and fluorouracil for time to progression and OS, but with a high proportion of grade 3–4 myelosuppression.[10] Application of the triplet regimen is limited in clinical application. The effectiveness of non-platinum regimens containing docetaxel was observed in a number of phase II single-arm studies. Korkeila et al. reported that docetaxel and capecitabine were used biweekly as first-line treatment for advanced gastric and esophageal cancer, with a median OS of 8.8 months and median PFS of 6.2 months. The most common grade 3 or 4 toxicity was inneutropenia (47%).[11] Although previous investigations comparing platinum-containing and nonplatinum-containing regimens have been performed,[12–14] the research time was too long ago and the methods applied were obsolete. The purpose of this study was to compare the efficacy and safety of capecitabine and oxaliplatin (platinum-based), with that of capecitabine and docetaxel (platinum-free), in the first-line treatment of advanced gastric cancer.

2. Patients and methods

2.1. Patient characteristics

Patients ≥18 years old who had histopathologically confirmed adenocarcinoma of the stomach, or esophagogastric junction adenocarcinoma, were eligible for enrollment. Other major inclusion criteria were: at least one measurable lesion according to the response evaluation criteria in solid tumors version 1.1; Eastern Cooperative Oncology Group performance status 0–2; no prior palliative chemotherapy or adjuvant chemotherapy completed more than 6 months before relapse; and adequate bone marrow, hepatic, renal, and heart function. Patients were excluded if they were unable to take oral medication, had uncontrolled bleeding, ascites, or obstruction of the upper digestive tract. Other anticancer treatments were not allowed during the study. The protocol was approved by the Ethics Committee of West China Hospital, and all patients had signed informed consent.

2.2. Treatment regimens

Eligible patients were randomly and equally assigned to either the XELOX or docetaxel and capecitabin (DX) groups. In the XELOX group, capecitabine (1,000 mg/m^2 twice daily) was administered orally on days 1–14, and oxaliplatin (130 mg/m^2) was administered intravenously over 3 hours on day 1 of every 3 weeks. In the DX group, capecitabine (1,000 mg/m^2 twice daily) was administered orally on days 1–14, and docetaxel (75 mg/m^2) was administered intravenously over 1 h on day 1 of every 3 weeks. In both groups, oxaliplatin or docetaxel was administered for a maximum of 8 cycles. Patients who did not progress after 8 cycles of chemotherapy would be treated with capecitabine (Xeloda) alone, until disease progression, intolerable toxicity, death, or consent withdrawal.

2.3. Evaluation of efficacy and toxicity

Baseline examinations included a physical examination, blood chemistries, and ECG. Physical and laboratory examinations were conducted within 3 days, before and after each treatment, and imaging examinations, like computed tomography scanning of the chest and abdomen, were performed at baseline and every 2 cycles thereafter. The efficacy was evaluated according to response evaluation criteria in solid tumors version 1.1, by two radiologists. Adverse events, corresponding processing methods, drug reduction, and patient compliance were recorded at each follow-up. Adverse events were evaluated according to the common terminology criteria for adverse events version 3.0.[15]

2.4. Statistic analysis

The primary endpoint was the ORR. Secondary end points included DCR, PFS, OS, and safety. According to related references[3,4,16–18] and the treatment efficacy of our center, the estimated ORR of the XELOX regimen in the control group was 35%, and the DX regimen in the experimental group was predicted to increase ORR by 15%. Accordingly, the expected response rate of DX was 50%. This study therefore required 33 patients in each group to ensure 90% power for a two-sided log-rank test, at a significance level of 0.05.

The Kaplan–Meier estimates and Cox proportional hazards model were used to analyze time-event variables. Patient characteristics and response rates were compared between the two treatment groups with the use of the χ2-test or Fisher's exact test, as appropriate. To compare continuous variables, the Mann–Whitney *U*-test for nonparametric data was used. All tests were two-sided, and p values <0.05 were considered to indicate statistical significance. The data were processed using SPSS v20.0.

3. Results

3.1. Patients

From April 2012 to August 2016, a total of 90 patients in West China Hospital were randomized to two groups (XELOX = 45,

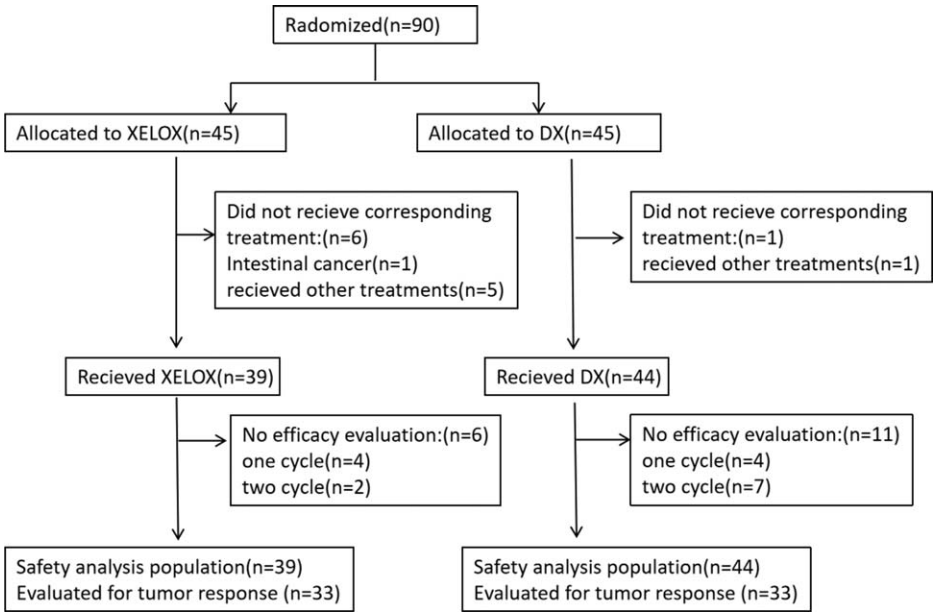

Figure 1. Consort diagram.

DX = 45). Of these, seven (7.8%) did not receive appropriate treatment or did not meet other requirements (six patients in the XELOX and one in the DX), and 17 patients (18.9%) received only one or two cycles of chemotherapy without efficacy evaluations. In the end, 33 patients in each group received the required chemotherapy and completed the corresponding efficacy evaluations (Fig. 1).

Patient characteristics are listed in Table 1. There were no significant differences in age, sex, performance status, primary tumor location, and histological type between the two groups. In terms of metastatic sites, the XELOX group had more cases of metastasis to the lung and liver, whereas the DX group had more distant metastasis to the peritoneum and abdominal lymph nodes.

3.2. Efficacy

The median treatment cycles in XELOX and DX were 5 and 4, respectively. The median actual dose intensities were similar in both arms. Of the 39 patients in the XELOX group, six patients did not undergo efficacy evaluation due to treatment for only one or two cycles and loss to follow-up. Therefore, 33 patients were included in the response rate analysis. In the DX group, the efficacy of 33 cases was evaluated. Finally, the ORR in the DX group was identical to the XELOX group (24.2% vs 24.2%, $p = 1.000$). DCR in the XELOX group was slightly, but not significantly higher than that in the DX group (90.9% vs 75.8%, $P = .099$) (Table 2).

The median follows up was 10.2 months for all 66 patients. The median PFS was 6.1 months in the XELOX group, and 4.1 months in the DX group (HR 0.78, 95% CI, 0.46–1.31, $P = .346$). The median OS in the XELOX group was 8.8 months, and 9.0 months in the DX group (HR 0.99, 95% CI, 0.60–1.65, $P = .973$), suggesting similar overall survival for both groups (Fig. 2).

3.3. Toxic effects

We counted adverse events in all 83 patients, regardless of whether it resulted from chemotherapy. Major adverse events are listed in Table 3. Among them, myelosuppression and peripheral neuropathy were more common in the XELOX group, whereas liver function impairment occurred more frequently in the DX group. In terms of the incidence of toxicities, there was no significant difference between the two groups. The majority of adverse reactions were grade 1 to 2, with 21 patients having adverse events of grade 3 or higher (13 in XELOX and 8 in DX), including myelosuppression, peripheral neuropathy, diarrhea, hand–foot syndrome, and impaired liver function. More frequent grade 3 or higher toxicities in the XELOX and DX groups were peripheral neuropathy and hematological toxicity, respectively. No treatment-related deaths were observed.

4. Discussion

This randomized, phase II clinical study compared the efficacy and safety of two treatment regimens (XELOX and DX), which were most commonly adapted in Asian patients with advanced gastric cancer as first-line therapy. Our study showed no significant difference in ORR, DCR, PFS, and OS between the two groups. The DX regimen showed no superiority to XELOX.

Although some control studies comparing platinum-containing and non-platinum regimens have been done, no head-to-head randomized controlled studies were performed to compare the XELOX and DX regimens. Even control studies, results were mixed and ambiguous. A meta-analysis conducted by Chen et al,[12] suggested that, compared to non-platinum regimens, the use of platinum-based regimens was associated with improved response (RR 1.94, 95% CI [1.48, 2.55], $P < .001$), and an increase in overall survival (HR 0.85, 95% CI [0.78, 0.92], $P < .001$). However, in another meta-analysis by Petrelli et al, chemotherapy regimens without cisplatin significantly improved

Table 1

Baseline characteristics of patients.

	XELOX (n = 39)	DX (n = 44)	*P* value
Sex			.345
Male	31	31	
Female	8	13	
Age, yr			.141
Median	59	60	
>65	10	13	
BMI (kg/m^2)	20.5	23.3	.473
ECOG performance status			.156
0	15	24	
1	23	19	
2	1	1	
Histological type			.354
Signet-ring cell carcinoma	5	9	
Adenocarcinoma& others	34	35	
CEA			.540
<3.4 ng/ml	16	21	
≥3.4 ng/ml	23	23	
CA19-9			.151
<22 U/ml	16	25	
≥22 U/ml	23	19	
Primary tumor location			.053
Esophagogastric junction	16	15	
Gastric body	17	12	
Gastric antrum	6	17	
Metastatic sites			.001
Lung	7	1	
Liver	16	2	
Distant lymph nodes	19	25	
Peritoneum	6	10	
Bone	2	2	
Ovary	0	3	
Others	2	4	
The number of metastatic organs			.116
Single	19	29	
Multiple	20	15	
Radiation therapy			.432
Yes	4	3	
No	35	41	
Surgery			.244
Yes	13	19	
No	26	25	
Adjuvant therapy			.110
Yes	4	10	
platinum-containing	4	7	
No	35	34	

BMI = body mass index; DX = docetaxel and capecitabin; ECOG = Eastern Cooperative Oncology Group; XELOX = capecitabine and oxaliplatin.

Table 2

Best overall response rate.

	XELOX (n = 33)		DX (n = 33)		
Response	**N**	**%**	**N**	**%**	***P* value**
Complete response	1	3.0	0	0.0	1.000
Partial response	7	21.2	8	24.2	.769
Stable disease	22	66.7	17	51.5	.211
Progressive Disease	3	9.0	8	24.2	.099
Response rate	8	24.2	8	24.2	1.000
Disease control rate	30	90.9	25	75.8	.099

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

OS, PFS, and RR.[13] Therefore, our study can serve as a reference for future investigations. In our study, results showed that DX was not superior to XELOX, but instead had similar efficacy. Docetaxel did however have some advantages over oxaliplatin, like clinical ease-of-use and improved tolerability, especially as peripheral neurotoxicity is far less severe in docetaxel compared with oxaliplatin.[19] Additionally, the DX regimen may be a suitable alternative for patients with platinum allergies. In the past, several phase II studies have tested capecitabine, in combination with docetaxel, as first-line therapy in patients with advanced gastric cancer.[20–24]

In previous DX studies, RR was about 39.0% to 43.8%, PFS ranged from 4.2 to 5.0 months, and OS ranged from 9.4 to 12 months.[20–22] In our study, PFS and OS were similar to those in previous studies, whereas RR was relatively low. As far as we are concerned, the use of domestic capecitabine might be a reason for the reduced RR. In addition, the efficacy evaluation was mainly done by radiologists rather than the researchers themselves. Therefore, the results could be influenced by the subjective judgments of the evaluators. However, both groups were given domestic drugs and had the same assessors. Therefore, bias toward either group was avoided, and it could not affect our conclusion.

As for adverse events, both groups were well tolerated and had a similar safety profile. Toxicities of grade 3 or 4 mainly occurred in the XELOX group, mostly caused by bone marrow suppression and peripheral neurotoxicity, but without significant differences. Additionally, no treatment-related deaths were reported for this study. The advent event rates were similar to previous studies.[2,3,25]

There are some limitations in this study. First, we did not set up subgroups at baseline. We were therefore unable to further explore the impact of clinical factors on our endpoints. Secondly, our sample size was small, which could be responsible for the

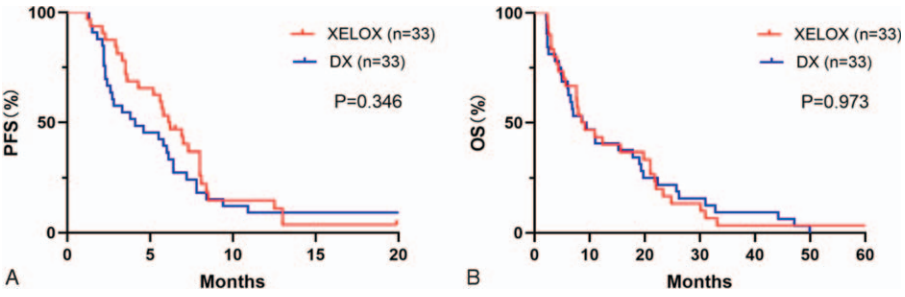

Figure 2. Kaplan–Meier estimates of progression-free survival (A) and overall survival (B).

Table 3

Adverse events (safety population).

	XELOX (n = 39)				DX (n = 44)				
Grade	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	***P* value**
Anemia	11	13	3	0	6	13	3	1	.689
Leukopenia	6	4	0	0	4	3	1	0	.544
Neutropenia	6	6	0	0	1	2	1	1	.082
Thrombocytopenia	8	2	2	0	4	1	0	0	.511
Peripheral neuropathy	10	2	3	1	4	2	0	0	.606
Nausea	22	1	0	0	17	1	0	0	.860
Vomiting	7	0	0	0	4	1	0	0	.237
Diarrhea	1	1	1	0	2	0	0	0	.197
Fatigue	2	0	0	0	2	0	0	0	1.000
Hand-foot syndrome	0	1	2	0	1	0	0	0	.157
Hemorrhage	2	0	0	0	1	0	0	0	1.000
Liver function damage	10	8	1	0	16	5	1	0	.210

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

imbalance of metastatic sites in the 2 groups. Finally, at the beginning of our study, Herceptin was not approved in China, and many patients did not do the HER2-status test at all due to limited conditions. Therefore, potential HER2-positive patients were unable to receive anti-Her2 therapy.

In general, the DX regimen did not show superiority over XELOX. Thus, it cannot replace XELOX as a standard first-line treatment. Compared with the three-drug regimen used in European and American countries, the safety of the two-drug regimen can be better guaranteed with higher tolerance in most Asian patients. Platinum-containing regimens are therefore the preferred first-line option for advanced gastric and gastroesophageal adenocarcinoma. Although many targeted therapies are being rapidly developed, combinative chemotherapy remains the conventional treatment for most patients with advanced gastric cancer. In the future, biomarkers predicting the sensitivity of chemotherapy may improve the clinician's ability to select from different treatment regimens to achieve precise chemotherapy strategies.

Acknowledgments

In addition to the investigators in the author list, we thank all the patients for their participation.

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Writing – review & editing: Lu Ni, Weihan Zhang, Ye Chen, Weibing Leng, Hongfeng Gou, Jiankun Hu, Meng Qiu.
Meng Qiu and Lu Ni conceived the idea. Lu Ni collected and analyzed the data. All authors discussed the results, critically reviewed the article and approved the contents.

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